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Photo-Isomerizable Self-Complementary Hydrogen Bond Arrays

Iamnica Janic Linares Mendez
The University of Western Ontario

Supervisor
James A. Wisner
The University of Western Ontario

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Abstract

The combination of photoswitchable molecules and supramolecular complexes has provided valuable contributions to materials science. The scope of applications where these smart materials could contribute drives the efforts toward developing systems that provide a range of responses, sensibilities and stabilities. This thesis exploits the use of a well-known photochromic system in a self-complementary hydrogen bond array; i.e. the azo group, R-N=N-R. The novelty of the approach described in this thesis resides in the double function of the azo group within the array: as a hydrogen bond acceptor site and as a functional element that promotes a structural change capable of disrupting the complexation equilibrium when irradiated with light.

The photo-isomerizable self-complementary hydrogen bond arrays presented in this document are obtained by a general and practical synthetic method from inexpensive starting materials. Their self-complementary recognition was corroborated by \(^1\)H NMR dilution experiments and single crystal X-ray structures. In the course of these studies, it was observed that the electron withdrawing character of the substituents employed, the presence of solvent-solute interactions and the disposition of the binding sites have a significant effect over the dimerization constants obtained.

Likewise, some photochemical properties of these systems were studied, such as their UV-Vis absorption spectra, the \textit{cis/trans} ratio at their photostationary state after \textit{trans-} to \textit{cis-} photoisomerization, the stability of the complexes present in solution after UV- light irradiation, and the decay profile of their \textit{cis}-isomeric forms. The distribution profiles (or speciation diagrams) of monomers and dimers in toluene-\textit{d}_8 solutions at different \textit{cis/trans}
ratios of four of our photoswitchable self-complementary hydrogen bond arrays were obtained. From these speciation diagrams we were able to confirm that the mathematical approach employed to describe the systems’ equilibria provided us a reliable approximation of all complexation constants in solution after photoisomerization.

Keywords
azoheteroaromatic compounds, photoisomerization, self-complementary arrays, smart materials, hydrogen bond.
Co-Authorship Statement

Jeffrey S. Pleizier synthesized and crystallized compound 4a. All X-ray crystal structure were solved by Dr. Paul D. Boyle (X-Ray facility manager). Mass spectrometry of all compounds presented in this work was carried out by Doug Hairsine (Mass Spec facility manager).

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All of the remaining work in this thesis was performed by the author herself.
Acknowledgments

“Science, my lad, is made up of mistakes, but they are mistakes which it is useful to make, because they lead little by little to the truth”

-Jules Verne

This thesis is the result of a five years journey where I had the opportunity to work and learn in the company of many people. I want to take these lines to publicly acknowledge their contribution to this project.

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<tbody>
<tr>
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<td>A</td>
<td>hydrogen bond acceptor</td>
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<td>α</td>
<td>hydrogen bond donor properties</td>
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Chapter 1

1 Introduction

1.1 Supramolecular Chemistry

In Jean-Marie Lehn’s words, Supramolecular Chemistry is “… a highly interdisciplinary field of science covering the chemical, physical, and biological features of chemical species of higher complexity, which are held together and organized by means of intermolecular (noncovalent) binding interactions”.¹

The roots of this relatively young area can be traced back to the nineteenth century with contributions from studies in organic chemical and biological systems. The synthesis of the first (and arguably most employed) host molecules, the cyclodextrins by Antoine Villiers in 1891,² the introduction of “lock-and-key” concept by Emil Fischer in 1894,³ the “induced fit” concept by Daniel E. Koshland in 1958,⁴ and the description of an observed carboxylic acid complex as “Übermoleküle” (supramolecule in German) by Karl Lothar Wolf in 1937,⁵ were some of the earliest contributions that made possible the emergence of more advanced tailored hosts such as the crown ethers of Charles Pedersen in 1967,⁶,⁷ the cation and anion cryptates of Jean-Marie Lehn in 1969⁸,⁹ and the spherands of Donald J. Cram in 1973.¹⁰,¹¹ The latter three were awarded the Nobel Prize for Chemistry in 1987 for their work in supramolecular chemistry.¹²

More recently, supramolecular chemistry has evolved and broadened its scope. It no longer only serves as a means to explain physical properties of pure substances and
mixtures such as the transportation of alkali metal ions through cell membranes\cite{13,14}, and the enzyme-substrate catalysis in living systems\cite{13-16}. Supramolecular chemistry now creates its own subjects to study by developing sophisticated and complex arrays to serve specific purposes in different fields\cite{19-21}.

The aim of this first chapter is to provide the context to understand and locate the contribution of the systems presented in the following chapters. It will cover basic concepts that describe supramolecular complexes and the specific intermolecular interactions that operate in our arrays. Likewise, this chapter will present the photochemical basis that operates in our proposed arrays and the state of the art regarding the use of photochromic compounds in supramolecular chemistry.

### 1.2 Molecular Recognition

Molecular recognition is known as the strong, selective and reversible stabilizing interaction of one molecule with another to form a well-defined spatial arrangement between them. Initially, the term molecular recognition was exclusively employed to describe biological systems. However, it was discovered that the occurrence and effects of this event were not limited to that discipline and that it could be applied in a wide range of other scientific and technologic fields\cite{22}.

Based on the definition provided in the previous paragraph, it could be said that there are two main features that characterize molecular recognition: the intermolecular interactions and their spatial arrangement.
1.3 Intermolecular Interactions

Also known as supramolecular and non-covalent interactions, intermolecular interactions are the overall result of attractive and repulsive forces between identified separated entities, i.e. molecules, chemical groups within the same molecule, ions, and/or atoms. The energies associated with these interactions range from $< 2 \text{ kJ mol}^{-1}$ for dispersion interactions to $300 \text{ kJ mol}^{-1}$ for ion – ion interactions in non-polar media\(^\text{23}\) (Table 1.1).

At a macroscopic level, these interactions are responsible for aspects of many important physical properties of matter such as density, boiling point, solvation, surface tension and redox potentials. In biology, intramolecular interactions explain the three dimensional structures of proteins,\(^\text{24-26}\) DNA\(^\text{27}\) and RNA. Likewise, they participate in well-known processes such as carbohydrate recognition\(^\text{28,29}\) and the transport of cations in biological systems.\(^\text{30,31}\) Lastly, these interactions are useful in materials science to create specific crystal packing systems (crystal engineering),\(^\text{32,33}\) molecular systems with mechanical properties for specific environments,\(^\text{34}\) and to modulate optical properties of some materials.\(^\text{35,36}\)
Table 1.1 Intermolecular Interactions.23

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Strength (kJ mol(^{-1}))</th>
<th>Example</th>
<th>Directionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ion – ion</td>
<td>200 – 300</td>
<td>Tetrabutylammonium chloride</td>
<td>Low</td>
</tr>
<tr>
<td>Dipole – dipole</td>
<td>5 – 50</td>
<td>Acetone</td>
<td>Medium</td>
</tr>
<tr>
<td>Hydrogen Bonding</td>
<td>4 – 120</td>
<td></td>
<td>Medium</td>
</tr>
<tr>
<td>Cation - π</td>
<td>5 – 180</td>
<td>K(^+) in benzene</td>
<td>Medium</td>
</tr>
<tr>
<td>π-π</td>
<td>0 – 50</td>
<td>Benzene and graphite</td>
<td>Medium</td>
</tr>
<tr>
<td>van der Waals</td>
<td>&lt; 5</td>
<td>Argon, packing in molecular crystals</td>
<td>Low</td>
</tr>
<tr>
<td>Hydrophobic</td>
<td>Related to solvent –</td>
<td>Cyclodextrin inclusion compounds.</td>
<td>Low</td>
</tr>
<tr>
<td>(solvophobic)</td>
<td>solvent interaction energy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From the intermolecular interactions listed above, hydrogen bonds have arguably received the most attention since they are often a central interaction in determining molecular recognition and aggregation in chemical and biological systems. Similarly, due to their strength and directionality, hydrogen bonds have been one of the primary strategies employed in the construction of many novel materials.
1.4 Hydrogen Bond.

1.4.1 Definition.

In 2011, IUPAC presented a technical report in which a new definition of hydrogen bond was provided. This definition states that the hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment \( X-H \) in which \( X \) is more electronegative than \( H \), and an atom or group of atoms in the same or a different molecule (\( Y \)), in which there is evidence of bond formation (Scheme 1.1).\(^{37}\)

\[
\begin{array}{c}
X-H + Y \\
\leftrightarrow \\
X-H\cdots Y
\end{array}
\]

**Scheme 1.1** Hydrogen Bond Interaction.

The definition provided by IUPAC is broad and requires evidence of bond formation. According to IUPAC, there are some criteria of what is considered bond formation evidence which includes:

1) Geometry: The angle formed between the three atoms that participate in the hydrogen bond interaction usually tends to be linear.

2) The nature of the physical forces involved: Although a hydrogen bond is not considered to be purely electrostatic, it is recognized for its substantial contribution due to the directionality of this interaction. Other contributions to the hydrogen bond are polarization, charge transfer, exchange repulsion and dispersion forces (the last two included in van der Waals interactions).\(^{38,39}\)
3) Spectroscopy: The effects of the hydrogen bond in the absorption of different types of energy is observed in the red shifting in the X-H vibrational frequency in an IR spectrum and the deshielding of H in HX in a $^1$H NMR spectrum.

1.4.2 Classification.

Throughout the literature, the hydrogen bond has been classified into three main categories based on geometry, energy, thermodynamics and function in nature, which are summarized in Table 1.2. 40-42

<table>
<thead>
<tr>
<th>Bond Energy (kcal/mol)</th>
<th>Very Strong or Strong</th>
<th>Strong or Moderate</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction Type</td>
<td>Strongly Covalent</td>
<td>Mostly Electrostatic</td>
<td>Electrostatic/Dispersed</td>
</tr>
<tr>
<td>Directionality</td>
<td>Strong</td>
<td>Moderate</td>
<td>Weak</td>
</tr>
<tr>
<td>D (X·····Y) range (Å)</td>
<td>2.2 - 2.5</td>
<td>2.5 - 3.0</td>
<td>3.0 - 4.0</td>
</tr>
<tr>
<td>θ (X-H···Y) (°)</td>
<td>175 – 180</td>
<td>130 – 180</td>
<td>90 – 180</td>
</tr>
<tr>
<td>Effect on Crystal Packing</td>
<td>Strong</td>
<td>Distinctive</td>
<td>Variable</td>
</tr>
<tr>
<td>IR ν, relative shift</td>
<td>&gt; 25 %</td>
<td>5 – 25 %</td>
<td>&lt; 5 %</td>
</tr>
<tr>
<td>$^1$H Chemical Shift Downfield (ppm)</td>
<td>14 – 22</td>
<td>&lt; 14</td>
<td>-</td>
</tr>
<tr>
<td>Examples</td>
<td>[F···H···F]</td>
<td>O – H···O=C</td>
<td>C – H···O</td>
</tr>
<tr>
<td></td>
<td>[N···H···N]</td>
<td>N – H···O=C</td>
<td>O – H···π</td>
</tr>
</tbody>
</table>
This classification is meant to be a broad guide to the hydrogen bond interactions observed in nature and used in the design and construction in crystal engineering and supramolecular chemistry. The terminology employed would depend on the author referred. Desiraju and Steiner classified hydrogen bonds as very strong, strong and weak based on the observation that hydrogen bonds that fall into the category of strong are interactions that are able to control crystal and supramolecular structure effectively. On the other hand, Jeffrey named the same categories as strong, moderate and weak in order to be in tune with biological literature since moderate hydrogen bond interactions are usually observed in chemistry and nature, as the other two categories being the minority exception.

Another way to classify the hydrogen bond interaction is in accordance to the different spatial arrays formed between the hydrogen bond donors (which are the molecular fragments $X$-$H$), $D$, and the hydrogen bond acceptors (the counterparts $Y$), $A$ (Scheme 1.1 and Figure 1.1). The appearance of different hydrogen bond arrays is explained due to the attractive force of extra binding sites; i.e. donors and/or acceptors. The angles described are often significantly different from linearity; therefore, these types of arrays are not expected in very strong (or strong according to Jeffrey’s classification) hydrogen bond interactions. These configurations are known as donating bifurcated, accepting bifurcated, trifurcated and three centre bifurcated (Figure 1.1). \textsuperscript{41-45}
1.4.3 Strength of the Hydrogen Bond in Supramolecular Arrays.

There are different ways to modulate the strength of the hydrogen bond interactions in a supramolecular array. The three main strategies are:

(i) the manipulation of some chemical properties of the hydrogen bond donor and acceptor sites; i.e. the electron density of these sites\(^ {46} \) and the polarization of the X\( \cdot \)H bond;\(^ {47} \)

(ii) the addition of more intramolecular interactions to create a cooperative effect;\(^ {48} \) and

(iii) the arrangement of the hydrogen bond donor and acceptor sites that participate in the interaction.\(^ {49} \)
1.4.3.1 Electron density of binding sites.

The first feature refers to the possibility of controlling the electron density in donor and acceptor sites through substituent effects. In this sense, it is desired to have a low electron density in hydrogen bond donor sites and a high electron density in hydrogen bond acceptor sites in order to observe a strong hydrogen bond interaction. Therefore, it is commonly observed in the literature that electron-withdrawing groups are bonded near hydrogen bond donors and electron-donating groups are bonded near hydrogen bond acceptors.

One example of this effect was reported by Wisner and coworkers through DDD-AAA hydrogen bond arrays. In this work, the comparison of the association constants of a set of different DDD units with an AAA unit proved that as more electron-withdrawing groups were added to the DDD unit higher association constants were obtained (Figure 1.2, Table 1.3). Likewise, the addition of electron-donating groups to the AAA unit showed higher association constants than the addition of electron withdrawing groups when complexed to the same DDD unit.

**Figure 1.2** DDD-AAA hydrogen bond arrays studied by Wisner and coworkers.
Table 1.3 Comparison of the effect of electron-withdrawing functional groups attached to DDD units on the association constant ($K_a$) in CDCl$_3$ at 298 K.

<table>
<thead>
<tr>
<th>DDD</th>
<th>X</th>
<th>Y</th>
<th>$K_a$ with 7 [M$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>H</td>
<td>H</td>
<td>3.7x10$^3$</td>
</tr>
<tr>
<td>6b</td>
<td>Br</td>
<td>H</td>
<td>7x10$^3$</td>
</tr>
<tr>
<td>6c</td>
<td>H</td>
<td>CO$_2$Et</td>
<td>1.1x10$^4$</td>
</tr>
<tr>
<td>6d</td>
<td>Br</td>
<td>CO$_2$Et</td>
<td>2.6x10$^4$</td>
</tr>
<tr>
<td>6e</td>
<td>H</td>
<td>CN</td>
<td>2.9x10$^4$</td>
</tr>
<tr>
<td>6f</td>
<td>CN</td>
<td>Br</td>
<td>4.9x10$^4$</td>
</tr>
<tr>
<td>6g</td>
<td>CO$_2$Et</td>
<td>CO$_2$Et</td>
<td>5.4x10$^4$</td>
</tr>
<tr>
<td>6h</td>
<td>CN</td>
<td>CN</td>
<td>1.1x10$^5$</td>
</tr>
</tbody>
</table>

1.4.3.2 Number of hydrogen bond sites.

Cooperativity refers to two or more binding sites acting in a concerted fashion to produce a combined interaction that is stronger than when the binding sites act independently. In other words, the stability of a hydrogen bond array is proportional to the number of hydrogen bond interactions present. This effect is well documented in the literature by Zimmerman and Murray, who reported the effect of extra donors and acceptors on the stability of hydrogen bond complexes.$^{51,52}$

As illustrated in Figure 1.3, the complex with the highest number of hydrogen bond sites, DDD-AAA, has the highest association constant ($K_a \geq 10^5$ M$^{-1}$), whereas the complex with the lowest number of hydrogen bond sites, DD-AA, has the lowest association constant ($K_a = 260$ M$^{-1}$). The authors observed that the addition of an extra
A hydrogen bond donor site has a greater influence on the stability of the complex than the addition of an extra hydrogen bond acceptor site. Hence, the DD-AAA complex has an association constant of $3 \times 10^3$ M$^{-1}$ compared with the DD-AAA complex with an association constant of 848 M$^{-1}$. It follows that, these last two complexes display higher association constants than the DD-AA complex.

**Figure 1.3** The effect of the number of hydrogen bonding sites on the stability ($K_a$) of different arrays.
1.4.3.3 Secondary Hydrogen Bond Interactions.

The last feature that contributes to the strength of the hydrogen bond array refers to the distribution of the hydrogen bond sites between units. Supramolecular complexes with the same number of donor and acceptor sites have different association constants when the sequence of those binding sites is different.

![Figure 1.4 Hydrogen Bond Arrays studied by Jörgensen and Pranata](image)

Jörgensen and Pranata observed this peculiarity in some hydrogen bond complexes, (Figure 1.4). As can be noted, all complexes in Figure 1.4 comprise the same number of donors and acceptors. However, the difference between the lowest association constant ($K_a = 90 \text{ M}^{-1}$) and the highest one ($K_a = 10^4 \text{ -- } 10^5 \text{ M}^{-1}$) is significant. The authors explained these differences due to the repulsive or attractive effect of the secondary hydrogen bond interactions. The contribution of these interactions was estimated through different computational methods.

Secondary interactions occur among neighboring hydrogen bond donor/acceptor sites (Figure 1.5). The proximity between them in the arrays (2 - 4 Å) is sufficient to exhibit substantial electrostatic repulsions and attractions. According to this model, an array that
alt. dons and accps, ADA-DAD, is less favored since it displays four repulsive 
sec. interactions. On the other hand, the most favored array is the one that comprises 
all dons on one unit and all accps in the other one, DDD-AAA. After Jörgensen and 
Pranata’s studies, Zimmerman and Murray supported this model by comparing a set of 
arrays that represented all the possible combinations with three dons and three accps 
(Figure 1.6).51

![Secondary hydrogen bond interactions in triply hydrogen bonded arrays.](image1)

**Figure 1.5** Secondary hydrogen bond interactions in triply hydrogen bonded arrays.

![Triple hydrogen bond complexes studied by Zimmerman and Murray.](image2)

**Figure 1.6** Triple hydrogen bond complexes studied by Zimmerman and Murray.

Moreover, the energetic contributions of the primary and sec. hydrogen bond 
interactions estimated by Jörgensen and Pranata were confirmed by another study carried
out by Sartorius and Schneider.\textsuperscript{57} Based on multiple linear regression analysis of association energies of 58 different complexes, Sartorius and Schneider calculated that the average value of the free energy of a primary hydrogen bond interaction is $7.9 \text{ kJ mol}^{-1}$ and for a secondary hydrogen bond interaction is $2.9 \text{ kJ mol}^{-1}$ regardless of its character as an attractive or repulsive interaction.\textsuperscript{58}

### 1.5 Supramolecular Complexes.

A supramolecular complex is an entity formed by the molecules that participate in a molecular recognition event. It is characterized by its geometry, thermodynamic and kinetic features.\textsuperscript{59} Since a supramolecular complex requires more than one molecule, each molecule that participates is known as a monomer or monomeric unit. The supramolecular complex can also be defined as a collection of monomers or monomeric units arranged in a specific orientation to each other by intermolecular interactions. The chemical composition of each monomer in a supramolecular complex classifies it as complementary or self-complementary.

Complementary hydrogen bond arrays consist of two or more \textit{different} monomeric units which interact with each other to form a complex. Each monomeric unit incorporates a mutually complementary arrangement of donors and acceptors in order to form the hydrogen bonds. Natural examples of complementary arrays are nucleotide base pairs (Figure 1.7). The complementary arrays illustrated in the preceding pages (Figure 1.2 to 1.4 and 1.6) are the result of the studies and meticulous design of several research groups.
Self-complementary arrays comprise only one type of monomeric unit. The monomeric unit comprises hydrogen bond donors and acceptors disposed in such way that it can form a complex with itself. These complexes are generally characterized by an inversion center. One example of these arrays is provided by guanine tetramers discovered in eukaryotic chromosomes by Sundquist and Klug (Figure 1.8A). Likewise, there are many reports regarding the design and synthesis of self-complementary arrays, such as the molecular duplex reported by Chu and coworkers, illustrated in Figure 1.8B.

Figure 1.7 Nucleotide base pairs in DNA.

Figure 1.8 (A) A guanidine tetramer reported by Sundquist and Klung; (B) A molecular duplex reported by Chu and coworkers.
1.6 Preorganization

Besides the strength of non-covalent interactions present in a supramolecular complex, its stability can be affected by the monomer structure and the conformational disposition of binding sites. These two features are part of the preorganization principle described by Donald J. Cram.\textsuperscript{62,63}

The preorganization principle implies that a monomer (\(M^1\)) designed to have the binding sites in a fixed way perfectly complementary to the other monomer’s binding sites (\(M^2\)), prior to their complexation, will bind more strongly than a monomer (\(M^3\)) that needs to undergo a conformational rearrangement (\(M^{3*}\)) prior to the binding event (Scheme 1.2).\textsuperscript{5} Therefore, a key feature in the design of supramolecular complexes is the stability of the monomers’ conformation to ensure a perfect fit with each other. Otherwise, there will be an energetic cost due to the conformational re-arrangement needed to reach the proper binding geometry.

![Preorganization Principle](image)

**Scheme 1.2 Preorganization Principle.**

A good example of the importance of this principle was reported by Murray and Zimmerman through the complementary supramolecular arrays 3-2 and 9-2 (Figure 1.9).\textsuperscript{64} The authors observed that the 3-2 complex exhibited an association constant significantly lower than that anticipated by Jörgensen’s secondary interactions model. Molecular
mechanics calculations of the possible conformations for 3 showed that structure 3\(^{**}\), which presents a steric repulsive interaction with the 4-amino group, is the favorable conformer. Meanwhile, the same calculations showed that the structure where the alkoxy group is optimally positioned to participate in a secondary hydrogen bond interaction, 3\(^'\), is less stable by 4 kcal mol\(^{-1}\). This is, the geometrical prearrangement involved in order to engage monomers 3 and 2 into complexation has an energetic cost that is reflected in the 3\(\cdot\)2 complex \(K_{\text{ass}}\) value. This observation was supported by the association constant of the 9\(\cdot\)2 complex. In this complex, monomer 9 was specifically designed and synthesized to have an accessible oxygen acceptor atom to interact with the 4-amino group via a lactone moiety; the result was a higher association constant compared with 3\(\cdot\)2 complex. This study confirms that fixing a monomer into a geometrical structure that complements the other monomer’s interacting sites disposition has a positive effect on the stability of the complex.

\[
\begin{align*}
3'' & \quad \text{CH}_3 \quad \text{C}_3\text{H}_7 \\
2 & \quad \text{O}_2\text{CC}_4\text{H}_9 \quad \text{O}_2\text{CC}_4\text{H}_9 \\
\text{C}_4\text{H}_9\text{CO}_2 & \\
3' & \quad \text{CH}_3 \quad \text{C}_3\text{H}_7 \\
2 & \quad \text{O}_2\text{CC}_4\text{H}_9 \quad \text{O}_2\text{CC}_4\text{H}_9 \\
\text{C}_4\text{H}_9\text{CO}_2 & \\
9 & \quad \text{O}_2\text{CC}_4\text{H}_9 \quad \text{O}_2\text{CC}_4\text{H}_9 \\
\text{C}_4\text{H}_9\text{CO}_2 & \\
\end{align*}
\]

\(K_{\text{ass}} = 32 \text{ M}^{-1}\)

\(K_{\text{ass}} = 435 \text{ M}^{-1}\)

**Figure 1.9** Murray and Zimmerman DAA-ADD complex structures. Association constants (\(K_{\text{ass}}\)) calculated in a 5% DMSO-d\(_6\) – CDCl\(_3\) solvent system.
1.7 Tautomerization

As can be observed in the examples provided in previous sections, most of the hydrogen bonded supramolecular complexes comprise heteroaromatic moieties. They serve as good backbones since they have at least one heteroatom which is used as a hydrogen bond acceptor site. Likewise, different chemical groups (donor and acceptor sites) can be attached to them by known synthetic pathways. However, one of the complications involved with the use of heteroaromatic compounds is their ability to convert to different tautomeric forms due to a proton shift; which is known as prototropy.\(^{65}\)

Depending on the monomer’s design, it is often possible to obtain more than one tautomer (or protomer) able to participate in a hydrogen bond array. One popular example of these systems are the ureidopyrimidones developed by Meijer and coworkers. They noticed that the 6[1H]-pyrimidinone can tautomerize to 4[1H]-pyrimidinone or pyrimidin-4-ol. The last two tautomers can dimerize due to their DDAA and DADA disposition, respectively. Both arrays are preorganized by an intramolecular hydrogen bond (Scheme 1.3).\(^{66}\)
Scheme 1.3 Equilibria between tautomeric forms of 6[1H]-pyrimidinone.

Through this work, the authors observed that the preference of one tautomer over others depends on the nature of the substituent. Systems where R1 was an electron-withdrawing group provided the highest fractions of pyrimidin-4-ol tautomer. The rationalization behind this observation was the reduced stability of the enone in 4[1H]-pyrimidinone when an electron-withdrawing 6-substituent is present. In addition, the hydrogen bond acceptor competence of its carbonyl function is reduced.

Besides the effect of substituents, tautomerization can be affected by the solvent employed. In the ureidopyrimidones’ example, the dominant tautomers observed in chloroform and toluene correspond to 4[1H]-pyrimidinone and pyrimidin-4-ol in fixed ratios. In THF, the ratio of these two tautomers changes upon dilution. Lastly, in dimethyl sulfoxide solution, the 6[1H]-pyrimidinone is the only tautomer observed.
Another way to control the tautomeric ratio is by the addition of another monomer that forms a complex with only one of the possible tautomers. This strategy was applied by Zimmerman and coworkers who studied self-complementary hydrogen bond arrays able to tautomerize in five different ways\textsuperscript{65} (Scheme 1.4).

\begin{center}
\includegraphics[width=\textwidth]{scheme1_4.png}
\end{center}

\textbf{Scheme 1.4} Zimmerman’s group system tautomers.

In this study, it was observed that tautomers 6 and 7 were most abundant when toluene and chloroform were employed as solvents, respectively. This observation is reasonable due to the strength of DDAA-AADD self-complexation compared to the DADA-ADAD tautomeric complex. In both solutions, once a small excess of compound 11 is added, tautomers 6 and 7 fully disassociate to lead the formation of a DAAD-ADDA
complementary array with tautomer 9 or 10. The authors supported the formation of the 9-11 complex using computational and NOE studies.

1.8 Solvent Effect

It is likely, with the exception of crystal engineering, that most of the supramolecular chemistry studied to date has been observed in solution. Therefore, solvent plays a significant role in the binding event due to its interaction with the monomers and any complexes formed.

Solvation is the process wherein through intermolecular interactions the dispersed solute is surrounded by a sphere of solvent molecules, the solvation shell. The extent of solvation (i.e. the number and arrangement of solvent molecules around the solute) differs from one solvent to another due to differences in the interactions at work in each case, that are dependent on solvent’s nature. The importance of the solvent in complexation lies in the fact that the solvation shell generally blocks the binding sites of the monomers in solution. Hence, there is an amount of energy involved in the dissociation of solvent molecules from these binding sites (Scheme 1.5).\(^{67}\)

Scheme 1.5 Monomer desolvation upon complex formation. Scheme reproduce with permission (License number 3910300843589).
In other words, there is a competition for binding sites between solvent and the other monomer(s) involved in the complex. This solvent effect was examined by Taft, Abraham and Hunter among others. Hunter proposed a model to predict the association constant and the free energy implicated in the formation of a hydrogen bond complex in different solvents (Equations 1 and 2). The model is a simplification of possible interactions between solute and solvent in terms of their hydrogen bond donor and/or acceptor characteristics: \( \alpha \) and \( \alpha_s \) describe hydrogen bond donor properties of solute and solvent; and, \( \beta \) and \( \beta_s \) describe hydrogen bond acceptor properties of solute and solvent, respectively (i.e. Kamlet-Taft parameters).

\[
\Delta G = -(\alpha - \alpha_s)(\beta - \beta_s) + 6 kJ mol^{-1} \quad \text{Equation 1}
\]

\[
\Delta G = -\ln K_{\text{pred}} RT \quad \text{Equation 2}
\]

As a result of this model, a profile of the dominant interaction in a solute-solvent system can be summarized in Figure 1.10. According to this profile, a hydrogen bond array is favored either because solute - solute interactions or solvent – solvent interactions are dominant over solute – solvent interactions. The first scenario corresponds to designed arrays with a high molecular recognition level; i.e. the structural arrangement and interactions present result in a greatly stable complex. In contrast, the second scenario concerns the solvophobicity of the monomers in solution and the interaction of dissociated solvent molecules with bulk solution.
The accuracy of this model has been corroborated by the author through a number of studies. One of them involved the estimation of the association constant of perfluoro-tert-butyl alcohol and tris-n-butylphosphine oxide in different solvents. The values obtained applying this model are in agreement with those obtained experimentally, with the exception of alcohols whose case is special due to an underestimation of the polarity of such solvents.
1.9 Smart Materials.

Thanks to the examination and understanding of the physical properties of different chemical species, materials science now has a broad range of resources available to tailor materials that fulfill a specific purpose. This continued development has led to the emergence of complex and sophisticated materials with the ability to exhibit fast,repeatable, reversible and significant change in one of their physical properties in response to controlled external stimuli. These materials are referred in the literature as “smart” materials.

The nature of the external stimulus used in these materials can be:

- Chemical: changes in the pH, the ionic strength, the solvent system, gases present and redox-reactions.
- Physical: electric field, temperature changes, light irradiation and mechanical stress applied.
- Biochemical: antigens, enzymes or other biochemical agents present.

Some of the physical properties that can be modified in response to the stimuli can be changes in physical shape or aggregation pattern adopted, volume, viscosity, and porosity.

The increasing interest and development of novel smart materials relate to their potential applications in drug delivery, bioseparation of proteins, immunoassays, tissue scaffolds, generation of mechanical work at a microscopic level, sensors and nanowires and self-healing.
1.10 Supramolecular Photochemistry.

Supramolecular complexes can be described and characterized comparing the properties of each one of the monomers with those of the final resulting complex. In this sense, the properties of the latter cannot be assumed as a mere superposition of those of its units.\textsuperscript{91}

One property that can be affected after complexation is the interaction with light. The energy provided to a supramolecular system after light irradiation can generate a significant change in the structural and electronic organization of the complex. The study of these changes is the object of the supramolecular photochemistry.\textsuperscript{67}

1.11 Photoswitches

Photochromism is the term used to describe the efficient and reversible transformation of some organic molecules between, at least, two (meta) stable isomers induced by light absorption.\textsuperscript{67,92} Molecules that show this property are known as photochromic compounds or photoswitches.

Transformations observed in these compounds include E/Z isomerization, pericyclic reactions, intramolecular hydrogen transfer, intramolecular group transfer, dissociation processes and electron transfers (Scheme 1.6 to 1.9).\textsuperscript{93} After transformation, photoswitches generally exhibit changes in physicochemical properties such as absorption
spectra, dipole moment, refractive index, dielectric constant, oxidation/reduction potential and geometrical structure.

**Azo Aromatic Compounds**

![Azo Aromatic Compounds](image)

**Stilbenes**

![Stilbenes](image)

**Scheme 1.6** Photochromic compounds which transform via cis-trans (Z/E) isomerization ($h\nu_1 < h\nu_2$).

**Polycyclic Aromatic Compounds**

![Polycyclic Aromatic Compounds](image)

**Scheme 1.7** Photochromic compounds which transform via intermolecular pericyclic reactions ($h\nu_1 < h\nu_2$).
Scheme 1.8 Photochromic compounds which transform via intramolecular pericyclic reactions (hv$_1$<hv$_2$).
In living systems, photochromism is responsible for vision. For example, rhodopsin is a protein present in rod cells in the retina. This protein comprises chromophore 11-cis-retinal as its protonated Schiff base which isomerizes to all-trans-retinal after the visible light stimulus (Scheme 1.10). This structural change generates a cascade of events that lead to a neural signal and visual transduction.98

The interest in the study, development, and application of photoswitches lies in the advantages that light provides as a stimulus. It does not necessarily produce waste products and offers an accurate and effective remote control since one can selectively irradiate a specific area.92,99 For that reason, it is possible to find in the literature a wide variety of applications of these systems in smart materials.
Scheme 1.10 The visual cycle of Retinal/Retinol.

A good example is the control of Diels-Alder and retro Diels-Alder reactions by the use of diarylethenes. This controlled mechanism has been studied and applied by the Hecht and Branda groups as a means to control the release of small molecules and the adhesive properties of a polymer, respectively.

Hecht’s approach involved the synthesis of compounds 1c and 2c which are intended to retain a molecule of maleimide or N-ethylmaleimide. Once these compounds are irradiated with visible light (wavelengths higher than 400 nm) the compounds 1o and 2o are generated in quantitative yield, which under physiological conditions (phosphate-
buffered saline solution, body temperature) release maleimide via a retro-Diels-Alder reaction. The authors claim the potential of this method as a photoswitchable prodrug for maleimide-based reactive inhibitors (Scheme 1.11).

Scheme 1.11 Hecht and Gostl small molecules release system controlled via photoswitching.

On the other hand, Branda and coworkers reported the synthesis of a polymer with self-healing properties that can be turned “on” and “off” by controlling Diels-Alder reaction direction (Scheme 1.12). The synthesis of this polymer, \textbf{P1o}, involves cycloaddition between diarylfuran moieties of \textbf{M1} with maleimide groups of \textbf{M2}. Besides the polymerization, cycloaddition forms photochromic diarylethene groups in their open form. Irradiation of the polymer (\textbf{P1o}) with UV light triggers ring closing of diarylethene groups, which “locks” the system (\textbf{P1c}) and prevents the retro Diels-Alder reaction. Conversely, irradiation of \textbf{P1c} with visible light returns the open configuration of the diarylethene groups in the polymer, \textbf{P1o}, unlocking the system to a possible retro Diels-Alder reaction.
Scheme 1.12 Branda and coworkers’ polymer with adhesive properties controlled by photoswitching.

The last two examples outline the versatile applications of photochromic molecules. Extrapolating this attribute to the entire library of photochromic systems provides a good sense of how extensive the number of applications that could be developed are. In this sense, regardless of the photoswitching system selected for an expected purpose, there are two important properties that need to be evaluated to indicate its effectiveness: the photo-stationary state and photodegradation.
1.11.1 Photo Stationary State.

A photochemical transformation, like any reversible chemical process, will reach an equilibrium; i.e. a state wherein the rate of formation and disappearance are equal for each of the participant species. This is known in photochemistry as the photo stationary state (PSS)

Since the absorption of light is required to promote the transformation of a photoswitch from $A$ to $B$, the amount of $B$ formed, $n_B$, by irradiating $A$ at a specific wavelength, $\lambda_{irr}$, is proportional to the absorptivity of $A$, $\varepsilon_A'$, and the quantum yield of the transformation from $A$ to $B$, $\phi_{A\rightarrow B}$ (Equation 3). Likewise, as this transformation is taking place, the formed $B$ can absorb $\lambda_{irr}$ wavelength and trigger the conversion from $B$ to $A$; wherein the amount of $A$ formed, $n_A$, is proportional to the absorptivity of $B$, $\varepsilon_B'$, and the quantum yield of the reverse reaction $\phi_{B\rightarrow A}$ (Equation 4).
Figure 1.11 Absorption spectra of $A$ and $B$.

$$n_B \propto \varepsilon_A' \cdot \phi_{A \rightarrow B} \quad \text{Equation 3}$$

$$n_A \propto \varepsilon_B' \cdot \phi_{B \rightarrow A} \quad \text{Equation 4}$$

At the photo stationary state, the ratio $n_B/n_A$ is constant since the process has reached an equilibrium. This state can also be described in terms of the absorptivities and quantum yields (Equation 5).

$$\frac{n_B}{n_A} = \frac{\varepsilon_A' \phi_{A \rightarrow B}}{\varepsilon_B' \phi_{B \rightarrow A}} \quad \text{Equation 5}$$

Figure 1.11 and Equations 3 to 5 stress the importance of choosing a wavelength wherein the reactant shows a much higher absorptivity than the product in order to ensure maximum conversion of one form to its isomer (in this case the transformation from $A$ to
$B$, or vice versa). In other words, a wavelength wherein the absorption bands have minimal overlap.

### 1.11.2 Fatigue or Photodegradation.

One of the main characteristics of a photochromic system is that the two isomeric forms are (meta) stable; however, repeated exposition of light stimulus over time can promote the appearance of side reactions that can deteriorate the expected responses of a system. The loss of performance of a material is known as fatigue; and more specifically for photoresponsive materials, as photodegradation.\(^9^3\)

Generally, photodegradation of a photoswitch is caused by the reaction of the photoswitch’s excited intermediate with the environment wherein the transformation takes place: e.g. a polymeric matrix, solvent, oxygen, etc. The major cause of photodegradation is often oxidation due to the presence of molecular oxygen.\(^1^0^4,1^0^5\)

![Scheme 1.13 Photodegradation of Spirooxazines and Spiropyrans.](image)

\(^{10^6}\)
Fatigue is quantitatively described by the number of cycles that a system can significantly respond under well-defined environmental conditions. A complete cycle corresponds to transformation of a photoswitch from state \( A \) to state \( B \) and reversion from state \( B \) to state \( A \).

Figure 1.12 Cyclization plots of a (A) fatigue resistant material and (B) a non-fatigue resistant material after 10 cycles.

Alternatively, the degree of degradation allows calculating the fraction of the non-degraded material, \( y \), after \( n \) cyclization assuming that \( x \) is a fraction of degraded material per cycle (Equation 6).

\[
y = (1 - x)^n
\]

\textit{Equation 6}

Figure 1.12 shows two cyclization plots of a fatigue resistant system, (A), and a non-fatigue resistant system, (B). The first plot was obtained assuming a photodegradation percent of 0.01 \% (\( x = 0.0001 \)). In this case, after 10 cycles it can be extrapolated that 99.9\% of the material has not photodegraded. Therefore, it responds very nearly as
efficiently as it did in the first cycle. In contrast; the second plot was obtained assuming a
5 % degradation per cycle \( (x = 0.05) \). Under this conditions, there is little less than 60%
of non-photodegraded active material after 10 cycles. The response is significantly
decreasing over only a few cycles.

1.12 Azoaromatic Compounds

From the entire palette of photochromic compounds, azoaromatic compounds, and
more specifically azobenzenes, have captured the interest of a large part of the research
community. Azoaromatic compounds comprise an azo group \(-\text{N}=\text{N}-\) connected to
aromatic rings which undergoes \( E/Z \) isomerization (\( \text{trans}/\text{cis} \) isomerization) after
absorption of a specific wavelength of light. Of both isomeric forms, the \( E \) isomer (\( \text{trans} \))
is the most stable, and can be transformed to the \( Z \) isomer (\( \text{cis} \)) by UV light irradiation.
Conversely, the \( Z \) isomer is the less stable and can be reversed to the \( E \) isomer by visible
light irradiation or heat (Scheme 1.14).

![Scheme 1.14 Photoisomerization of azobenzene.](image)

The two isomeric forms of azoaromatic compounds are differentiated by their
absorption spectra. The UV-Vis absorption spectrum of the \( E \) isomer comprises two
absorption bands: one at larger wavelengths with lower absorptivity that corresponds to a symmetry forbidden n→π* transition, producing the S1 excited state; and, one at smaller wavelengths with higher absorptivity that corresponds to a symmetry allowed π→π* transition, giving the S2 excited state. After isomerization, there is a significant change in absorption spectrum: the n→π* band increases its absorptivity; and, the π→π* band dramatically decreases its absorptivity and shifts to shorter wavelengths (blue shifting or hypsochromic effect). In this way, differences between absorption spectra allow interconversion from one isomer to the other using a specific wavelength. In the case of azobenzene, irradiation at 313 nm produces the Z (cis) isomer in ~80% yield, and irradiation at 436 nm produces the E (trans) isomer in ~90% yield.108

Figure 1.13 Changes in the absorption spectrum of trans-azobenzene (E isomer) upon irradiation with 316 nm light. Figure reproduced with permission (License number 3910310008235)
The above description of an azoaromatic UV-Vis absorption profile is a generality since substituents have a substantial effect on absorption spectra. In this sense, azoaromatic compounds have been divided into three families based on their n-π* and π-π* transition energies:\textsuperscript{109,110}

**Azobenzenes**

Azobenzenes substituted with alkyl, aryl, halide, carbonyl, amide, nitrile, ester, carboxylic acid, nitro, 3-amino and 3-alkyloxy groups. Absorption spectra of these compounds are generally similar to unsubstituted azobenzene; i.e. the π→π* band is very intense in the UV region and the n→π* band weaker in the visible region. They usually exhibit a yellow color visually in the *trans*-isomeric form.

**Aminoazobenzenes**

This family comprises azobenzenes with electron donor substituents; i.e. with one or more amino or hydroxyl substituents in the 2- or 4- positions. In their absorption spectra, the π→π* transition band is shifted to higher wavelengths and overlaps with the n→π* transition band. In comparison with the preceeding family, aminoazobenzenes exhibit higher quantum yields and higher thermal isomerization yields. Due to the presence of amino or hydroxyl groups, hydrogen bond formation and tautomerization can occur. They usually exhibit an orange color in the *trans*-isomeric form.
Pseudostilbenes

This group comprises two types of azobenzenes: (i) protonated azobenzenes, and (ii) azobenzenes substituted with an electron donor and an electron acceptor substituent in the 4- and 4’- positions creating a push-pull effect. In both types, absorption spectra exhibit n→π* and π→π* transitions degenerate in energy, and occur in the visible region; i.e. the π→π* band is shifted to red, changing the appearance order with respect to the n→π* band. These compounds are characterized by an intense red color.

Despite much research, the E/Z isomerization mechanism is still being considered by the research community. The debate about the correct mechanism is among two pathways: rotation and inversion (Scheme 1.15). The first pathway involves the cleavage of the π bond between nitrogen atoms allowing rotational isomerization wherein the C-N-N-C dihedral angle changes while the N-N-C angle remains ~120°. This mechanism proceeds through the S₂ excited state. In the second pathway, the C-N=N-C dihedral angle remains unchanged (~0°) as the N=N-C angle increases towards 180° which leads to a transition in one sp hybridized nitrogen atom. This mechanism takes place through the S₁ excited state.¹⁰⁹
Historically, azoaromatic compounds were recognized as dyes and employed in food, fabrics, toys and cosmetics\textsuperscript{111-113} due to their intense red-orange color. However, right after their photochromic properties were identified, these compounds found opportunities in another niche as molecular switches. Some of the features that make azobenzenes one of the most employed photoswitches are:\textsuperscript{114}

a. relatively small influence that the environment (e.g solvent) has on the absorption profile and isomerization;

b. minimal photodegradation;

c. high quantum yield of transformation from one isomer to other;

d. large achievable concentration differences between \textit{cis} isomer and \textit{trans} isomer in photo stationary state;

\begin{center}
\textbf{Scheme 1.15} Proposed mechanism for the E/Z (\textit{trans}/\textit{cis}) photoisomerization of azoaromatic compounds.
\end{center}
e. ultrafast photoisomerization within few picoseconds and slower thermo-reversion (milliseconds to days); and

f. large structural differences between isomers.

The first two characteristics make azobenzene a reliable and robust photochromic system that can be introduced at a broad range of conditions; whereas the following three are related to the effective response to stimuli. Finally, the last feature refers to the role of the geometry of both isomeric forms in macroscopic properties of the entire system.

1.12.1 Azoaromatic Compounds in Self-Assembly Systems.

The transformation from one isomeric form in azoaromatic compounds to the other induces a significant change in the entire structure to which the photoswitch is a part. The impact of such change is dependent on the intended application of the system. In this sense, some of the most widespread applications in literature involve photoisomerization of the azo group as a means to produce movement,\textsuperscript{115} to study protein folding-models;\textsuperscript{113} and, to control self-assembly\textsuperscript{116} and/or molecular recognition.

Specifically regarding the control over supramolecular arrays, there are three approaches to the use of azoaromatic compounds. The most modest strategy is related to the planarity of $E$ (trans) isomeric form and its $\pi-\pi$ interactions with proximal aromatic groups. One example is a multi-stage host-guest complex developed by Rotello and coworkers, (Scheme 1.16). The host, 1, comprises an azobenzene moiety located parallel
to a diamino-1,3,5-triazine ring. The triazine ring has a DAD hydrogen bond array which complements the ADA array of the naphthalenediimide guest, 2.\textsuperscript{117}

**Scheme 1.16** A Multi-stage host-guest complex examined by Rotello and coworkers.

At first sight, hydrogen bonding seems to be the driving complexation interaction; yet, comparison of the association constants of the complex when azobenzene in 1 has a *trans* geometry, $1_{\text{trans}}$, against a *cis* geometry, $1_{\text{cis}}$, highlights the contribution of $\pi-\pi$ interactions in the complex’s stability (Table 1.4). Likewise, a $\pi-\pi$ contribution is observed in the differences in association constants when guest 2 is in different oxidation states: 2, 2$^-$, and 2$^2$. The highest constant corresponds to $1_{\text{trans}}\cdot2$ complex wherein the electron-rich azobenzene moiety is parallel to the electron-poor oxidized naphthalenediimide. After reduction of guest 2 to 2$^-$ and 2$^2$, the association constant decreases due to dipolar repulsion between the electron-rich reduced guest and azobenzene fragment.

**Table 1.4** Association constant of the six modalities of the 1·2 complex in CDCl$_3$ at 296 K.

<table>
<thead>
<tr>
<th>HOST</th>
<th>$K_a$ (2) M$^{-1}$</th>
<th>$K_a$ (2$^-$) M$^{-1}$</th>
<th>$K_a$ (2$^2$) M$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1_{\text{trans}}$</td>
<td>9750</td>
<td>2054</td>
<td>591</td>
</tr>
<tr>
<td>$1_{\text{cis}}$</td>
<td>575</td>
<td>228</td>
<td>136</td>
</tr>
</tbody>
</table>
A different use of an azoaromatic group to control supramolecular complexation refers to the ability of one isomer to block potential binding sites. Location of an azo group next to binding sites allows control over the surrounding space and the possibility of complementary binding sites’ access to that space. Jeong and coworkers reported in 2003 a pseudorotaxane controlled by photoisomerization of an azo group (Scheme 1.17). The axle, \textit{trans-1}, is a complementary terephthalamide group which is located parallel to an azobenzene group. Proximity between the axle and azo group, plus \(\pi-\pi\) interactions between aromatic groups, in \textit{trans-1} renders threading through the cavity of 6 difficult.\(^{118}\)

![Scheme 1.17 Photo-controlled assembly of pseudorotaxane.](image)

After irradiating \textit{trans-1} with UV light, the \textit{cis-1} isomer is produced with a 77\% yield. The structural disposition of the free aromatic ring in the azo group creates the space required for macrocycle 6 to encircle the terephthalamide axle. Control over the assembly of the pseudorotaxane is supported by the differences between the association constants of \textit{trans-1}\cdot6 and \textit{cis-1}\cdot6; which were estimated as \(\leq 1\) and \(5200 \pm 100\) M\(^{-1}\), respectively.

Finally, the last strategy to apply azoaromatic groups as a means to manipulate the aggregation pattern of supramolecular systems is by modifying the aromatic rings to
incorporate exogenous non-covalent binding sites. This way, the geometric disposition of the binding sites is affected by E/Z (trans-cis) isomerization; and, as a consequence, the supramolecular aggregation is affected. A good example is the use of azobenzene in a peptide system by Ghadiri’s group\textsuperscript{119} (Figure 1.14). A change from the E (trans) isomer to the Z (cis) isomer results in a rearrangement of hydrogen bonding sites from an intermolecular assembly to an intramolecular one (Scheme 1.18).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ghadiri_peptide_system.png}
\caption{Ghadiri’s peptide photoswitchable system.}
\end{figure}

\begin{scheme}[h]
\centering
\includegraphics[width=\textwidth]{aggregation_pattern_changes.png}
\caption{Aggregation pattern changes after photoisomerization.}
\end{scheme}
Beside supramolecular arrays, control over the availability of specific non-covalent binding sites by azoaromatic compounds has been studied in other fields such as catalysis. Recently, Pericas and coworkers reported the synthesis and effectiveness of a photoswitchable catalyst. The catalyst comprises a thiourea group which is an active catalytic site when the system is in its $E$ (trans) form. Once the system is switched to its $Z$ (cis) form, a hydrogen bond acceptor group is located close to the thiourea. An intramolecular hydrogen bond interaction blocks the active site shutting down the catalyst effect in the reaction (Scheme 1.19).

Scheme 1.19 Photoswitchable catalyst by Pericas and coworkers.

1.13 Scope of the Thesis

The development of self-complementary hydrogen bond arrays whose stability can be reversibly modulated by an external stimulus is an opportunity regarding the expansion of the smart materials family. The aim of this Ph.D. project was the development of light responsive self-complementary hydrogen bond arrays. The novelty of these arrays lies in
the use of a photochromic group (i.e. the azo group, –N=N-) as a hydrogen bond acceptor in the supramolecular complex. An account of the impact that the external stimulus has in our systems was a key element in order to define the properties that characterize and differentiate these arrays with the present state of the art. Therefore, the main challenge during this project was the description once the structural change of these systems was triggered via light irradiation; i.e. trans- to cis- photoisomerization. In other words, to measure the stability of the complex(es) present in solution after the photochemical change. In the following chapters, the design, synthesis and characterization of photoswitchable self-complementary DDAAA hydrogen bond arrays are reported and discussed. This report includes the approach to the mathematical model employed to describe these systems’ change after photoisomerization.

1.14 References


Chapter 2

2 Synthesis and Characterization of Photoswitchable Self-Complementary DDAAA Hydrogen Bond Arrays

2.1 Introduction

Supramolecular chemistry has evolved from explaining properties associated with molecular aggregation to the design and creation of novel and potentially useful systems. In this sense, supramolecular polymers are examples of applications that supramolecular chemistry can contribute to.\(^1\) Traditional polymers are formed by monomers joined through covalent bonds. Supramolecular monomeric units are independent molecules linked via non-covalent interactions. The reversibility of the interactions makes it possible to obtain materials with improved processing, self-healing behaviour and, if desired, crystallinity.\(^2\) Meanwhile, polymer-like properties such as viscosity, elasticity, fiber formation and other hierarchical arrangements can be obtained through a careful design of the interacting sites and the use of specific spacers or different monomeric blocks (e.g. Figure 2.1, Scheme 2.1).\(^2,3\)
**Figure 2.1** Theoretical plot of the relation between association constant and degree of polymerization as a function of concentration of a self-associating (A-A) monomer.

**Scheme 2.1** Supramolecular thermoplastic elastomer obtained by functionalizing poly(ethylene-butylene) with self-associating ureidopyrimidinone ending groups.\textsuperscript{4}
Efforts toward the development of these types of polymers have responded to specific needs the materials are intended to cover. Applications vary from rheological modifiers, super-hydrophobic coats, scaffolds for tissue engineering, self-healing materials, drug delivery and bioimaging among many. In these cases, control over the aggregation relies on environmental changes such as temperature, solvent system, pH and enzymatic action. More sophisticated means of control involve molecular switches. Specifically, aromatic azo compounds have been employed, where changes in the geometric distribution of exogenous binding sites before and after photoisomerization have been the most exploited (Chapter 1 Section 1.12.1). However, this property is not the only possible contribution from the azo group in this context.

In principle, the two sp² nitrogen atoms in the azo group (-N=N-) can perform as hydrogen bond acceptor sites. This feature has been observed in intramolecular hydrogen bonds between one of the nitrogen atoms of an aromatic azo group and hydroxyl, carboxylic acid and/or amino groups located ortho- to the azo function (Figure 2.2). Nevertheless, though this property is well known and documented in the literature, it has not been intentionally employed as part of an intermolecular hydrogen bond array to date.
Figure 2.2 Examples of aromatic azo compounds that display intramolecular hydrogen bonds.

Recently, Wisner and coworkers reported the crystal structure of a hydrogen bond complex between 2,6-diaminopyridinium tetraphenylborate and 1,2-bis(5,7-dimethyl-1,8-naphthyridin-2-yl)diazene.\textsuperscript{18} The 1,8-naphthyridine moiety is a known hydrogen bond acceptor array.\textsuperscript{19,20} The novelty of this complex lies in the participation of the azo group as an intermolecular hydrogen bond acceptor. Likewise, the \textit{trans} disposition of the azo-group allows the two 1,8-naphthyridine rings to enclose the diaminopyridinium cation with the maximum number of primary hydrogen bond interactions to all but one hydrogen bond donor (Figure 2.3).

Figure 2.3 (A) Schematic representation of 2,6-diaminopyridinium tetraphenylborate-1,2-bis(5,7-dimethyl-1,8-naphthyridin-2-yl)diazene (1/1) complex. (B) Solid state structure obtained by single crystal X-ray diffraction.
Elucidation of the structure of the complex in the solid state led to speculation whether azoheteroarene-containing species could find further use as host molecules. Furthermore, since some azoheteroaromatic compounds show photoisomerization properties,²¹,²²,²³ the participation/inclusion of these moieties could potentially be a method to control efficacy of a complexation event.

2.2 Design of Photoswitchable Self-Complementary Hydrogen Bond Arrays

Once azoheteroaromatic compounds were recognized as potential hydrogen bond acceptor moieties, it was considered how to exploit this feature. As depicted in Figure 2.3, one strategy is the synthesis of two complementary molecules wherein acceptor binding sites are provided by the azoheteroaromatic compound and donor binding sites are provided by a complementary array. An alternative approach involves the synthesis of an array comprising both donor and acceptor sites and able to form a self-complementary complex; a homodimer. This is the aim of this project.

The first element to consider in designing a self-complementary array is the backbone that will hold the donor and acceptor sites. In this case, it was the selection of the azoheteroaromatic component. Based on the complex formed in Figure 2.3, the azo derivative selected has to have a nitrogen atom positioned ortho to the azo group on the heteroaromatic ring in order to have at least two acceptor sites at one end of the array. In this sense, 2,2’-azopyridine was a good reference point to start with since its photochemical
properties are similar to those of azobenzene derivative and its synthesis is straightforward.\textsuperscript{21}

The second element to deliberate was the hydrogen bond donor group selected and its position in the azoheteroaromatic backbone. In this regard, amino and amido groups have been employed as hydrogen bond donors in most of the hydrogen bond arrays reported in the literature. They are often the best option since the polarization of the N-H bond locates a low electrostatic potential on the hydrogen atom, which is optimal for a good donor site.\textsuperscript{24} Likewise, the lone pair of electrons on the nitrogen atom can engage in conjugation with the heteroaromatic ring; this adds a resonance-assisted hydrogen bond effect which could further favour dimer stability.\textsuperscript{25,26} Regarding the position of this donor group, a structural analysis indicated that the optimal position was meta to the azo group (Figure 2.4). Locating an amino group in the ortho position favors an intramolecular hydrogen bond between amino and azo groups, leaving only one hydrogen atom available for an intermolecular hydrogen bond and inhibiting photoisomerization. In the case of the para isomer, the amino group would be able only to interact with the nitrogen atom from the pyridine ring, without including the azo group as an acceptor site. The azo and pyridyl nitrogen acceptors could participate in C-H…N interactions with the proton ortho to the azo and amino groups from another molecule. However, the C-H contribution as a donor site would not be polarized enough in order to obtain a stable dimer.\textsuperscript{27} Lastly, the meta isomer allows the alignment of the amino group hydrogen atoms toward the opposing azo group and pyridine ring acceptors, which could optimally provide six hydrogen bond interactions in a potential DDAAA array.
Based on this model, our first attempts were directed to synthesizing (E)-6-(pyridin-2-yldiazenyl)pyridin-2-amine, the highlighted meta isomer in Figure 2.4. However, all known and reported syntheses of azoaromatic compounds were attempted without the desired results. Hence, it was necessary to seek alternatives that provide the structural properties outlined but were more feasible to obtain.

With this in mind, our attention turned to cyanuric chloride (2,4,6-chloro-1,3,5-triazine) which was employed by Whitesides and coworkers as starting material in the synthesis of a variety of melamine derivatives that participate in hydrogen bond arrays. Cyanuric chloride has an advantage over many other heteroaromatic systems due to the possibility to selectively and easily replace each chloride substituent with a nucleophile by controlling the reaction temperature and sequence of nucleophiles applied (Figure 2.5(A)). According to the literature, substitution yields are often over 95% and a trisubstitution is achievable in some cases by one pot synthesis. For the purpose of the desired system, cyanuric chloride offered the opportunity to selectively add: (i) a
donor group, (ii) an RX group, and (iii) an acceptor sites precursor, following a systematic method in order to develop a family of photoswitchable hydrogen bond arrays (Figure 2.5(B)). Likewise, it fulfills the location requirements of donor and acceptor sites in the azoheteroaromatic backbone. Lastly, the addition of an RX group to the photoswitchable hydrogen bond array would allow us to create a library of products wherein the electron withdrawing/donating character of RX could contribute variously to the strength of dimerization.

**Figure 2.5** (A) Selective systematic substitution of cyanuric chloride at different temperatures. (B) Selective systematic substitution strategy employed.

In this way, the backbone of our photoswitchable self-complementary hydrogen bond array corresponded to the non-symmetrical azoheteroaromatic compound illustrated in Scheme 2.2. The aim of the designed system was to dimerize as the *trans* isomer (or *E* isomer). Control over dimerization would come after irradiating with UV light promoting the formation of *cis* isomer (or *Z* isomer) whose ability to dimerize should be greatly reduced in comparison with the *trans* isomer.
Scheme 2.2 A proposed photoswitchable self-complementary DDAAA hydrogen bond array and its idealized function.

2.3 Results and Discussion

2.3.1 Synthesis of Photoswitchable Self-Complementary Hydrogen Bond Arrays

Synthesis of our systems started with cyanuric chloride as shown in Scheme 2.3, and proceeded by typical literature methods.34,35

Scheme 2.3 Synthesis of photoswitchable self-complementary DDAAA hydrogen bond arrays 4a-p.
The first substitution corresponded to the addition of the donor group; i.e. the amino group. Synthesis of intermediate 1 was performed according to a procedure reported by Baliani and coworkers\textsuperscript{34} to give a 78 % yield in our hands.

Regarding the second substitution, it was our plan to add the acceptor sites’ precursor 2-hydrazinylpyridine, and later obtain the azo functionality by oxidation. Finally, we would substitute the final chloride leaving group of a common intermediate with an “RX” group in order to develop a library of arrays. However, after many attempts using this strategy, we concluded that the addition of the RX group was not workable by this synthetic sequence. Therefore, we proceeded to switch the order of addition and add the RX group at the second stage. Selection of the base employed in the second addition was dependent on the pKa of the RX group (Table 2.1). The reaction was carried out initially at low temperature (0 °C). Once the RXH and base were added, the reaction mixture was allowed to slowly reach room temperature. Intermediates 2a-p were isolated from the reaction mixture after removing the solvent under reduced pressure and washing the crude material with distilled water to remove salts since, in most cases, the intermediates 2a-p were not soluble in water. With few exceptions, these intermediates did not required further purification in order to proceed with the following steps.

The last substitution performed on the triazine ring was the addition of 2-hydrazinylpyridine in the presence of one equivalent of potassium carbonate in THF. Apart from two exceptions (the chloro- and iodo- derivatives), the reaction mixtures were refluxed for at least 6 hours in order to obtain intermediates 3a-p. The addition of 2-hydrazinylpyridine to the chloro and iodo intermediates (2g and 2h, respectively) could be carried out at room temperature. As with the intermediates 2a-p, intermediates 3a-p were
isolated by removing solvent under reduced pressure and washing the crude material with deionized water. Intermediates 3a-p were employed in the next step without further purification.

Hydrazines 3a-p were oxidized in the presence of (diacetoxyiodo)benzene to obtain the desired final products 4a-p. The (diacetoxyiodo)benzene oxidation can be performed under mild conditions in good yields using a variety of solvent systems, which is an advantage over many other oxidants.\textsuperscript{35,36} In total, there were 16 derivatives synthesized of general structure 4 (Table 2.1).

The characterization of each of the intermediates and final products is located in the Synthetic Methods section at the end of this chapter (Section 2.5.2). The UV-Vis absorption spectra of 4a-p are described in Chapter 3 wherein the photochemical properties and effects on aggregation are discussed.
Table 2.1 Reactants, yields of intermediates 2a-p and overall yields of photoswitchable self-complementary hydrogen bond arrays 4a-p.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>RXH</th>
<th>Basea</th>
<th>Intermediate 2 Yield (%)</th>
<th>Product 4 Overall Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Piperidine</td>
<td>(CH₃CH₂)₃N</td>
<td>57</td>
<td>13</td>
</tr>
<tr>
<td>4b</td>
<td>methanolc</td>
<td>NaOCH₃</td>
<td>81</td>
<td>40</td>
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<td>NaOH</td>
<td>99</td>
<td>20</td>
</tr>
<tr>
<td>4j</td>
<td>4'-nitrophenol</td>
<td>NaOH</td>
<td>97</td>
<td>37</td>
</tr>
<tr>
<td>4k</td>
<td>4'-tert-butylphenol</td>
<td>K₂CO₃</td>
<td>59</td>
<td>6</td>
</tr>
<tr>
<td>4l</td>
<td>3-(trifluoromethyl)phenol</td>
<td>K₂CO₃</td>
<td>87</td>
<td>15</td>
</tr>
<tr>
<td>4m</td>
<td>3,5-bis(trifluoromethyl)phenol</td>
<td>K₂CO₃</td>
<td>96</td>
<td>31</td>
</tr>
<tr>
<td>4n</td>
<td>Perfluorophenol</td>
<td>K₂CO₃</td>
<td>92</td>
<td>23</td>
</tr>
<tr>
<td>4o</td>
<td>benzyl alcohol</td>
<td>NaH</td>
<td>99</td>
<td>14</td>
</tr>
<tr>
<td>4p</td>
<td>4-tritylphenol</td>
<td>K₂CO₃</td>
<td>71</td>
<td>8</td>
</tr>
</tbody>
</table>

a One equivalent added at 0 ºC. b Percent yield over 3 synthetic steps starting from intermediate 1. c Excess (Solvent system). d Chloro is already in place in intermediate 1. e Base added until acid was neutralized.
2.3.2  

$^1$H NMR Dilution Experiments: Stability of trans-trans dimers.

Once the syntheses of our proposed hydrogen bond arrays were achieved, we proceeded to the study of their dimerization in solution.

Dimerization is a dynamic process represented by Scheme 2.4, wherein the dimerization constant ($K_{t\cdot t}$) is calculated from trans monomer ($[t]$) and trans dimer ($[t\cdot t]$) concentrations at equilibrium and described by Equation 1.

\[
K_{t\cdot t} = \frac{[t\cdot t]}{[t]^2}
\]

\textit{Scheme 2.4} Dimerization equilibrium of 4a-p.

Experimentally, dimerization constants are calculated based on the change of an observed physical property.\textsuperscript{37} In the present case, the physical property observed was the chemical shift of the proton signals from the amino group. As a dimer is formed, hydrogen bond interactions decrease the electron density of these protons, which leads to a deshielding effect detected in the $^1$H NMR spectrum.\textsuperscript{38}
The observed chemical shift ($\delta_{\text{Obs}}$), is a weighted average of the chemical shift of monomer ($\delta_m$) and dimer ($\delta_d$) in solution (Equation 2) when complexation is fast on the NMR timescale.

$$\delta_{\text{Obs}} = \delta_m \cdot \frac{[t]}{[t_0]} + \delta_d \cdot \frac{2 \cdot [t \cdot t]}{[t_0]}$$  \hspace{1cm} \text{Equation 2}

$$[t_0] = [t] + 2 \cdot [t \cdot t]$$ \hspace{1cm} \text{Equation 3}

In this way, it is possible to monitor changes in the observed chemical shift while increasing the total monomer concentration, $[t]_0$. The dependency of the observed chemical shift on monomer total concentration allows the use of an iterative fitting procedure to calculate monomer shift, dimer shift and dimerization constant.\cite{39} The method consists in fitting the relationship between experimental data $\delta_{\text{Obs}}$ versus $[t]_0$ (also known as dimerization isotherm, Figures 2.9, 2.10, 2.14 and 2.15) to a dimerization model (Equation 4).

$$\delta_{\text{Obs}} = \delta_m + (\delta_d - \delta_m) \cdot \frac{[1 + 8 \cdot K_{t \cdot t} \cdot [t]_0]^{1/2} - 1}{[1 + 8 \cdot K_{t \cdot t} \cdot [t]_0]^{1/2} + 1}$$ \hspace{1cm} \text{Equation 4}

In addition to precisely measured experimental data, there are other elements to consider before the experiment: \cite{40}

(i) Reliability of the method. $^1$H NMR determinations of association and dimerization constants are typically reliable in the range $1 - 10^5$ M$^{-1}$. Small association and dimerization constants (lower than 10 M$^{-1}$) often involve large $\Delta\delta_{\text{max}}$ extrapolation errors. On the other hand, supramolecular complexes with
large association constants (>10^5 M^-1) show little curvature at detectable concentrations which makes it difficult to fit to an isotherm.

(ii) The difference between monomer and dimer chemical shifts needs to be as large as possible to be considered significantly different; i.e. total Δδ ≥ 0.5 ppm (the accuracy of the method depends on the spectrometer resolution; e.g. in a 400 MHz ¹H NMR spectrum a sharp singlet can be measured with an accuracy of ≈ ±0.005 ppm).

(iii) Concentration increments. The range of data obtained in a dilution experiment should provide good coverage of the isotherm. In this sense, it has been demonstrated that it is advisable to collect a minimum of 10 data points within a range of 20% to 80% of the complex concentration in a dilution experiment.⁴¹

In the present case, dilution experiments with 4a-p were performed in CDCl₃, with the exception of 4b, 4e, 4g, 4h and 4j due to insolubility (Table 2.2). Additionally, dilution experiments with 4c, 4f, 4k and 4n were also performed in toluene-d₈ since they were soluble in this solvent (Table 2.3). The general experiment consisted of adding aliquots of a highly concentrated solution of 4 to an NMR tube filled with 500 μL of pure solvent. Thus, as the concentration of 4 increased, the chemical shifts of the amino protons increased (i.e. moved downfield, Figure 2.6 and 2.7).
Table 2.2 Dimerization constants, free energies of dimerization, calculated chemical shifts of monomer (δ_m) and dimer (δ_d) species studied, and the total change in chemical shift (Δδ_max) in CDCl₃ at 298 K.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>RX</th>
<th>( K_{t,t} ) in CDCl₃ (M⁻¹) (^a)</th>
<th>( \Delta G_{t,t} ) (kJ mol⁻¹) (^a)</th>
<th>δ_m (ppm) (^a)</th>
<th>δ_d (ppm) (^a)</th>
<th>Δδ_max (ppm) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>-NC₅H₁₀</td>
<td>8.4 ± 2</td>
<td>-5.27 ± 0.66</td>
<td>5.14 (2H)</td>
<td>6.92 (2H)</td>
<td>1.78</td>
</tr>
<tr>
<td>4c</td>
<td>-O(n-C₅H₆)</td>
<td>32 ± 7</td>
<td>-8.61 ± 0.57</td>
<td>5.49 (2H)</td>
<td>6.80</td>
<td>1.31</td>
</tr>
<tr>
<td>4d</td>
<td>-O(n-C₅H₁₇)</td>
<td>36 ± 5</td>
<td>-8.87 ± 0.36</td>
<td>5.50</td>
<td>6.78</td>
<td>1.28</td>
</tr>
<tr>
<td>4f</td>
<td>-S(n-C₅H₁₃)</td>
<td>32 ± 3</td>
<td>-8.62 ± 0.22</td>
<td>5.38</td>
<td>6.80</td>
<td>1.42</td>
</tr>
<tr>
<td>4i</td>
<td>-OC₅H₅</td>
<td>59 ± 11</td>
<td>-10.10 ± 0.48</td>
<td>5.55</td>
<td>6.77</td>
<td>1.22</td>
</tr>
<tr>
<td>4k</td>
<td>-OC₅H₄-4'-(C(CH₃)₃)</td>
<td>50 ± 7</td>
<td>-9.68 ± 0.36</td>
<td>5.53</td>
<td>6.70</td>
<td>1.17</td>
</tr>
<tr>
<td>4l</td>
<td>-OC₅H₄-3'-(CF₃)</td>
<td>62 ± 1</td>
<td>-10.24 ± 0.05</td>
<td>5.57</td>
<td>6.80</td>
<td>1.23</td>
</tr>
<tr>
<td>4m</td>
<td>-OC₅H₃-3',5'-bis(CF₃)</td>
<td>96 ± 6</td>
<td>-11.31 ± 0.16</td>
<td>5.63</td>
<td>6.57</td>
<td>0.95</td>
</tr>
<tr>
<td>4n</td>
<td>-OC₅F</td>
<td>180 ± 14</td>
<td>-12.92 ± 0.19</td>
<td>5.67</td>
<td>6.48</td>
<td>0.80</td>
</tr>
<tr>
<td>4o</td>
<td>-OCH₂C₅H₅</td>
<td>49 ± 8</td>
<td>-9.63 ± 0.39</td>
<td>5.54</td>
<td>7.08</td>
<td>1.54</td>
</tr>
<tr>
<td>4p</td>
<td>-OC₅H₄-4'-(C(C₅H₅)₃)</td>
<td>64 ± 25</td>
<td>-10.28 ± 0.94</td>
<td>5.56</td>
<td>6.68</td>
<td>1.12</td>
</tr>
<tr>
<td>5c</td>
<td>-O(n-C₅H₄)</td>
<td>5.5 ± 0.3</td>
<td>-4.43 ± 0.14</td>
<td>5.53</td>
<td>6.87</td>
<td>1.34</td>
</tr>
<tr>
<td>5f</td>
<td>-S(n-C₅H₁₃)</td>
<td>4.8 ± 0.9</td>
<td>-3.90 ± 0.45</td>
<td>5.50</td>
<td>5.70</td>
<td>0.20</td>
</tr>
<tr>
<td>5k</td>
<td>-OC₅H₄-4'-(C(CH₃)₃)</td>
<td>11 ± 3</td>
<td>-5.85 ± 0.73</td>
<td>5.53</td>
<td>6.80</td>
<td>1.27</td>
</tr>
</tbody>
</table>

\(^a\) Average values obtained using Equation 5 and three separate dilution experiments. Errors calculated from twice the standard deviation to give a 95% confidence interval.

\(^b\) Resonance used in fitting process assigned to the H₆ proton in Figure 2.8.
Figure 2.6 $^1$H NMR spectra displaying the concentration-dependent behavior of 4o in CDCl$_3$ at 298 K. (i) $5.59 \times 10^{-4}$ M, and (ii) $1.61 \times 10^{-2}$ M.

Figure 2.7 $^1$H NMR spectra displaying the concentration-dependent behavior of 4f in Toluene-$d_8$ at 298 K. (i) $2.45 \times 10^{-3}$ M (H$_a$ signal covered by the toluene reference signal), (ii) $8.56 \times 10^{-3}$ M, and (iii) $1.61 \times 10^{-2}$ M.
Once experimental data for a dilution experiment was collected, an iterative fitting process of the dimerization isotherm was performed on the chemical shift observations. Generally, the proton signal chosen to fit the isotherm was that showing the largest change during the dilution experiment and the one that was not occluded by solvent signals during the dilution. This signal was tentatively assigned as proton H_a since it was expected to interact with two acceptor sites forming a donating bifurcated hydrogen bond (Figure 2.8); and therefore, the deshielding effect on that proton would be anticipated to be larger than H_b as the solution becomes more and more concentrated. Compound 4a was the only exception since it showed only one signal which integrated for both amino protons over the entire dilution. It is important to note that 1H NOESY experiments were carried out in order to corroborate the proximity of the H_b proton with the proton ortho- to the pyridyl nitrogen. However, no correlation peak between these protons was observed in these experiments for derivatives 4a, 4c, 4f, 4k and 4n.

![Figure 2.8 Amino’s proton assignment based on chemical shift in compounds 4a-p.](image)

As can be observed in Table 2.2, dimerization constants in CDCl_3 ranged from 8.4 to 180 M^{-1}; wherein the weakest dimerization isotherm calculated corresponded to the piperidin-1-yl derivative 4a (Figure 2.9) and the strongest corresponded to the
perfluorophenoxy derivative 4n (Figure 2.10). From the range of results obtained, we generally observed that as stronger electron withdrawing moieties were added as substituent RX, dimerization constants increased. For example, phenoxy derivative 4i showed a dimerization constant of 59 M\(^{-1}\); meanwhile, the inclusion of two meta-trifluoromethyl groups to the phenyl ring increased the \(K_{\text{et}}\) value to 96 M\(^{-1}\) for derivative 4m. Thus, the perfluorophenoxy derivative 4n had the highest dimerization constant of those studied (\(K_{\text{et}} = 180\) M\(^{-1}\)).

**Figure 2.9** Dimerization isotherm of 4a with \(K_{\text{et}}\) value and free energy calculated from fitting of the data to a 1:1 dimerization model. Blue, green and red dots correspond to first, second and third separate dilution experiments, respectively. Solid line corresponds to the theoretical dilution curve obtained from the average \(K_{\text{et}}\) of three separate dilution experiments.
Figure 2.10 Dimerization isotherm of 4n with $K_{t\times t}$ value and free energy calculated from fitting of the data to a 1:1 dimerization model. Blue, green and red dots correspond to first, second and third separate dilution experiments, respectively. Solid line corresponds to the theoretical dilution curve obtained from the average $K_{t\times t}$ of three separate dilution experiments.

Given the range of data gathered for the dimerizations in solution, we were interested in whether the characters of the substituents in derivatives 4a-p could be correlated with our results. To this end, the maximum change in the chemical shift of all the derivatives 4a-p in CDCl$_3$ was plotted against $\Delta G_{t\times t}$ (Figure 2.11). From this plot, it was observed that there is a roughly linear correlation between these two values ($r = 0.81396$); i.e. as the difference between monomer and dimer chemical shift increases, the $\Delta G_{t\times t}$ also increases. Interestingly, the derivative with the lowest dimerization constant (the piperidine derivative 4a) was an obvious outlier from this trend.
Figure 2.11 Plot of $\Delta G_{t:t}$ vs $\Delta \delta_{\text{max}}$ for derivatives 4a-p in CDCl$_3$ at 298 K. Dotted line corresponds to the linear least squares correlation for derivatives 4a-p excluding 4a ($r = 0.81396$).

Another correlation explored corresponded to the $\sigma_m$ values of the RX moieties in derivatives 4c and 4i and the approximation to the $\sigma_m$ values of the RX moieties in derivatives 4a, 4d, 4f, 4k and 4n with the free energy of dimerization $\Delta G_{t:t}$ ($r = -0.9725$, Figure 2.12). In this sense, it was noted that as the $\sigma_m$ value increases, the $\Delta G_{t:t}$ value decreases. Since $\sigma_m$ is the major contributor to the inductive parameter ($I$), a very similar relationship is observed between $I$ and $\Delta G_{t:t}$ ($r = -0.9699$, Figure 2.13). This observation is in agreement with the influence of the inductive withdrawing effect ($-I$) of the RX substituents evaluated. The inductive withdrawing effect polarizes the amino N-H bonds increasing their donor strength, which contributes to the stability of the dimer structure.
Figure 2.12 Plot of $\Delta G_{\text{t-t}}$ vs $\sigma_m$ of derivatives 4a, 4c, 4d, 4f, 4i, 4k and 4n in CDCl$_3$ at 298 K. Dotted line corresponds to the least squares correlation line ($r = -0.9861$).

Figure 2.13 Plot of $\Delta G_{\text{t-t}}$ vs $I$ of derivatives 4a, 4c, 4d, 4f, 4i, 4k and 4n in CDCl$_3$ at 298 K. Dotted line corresponds to the least squares correlation line ($r = -0.9848$).
Considering the design of the system and based on the number of hydrogen bond interactions expected in the array, it was disappointing to observe dimerization constants lower than $10^2 \text{ M}^{-1}$ in CDCl$_3$. In this sense, it raised the issue of whether the pyridine ring was participating as an acceptor in the complexation. To probe this interaction, phenyl analogues 5c, 5f and 5k were synthesized in order to eliminate the interaction of the pyridine acceptor in the dimerization equilibrium (Scheme 2.5).

![Scheme 2.5 Synthesis of (E)- 6-(phenyldiazenyl)-1,3,5-triazin-2-amine, derivatives 5c, 5f and 5k.](image)

Compounds 5c, 5f and 5k exhibited dimerization constants of 6, 5 and 11 M$^{-1}$ respectively, which are comparable with the weakest constant obtained for array 4a. Likewise, comparing 5c, 5f and 5k with derivatives 4c, 4f and 4k, it is observed that derivatives 4 have dimerization constants at least fourfold larger than 5 (Table 2.2). In this sense, it is important to outline that the main difference between derivatives 4 and 5 is the absence of an extra hydrogen bond acceptor in the latter. This can be translated as an energetic contribution of approximately 4 kJ mol$^{-1}$ in CDCl$_3$ ($\Delta\Delta G_{\text{Butoxy}} = -4.18 \text{ kJ mol}^{-1}$, $\Delta\Delta G_{\text{Hexylthiol}} = -4.72 \text{ kJ mol}^{-1}$, and $\Delta\Delta G_{4'-\text{tert-butylphenoxy}} = -3.83 \text{ kJ mol}^{-1}$) from both pyridine moieties (or 2 kJ mol$^{-1}$ per pyridine moiety) to the dimerization event in this case.
Table 2.3 Dimerization constants, free energies of dimerization, calculated chemical shifts of monomer ($\delta_m$) and dimer ($\delta_d$) species studied, and the total change in chemical shift ($\Delta\delta_{max}$) in Toluene-$d_8$ at 298 K.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>RX</th>
<th>$K_{t-t}$ in Toluene-$d_8$ (M$^{-1}$) $^a$</th>
<th>$\Delta G_{t-t}$ (kJ mol$^{-1}$)</th>
<th>$\delta_m$ (ppm) $^a$</th>
<th>$\delta_d$ (ppm) $^a$</th>
<th>$\Delta\delta_{max}$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4c</td>
<td>O($n$-C$_4$H$_9$)</td>
<td>900 ± 70</td>
<td>-16.80 ± 0.20</td>
<td>4.33</td>
<td>7.13</td>
<td>2.80$^b$</td>
</tr>
<tr>
<td>4f</td>
<td>S($n$-C$_6$H$_13$)</td>
<td>590 ± 90</td>
<td>-15.80 ± 0.38</td>
<td>4.11</td>
<td>6.89</td>
<td>2.78$^b$</td>
</tr>
<tr>
<td>4k</td>
<td>-OC$_6$H$_4$-4'-C(CH$_3$)$_3$</td>
<td>1200 ± 600</td>
<td>-17.70 ± 1.15</td>
<td>4.12</td>
<td>6.97</td>
<td>2.85$^b$</td>
</tr>
<tr>
<td>4n</td>
<td>OC$_6$F$_5$</td>
<td>3700 ± 280</td>
<td>-20.35 ± 0.19</td>
<td>4.02</td>
<td>6.25</td>
<td>2.23$^b$</td>
</tr>
<tr>
<td>5c</td>
<td>O($n$-C$_4$H$_9$)</td>
<td>18 ± 1</td>
<td>-7.16 ± 0.04</td>
<td>4.29</td>
<td>7.15</td>
<td>2.86$^b$</td>
</tr>
<tr>
<td>5f</td>
<td>S($n$-C$_6$H$_13$)</td>
<td>26 ± 2</td>
<td>-8.13 ± 0.19</td>
<td>4.18</td>
<td>6.21</td>
<td>2.03</td>
</tr>
<tr>
<td>5k</td>
<td>-OC$_6$H$_4$-4'-C(CH$_3$)$_3$</td>
<td>46 ± 7</td>
<td>-9.46 ± 0.42</td>
<td>4.11</td>
<td>6.39</td>
<td>2.28</td>
</tr>
</tbody>
</table>

$^a$ Average values obtained using Equation 5 and three separate dilution experiments. Errors calculated from two times the standard deviation to give a 95% of confidence interval $^b$ Resonance used in fitting process assigned to H$_b$ in Figure 2.8.

Dimerization constants obtained for 4c, 4f, 4k and 4n in toluene-$d_8$ were significantly higher than the values obtained in CDCl$_3$ (Table 2.3). The range of dimerization constant values was from 600 to 3700 M$^{-1}$. These results can be rationalized based on the hydrogen bond donor character of the solvent system wherein the intermolecular interactions take place. Comparing chloroform and toluene as solvents for complexation, chloroform is known as a better hydrogen bond donor ($\alpha_{CHCl_3}$ = 2.2, $\alpha_{Benzene}$ = 1.0)$^{44}$ Since compounds 4a-p have more acceptors than donors, chloroform likely forms stronger solute-solvent complexes than toluene. Therefore, the energetic cost to break these strong solute-solvent interactions would be reflected by lower dimer stability in CDCl$_3$. This is in agreement with the dimerization values obtained in CDCl$_3$ and toluene-$d_8$. 


An effect of the RX group character was also observed in differences between $K_{t-t}$ values of derivatives 4. For example, perfluorophenoxy derivative 4n displayed the highest dimerization constants in CDCl$_3$ and toluene–$d_8$ due to the electron withdrawing effect of the five fluorine substituents. On the other hand, the derivatives 4c and 4f showed nearly identical $K_{t-t}$ values in CDCl$_3$. However, in toluene–$d_8$ $K_{t-t}$ for 4c was higher (900 M$^{-1}$) than that for 4f (590 M$^{-1}$). This difference is also in agreement with the electron withdrawing nature of the alkoxy group compared with the thiol group. Both substituents have as heteroatom an element of the same group; i.e. oxygen and sulfur. Since oxygen is the more electronegative element, it has a higher electron withdrawing inductive effect ($-I$)$^{42}$ on the amino group polarizing the N-H bond. Conversely, both elements hold lone pairs of electrons that can provide an electron donating resonance effect ($+R$) to the nitrogen acceptor in the triazine ring. In this case, oxygen also provides a greater resonance effect due to a better orbital overlap with the $\pi$-bonds of the heteroaromatic ring (all elements of the second row) compared with sulfur (element of the third row). Hence; both effect favor the oxygen substituent as having the higher $K_{t-t}$.

Lastly, Table 2.3 can be used to estimate the effect of the hydrogen bond acceptor site located on the pyridine ring in toluene–$d_8$. Compounds 5c, 5f and 5k displayed dimerization constants of 18, 26 and 46 M$^{-1}$, respectively (e.g. dimerization isotherm of 5c, Figure 2.14); meanwhile, 4c, 4f and 4k had values of 900, 590 and 1200 M$^{-1}$ (e.g. dimerization isotherm of 4c, Figure 2.15). That is, the energetic contribution of the extra acceptor can be estimated to be approximately 8 kJ mol$^{-1}$ in toluene–$d_8$ ($\Delta\Delta G_{\text{Butoxy}} = -9.64$ kJ mol$^{-1}$, $\Delta\Delta G_{\text{Hexylthiol}} = -7.67$ kJ mol$^{-1}$, and $\Delta\Delta G_{\text{4'-tert-butylphenoxy}} = -8.24$ kJ mol$^{-1}$); or 4 kJ
mol⁻¹ per pyridine ring. The higher value in this solvent is again likely reflective of the reduced solvent competition for the acceptor sites.

**Figure 2.14** Dimerization isotherm of 5c with $K_{t-t}$ value and free energy calculated from fitting of the data to a 1:1 dimerization model. Blue, green and red dots correspond to first, second and third separate dilution experiments, respectively. Solid line corresponds to the theoretical dilution curve obtained from the average $K_{t-t}$ of three separate dilution experiments.

**Figure 2.15** Dimerization isotherm of 4c with $K_{t-t}$ value and free energy calculated from fitting of the data to a 1:1 dimerization model. Blue, green and red dots correspond to first, second and third separate dilution experiments, respectively. Solid line corresponds to the theoretical dilution curve obtained from the average $K_{t-t}$ of three separate dilution experiments.
2.3.3 X-Ray Analysis of Self-Complementary Arrays.

Single crystal X-ray diffraction is potentially useful to corroborate our proposed dimer structure in the solid state. In this case, we were able to obtain X-ray crystal structures of 4a, 4d, 4f and 4k (Table 2.4). Crystal growth was carried out by slow evaporation or slow diffusion using various dry solvents or solvent mixtures. The solvent selection was based on solubility; i.e. most of 4a-p were highly soluble in CHCl₃, CH₂Cl₂, ethyl acetate and acetone, and poorly soluble or not soluble in toluene, hexanes and diisopropyl ether. In a typical crystal growing experiment 20 mg of 4 was dissolved in approximately 5 mL of a chosen solvent. The resulting solution was divided into four small vials. One of them was loosely capped for slow solvent evaporation. Each of the remaining vials was placed into a larger vial surrounded by either hexanes, toluene or diisopropyl ether, and tightly capped for slow diffusion. Vials were monitored regularly for the appearance of X-ray quality single crystals.
Table 2.4 Crystallographic parameters for 4a, 4d, 4f and 4k crystals.

<table>
<thead>
<tr>
<th></th>
<th>4a</th>
<th>4d</th>
<th>4f</th>
<th>4k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Formula</td>
<td>C\textsubscript{13}H\textsubscript{16}N\textsubscript{8}</td>
<td>C\textsubscript{16}H\textsubscript{23}N\textsubscript{7}O</td>
<td>C\textsubscript{14}H\textsubscript{19}N\textsubscript{7}S</td>
<td>C\textsubscript{19}H\textsubscript{20}Cl\textsubscript{3}N\textsubscript{7}O</td>
</tr>
<tr>
<td>Molecular Weight (g\textperiodcentered mol\textsuperscript{-1})</td>
<td>284.34</td>
<td>329.41</td>
<td>317.42</td>
<td>468.77</td>
</tr>
<tr>
<td>Crystal System</td>
<td>Triclinic</td>
<td>Triclinic</td>
<td>Triclinic</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space Group</td>
<td>(\text{P}\overline{1})</td>
<td>(\text{P}\overline{1})</td>
<td>(\text{P}\overline{1})</td>
<td>(\text{P2}_1/\text{n})</td>
</tr>
<tr>
<td>(a) (Å)</td>
<td>8.157 (3)</td>
<td>13.101 (3)</td>
<td>7.5968 (9)</td>
<td>13.7969 (17)</td>
</tr>
<tr>
<td>(b) (Å)</td>
<td>8.489 (2)</td>
<td>13.726 (4)</td>
<td>10.8490 (10)</td>
<td>17.697 (3)</td>
</tr>
<tr>
<td>(c) (Å)</td>
<td>10.736 (3)</td>
<td>15.153 (5)</td>
<td>13.2133 (17)</td>
<td>18.179 (3)</td>
</tr>
<tr>
<td>(\alpha) (°)</td>
<td>67.693 (12)</td>
<td>83.268 (10)</td>
<td>66.494 (7)</td>
<td>90</td>
</tr>
<tr>
<td>(\beta) (°)</td>
<td>79.709 (11)</td>
<td>82.181 (11)</td>
<td>83.486 (6)</td>
<td>100.985 (7)</td>
</tr>
<tr>
<td>(\gamma) (°)</td>
<td>89.079 (10)</td>
<td>74.493 (10)</td>
<td>71.772 (5)</td>
<td>90</td>
</tr>
<tr>
<td>(V) (Å\textsuperscript{3})</td>
<td>675.6 (4)</td>
<td>2591.9 (12)</td>
<td>948.44 (19)</td>
<td>4357.4</td>
</tr>
<tr>
<td>(Z)</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>(F(000))</td>
<td>300</td>
<td>1056</td>
<td>336</td>
<td>1936</td>
</tr>
<tr>
<td>(T) (K)</td>
<td>110</td>
<td>110</td>
<td>173</td>
<td>110</td>
</tr>
<tr>
<td>(\lambda) (Å)</td>
<td>0.71073</td>
<td>0.71073</td>
<td>1.54178</td>
<td>1.54178</td>
</tr>
<tr>
<td>(\rho_{\text{calc}}) (g\textperiodcentered cm\textsuperscript{-3})</td>
<td>1.398</td>
<td>1.266</td>
<td>1.111</td>
<td>1.429</td>
</tr>
<tr>
<td>(\mu) (mm\textsuperscript{-1})</td>
<td>0.094</td>
<td>0.085</td>
<td>1.571</td>
<td>4.031</td>
</tr>
<tr>
<td>Reflections Collected</td>
<td>35366</td>
<td>129610</td>
<td>14138</td>
<td>52827</td>
</tr>
<tr>
<td>Unique Reflections</td>
<td>5981</td>
<td>19753</td>
<td>3179</td>
<td>7640</td>
</tr>
<tr>
<td>Absorption Correction</td>
<td>multi-scan</td>
<td>multi-scan</td>
<td>multi-scan</td>
<td>multi-scan</td>
</tr>
<tr>
<td>Refinement Correction</td>
<td>(F^2)</td>
<td>(F^2)</td>
<td>(F^2)</td>
<td>(F^2)</td>
</tr>
<tr>
<td>Parameters Refined</td>
<td>198</td>
<td>925</td>
<td>275</td>
<td>586</td>
</tr>
<tr>
<td>(R(F_0)(l&gt;2\sigma(l)))</td>
<td>0.0614</td>
<td>0.0576</td>
<td>0.0304</td>
<td>0.0514</td>
</tr>
<tr>
<td>(R_w(F_0^2)(l&gt;2\sigma(l)))</td>
<td>0.1623</td>
<td>0.1456</td>
<td>0.0847</td>
<td>0.1363</td>
</tr>
<tr>
<td>(R(F_0)(\text{all data}))</td>
<td>0.1126</td>
<td>0.1044</td>
<td>0.0334</td>
<td>0.0640</td>
</tr>
<tr>
<td>(R_w(F_0^2)(\text{all data}))</td>
<td>0.1867</td>
<td>0.1735</td>
<td>0.0886</td>
<td>0.1482</td>
</tr>
<tr>
<td>GOF on (F^2)</td>
<td>1.063</td>
<td>1.016</td>
<td>1.058</td>
<td>1.031</td>
</tr>
</tbody>
</table>
Piperidine derivative 4a was crystallized by the slow evaporation of a chloroform solution to yield deep red plates that were suitable for single crystal X-ray diffraction analysis. The collected data was modeled in space group $P\overline{1}$ and yielded a structure with two symmetry-related molecules per unit cell. The two molecules take up the anticipated dimer configuration in which the self-complementary arrays pair up in an antiparallel manner through hydrogen bonds (Table 2.5) to stabilize a complex with inversion symmetry. The least squares planes of the aminotriazine rings in the complex are offset from each other by 0.79 Å and participate in a symmetry related pair of hydrogen bonds ($N_6$-$H_6B$···$N_7'$ = 3.16 Å; $\angle N$-$H$···$N = 168^\circ$). The dimer is further stabilized by more oblique hydrogen bond interactions between the amino N-H donors and the azo ($N_6$-$H_6B$···$N_2'$ = 3.01 Å; $\angle N$-$H$···$N = 118^\circ$) and pyridyl ($N_6$-$H_6A$···$N_1'$ = 3.55 Å; $\angle N$-$H$···$N = 135^\circ$) nitrogen acceptors. It is also notable that the distance from $H_6A$ to the nearest opposing pyridyl proton ($H_5'$) is 4.15 Å, likely outside or at the distance limit for detection by a $^1H$ NMR NOESY experiment. This is supported by the absence of such a contact when this dimer was subjected to NOESY analysis (see Section 2.3.2). The dimer takes up the expected disposition of complementary hydrogen bonds but is distorted from a (presumably) ideal planar arrangement of the two molecules. Deviations from coplanarity of the azo group and the adjacent heterocyclic rings ($11^\circ$ and $27^\circ$ for pyridine and triazine, respectively) result in interplanar angles between the two rings of $44^\circ$ both in an intramolecular and intermolecular sense in the dimer due to the symmetry of the space group. There are no other notable non-covalent interactions observed in the extended lattice structure between dimers.
**Table 2.5** Hydrogen bond distances and angles of complex 4a-4a X-ray crystal structure data.

<table>
<thead>
<tr>
<th>D···A</th>
<th>d NH···N (Å)</th>
<th>d NH···N (Å)</th>
<th>∠ NH···N (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N6-H6B···N7'</td>
<td>3.1551 (8)</td>
<td>2.3071 (6)</td>
<td>167.677 (34)</td>
</tr>
<tr>
<td>N6-H6B···N2'</td>
<td>3.0115 (7)</td>
<td>2.5070 (7)</td>
<td>118.145 (25)</td>
</tr>
<tr>
<td>N6-H6A···N1'</td>
<td>3.5477 (10)</td>
<td>2.8770 (8)</td>
<td>134.659 (20)</td>
</tr>
</tbody>
</table>

**Figure 2.16** Stick representation of the X-ray crystal structure of 4a dimer with intermolecular hydrogen bonds indicated (dashed orange lines). Blue, grey and white correspond to nitrogen, carbon and hydrogen atoms, respectively.
X-ray quality crystals of octyloxy derivative \(4d\) were obtained by slow diffusion of hexanes into a chloroform solution of the array. \(4d\) crystallized as red prisms in space group \(P\bar{1}\) with six molecules per unit cell designated as three molecules: A, B and C. These three molecules are organized into two dimer structures: 1) two molecules of A form a dimer with inversion symmetry; 2) molecules B and C form a non-centrosymmetric dimer (Figure 2.17). The \(4d\) dimer structures both display similar hydrogen bond interactions to those observed in the preceding \(4a\) dimer in the solid state. However, the intermolecular distances between hydrogen bond donor-acceptor sites in both \(4d\) dimers are generally shorter than the ones reported for the \(4a\) dimer (Table 2.6). Based on this observation it can be presumed that \(4d\) dimers are stabilized by stronger hydrogen bond interactions than the \(4a\) dimer. This is in agreement with the higher dimerization constant in CDCl\(_3\) for \(4d\) (32 M\(^{-1}\)) compared with \(4a\) (8.4 M\(^{-1}\)). In spite of the proximity of \(4d\) dimers, the distances between H5X2 (X = A, B/C) and the nearest opposing pyridyl proton H1X’ (X’ = A’, C/B) are still at or outside the limit for detection by a \(^1\)H NMR NOESY experiment (H5A2∙∙∙ H1A’ = 3.78 Å, H5B2∙∙∙ H1C = 3.57 Å and H5C2∙∙∙ H1B = 3.67 Å). The dimer formed by two A molecules can be considered planar since there is no heavy atom deviating from the least squares plane of all the heavy atoms in the dimer more than 0.30 Å. Conversely, molecules B and C form a dimer more distorted from planarity. The least squares planes of all the heavy atoms in the azoheteroaromatic cores (i.e. without taking into account the octyloxy and amino groups) in B and C form an angle of 157° with respect to each other. Individually, molecules A, B and C in the \(4d\) crystal structure show small deviations from coplanarity along the azoheterocyclic backbone (greatest heavy atom deviation from least squares planes of 0.13 Å for molecule A, 0.10 Å for molecule B and 0.21 Å for molecule
C). In addition to the expected hydrogen bond interactions in 4d, molecules A, B and C exhibit C3(A/B/C)-H3(A/B/C)···N7(A/C/B) hydrogen bonds at the opposing edges of the DDAAA array (Figure 2.18, Table 2.6). In the course of the three dilution experiments of 4d in CDCl₃ there were no observable changes in the chemical shift corresponding to the H3 proton; therefore, it is concluded that these hydrogen bond interactions are a result of crystal packing.

Figure 2.17 Stick representation of the X-ray crystal structure of 4d dimers with intermolecular hydrogen bonds indicated (dashed orange lines). Blue, grey, white and red correspond to nitrogen, carbon, hydrogen and oxygen atoms, respectively.
Table 2.6 Hydrogen bond distances and angles of complex 4d·4d X-ray from the crystal structure data.

<table>
<thead>
<tr>
<th>Dimer</th>
<th>D⋯A</th>
<th>d X⋯N (Å)</th>
<th>d X⋯N (Å)</th>
<th>∠ X⋯N (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A·A’ Dimer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N5A-H5A1⋯N4A’</td>
<td>3.0436 (8)</td>
<td>2.1531 (6)</td>
<td>176.147 (46)</td>
<td></td>
</tr>
<tr>
<td>N5A-H5A1⋯N2A’</td>
<td>2.9228 (6)</td>
<td>2.4367 (5)</td>
<td>114.601 (41)</td>
<td></td>
</tr>
<tr>
<td>N5A-H5A2⋯N1A’</td>
<td>3.3159 (8)</td>
<td>2.5775 (6)</td>
<td>140.401 (40)</td>
<td></td>
</tr>
<tr>
<td>C3A-H3A⋯N7A’</td>
<td>3.3815 (7)</td>
<td>2.4578 (5)</td>
<td>169.583 (41)</td>
<td></td>
</tr>
<tr>
<td><strong>B·C Dimer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N5B-H5B1⋯N4C</td>
<td>3.1785 (8)</td>
<td>2.3379 (6)</td>
<td>173.118 (52)</td>
<td></td>
</tr>
<tr>
<td>N5B-H5B1⋯N2C</td>
<td>3.0158 (5)</td>
<td>2.4981 (5)</td>
<td>120.456 (42)</td>
<td></td>
</tr>
<tr>
<td>N5B-H5B2⋯N1C</td>
<td>3.3145 (7)</td>
<td>2.5311 (6)</td>
<td>130.407 (37)</td>
<td></td>
</tr>
<tr>
<td>C3B-H3B⋯N7C</td>
<td>3.6602 (7)</td>
<td>2.6886 (5)</td>
<td>168.170 (38)</td>
<td></td>
</tr>
<tr>
<td>N5C-H5C1⋯N4B</td>
<td>3.1199 (8)</td>
<td>2.2146 (6)</td>
<td>169.261 (52)</td>
<td></td>
</tr>
<tr>
<td>N5C-H5C1⋯N2B</td>
<td>2.9262 (6)</td>
<td>2.4805 (5)</td>
<td>110.191 (40)</td>
<td></td>
</tr>
<tr>
<td>N5C-H5C2⋯N1B</td>
<td>3.2669 (7)</td>
<td>2.4955 (6)</td>
<td>138.273 (40)</td>
<td></td>
</tr>
<tr>
<td>C3C-H3C⋯N7B</td>
<td>3.3215 (7)</td>
<td>2.4140 (5)</td>
<td>157.109 (40)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2.18 Stick representation of the X-ray crystal structure of 4d with C-H···N interactions indicated (dashed orange lines). Blue, grey, white and red correspond to nitrogen, carbon, hydrogen and oxygen atoms, respectively.

Examining array 4f, single crystals of this derivative were obtained by slow evaporation from a solution in toluene-d8. The gold prismatic crystals obtained were solved in triclinic space group $P\overline{1}$, where each unit cell comprised two symmetry related molecules. As observed in the preceding crystal structures, dimers of 4f are present in the crystal lattice with a similar hydrogen bond array displayed by the dimers of 4d (Figure 2.19 and Table 2.7) in the solid state. The intermolecular least squares planes of the two symmetry related heterocyclic backbones are offset from each other by 0.25 Å with six hydrogen bond interactions stabilizing the dimer. There is a symmetry related pair of hydrogen bonds between an amino proton and a triazine nitrogen atom ($N_7$-$H_7A$···$N_6'$ = 3.15 Å; $\angle N$-$H$···$N = 178^\circ$), and two pairs of less linear hydrogen bonds between the amino protons and the azo ($N_7$-$H_7A$···$N_2'$ = 2.95 Å; $\angle N$-$H$···$N = 115^\circ$) and pyridyl ($N_7$-
H7B⋯N1’ = 3.28 Å; \( \angle \text{N-H⋯N} = 137^\circ \) nitrogen acceptors. The intermolecular distances displayed in the 4f dimer are similar in character to 4d dimers and generally shorter in length than the 4a dimer. This similarity between 4f and 4d dimers is consistent with the similar dimerization constants in CDCl\textsubscript{3} of both derivatives (32 M\textsuperscript{-1} and 36 M\textsuperscript{-1} for 4d and 4f, respectively). Likewise, the lack of a cross-relaxation peak between H7B and H1’ in a \(^1\text{H} \) NOESY experiment is again sustained by the distance between these two protons in the dimer (H7B⋯H1’ = 3.8 Å). The dimer is planar with no heavy atom deviating from the least squares plane described by all the non-hydrogen atoms in the molecule by more than 0.16 Å. Other intermolecular interactions appear in the crystal lattice such as C-H⋯N interactions at the opposite edges of the DDAAA hydrogen bond arrays (Figure 2.20 and Table 2.7) and \( \pi-\pi \) interactions between stacked aromatic planes of adjacent dimers (triazine ring centroid to least squares plane of adjacent molecule distance = 3.54 Å; pyridine ring centroid to least squares plane of adjacent molecule distance = 3.61 Å).\textsuperscript{45} Both interactions are attributed to crystal packing since dilution experiments did not show the expected changes in the chemical shift of protons likely to be affected by these interactions (i.e. pyridyl ring protons).
Figure 2.19 Stick representation of the X-ray crystal structure of 4f dimer with intermolecular hydrogen bonds indicated (dashed orange lines). Blue, grey, white and yellow correspond to nitrogen, carbon, hydrogen and sulfur atoms, respectively.

Table 2.7 Hydrogen bond distances and angles of complex 4f­4f X-ray from the crystal structure data.

<table>
<thead>
<tr>
<th>D···A</th>
<th>d NH···N (Å)</th>
<th>d NH···N (Å)</th>
<th>∠ NH···N (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N7-H7A···N6'</td>
<td>3.1500 (3)</td>
<td>2.2848 (2)</td>
<td>177.961 (10)</td>
</tr>
<tr>
<td>N7-H7A···N2'</td>
<td>2.9500 (4)</td>
<td>2.4723 (3)</td>
<td>115.468 (6)</td>
</tr>
<tr>
<td>N7-H7B···N1'</td>
<td>3.2831 (3)</td>
<td>2.5905 (3)</td>
<td>137.388 (8)</td>
</tr>
<tr>
<td>C3-H3···N4'</td>
<td>3.4354 (4)</td>
<td>2.5038 (3)</td>
<td>170.492 (6)</td>
</tr>
</tbody>
</table>
Finally, single crystals of 4k were obtained by slow evaporation from a chloroform solution to yield orange plates. The diffraction data from 4k was solved in space group $P2_1/n$ with eight molecules per unit cell arranged as four symmetry related pairs of two molecules: A and B. Solution of the crystal structure of 4k included the presence of chloroform solvent molecules occluded, as indicated in the chemical formula obtained (Table 2.4). Molecules A and B form a dimer in accordance with the previous crystal structures obtained (Figure 2.21). The intermolecular hydrogen bond distances observed in the 4k dimer are slightly shorter than to those observed in the 4d and 4f dimers (Table 2.8), which implies a stronger dimerization for derivative 4k compared with 4d and 4f. This observation is again consistent with their dimerization constants in CDCl$_3$ (36 M$^{-1}$, 32 M$^{-1}$ and 50 M$^{-1}$ for 4d, 4f and 4k, respectively). The intermolecular distances of the amino protons H1X4 (X = A or B) with the closest pyridyl proton from the opposing molecule
(H18X) also fall outside the $^1$H NOESY experiment detection distance ($H1A4\cdots H18B = 3.75 \text{ Å} \text{ and } H1B4\cdots H18A = 3.70 \text{ Å}$). Though the azoheterocyclic backbones in molecules A and B can each be considered planar (no heavy atom more than 0.44 \text{ Å} from least squares planes described by azoheterocyclic cores), the dimer formed by the two molecules deviates from overall coplanarity since their azoheterocyclic backbones converge at an angle of 156° between the least squares planes. In contrast, in both molecules the 4’-*tert*-butylphenoxy group is twisted nearly perpendicular to the triazine ring (63° and 88° for molecules A and B respectively). It is likely that because of this 4’-*tert*-butylphenoxy arrangement that C-H⋯N interactions similar to the preceding two structures are not observed in the solid state for 4k. However, the 4’-*tert*-butylphenoxy groups participate in C-H⋯π interactions involving H17X and H3X (X = A or B) protons (Figure 2.22, Table 2.8). Lastly, there are π-π interactions stacked along the crystal lattice’s $b$ direction. Molecules A and B are arranged above one another in an antiparallel manner with distances from ring centroids to azoheterocyclic core least squares planes of 3.27 \text{ Å} \text{ and } 3.30 \text{ Å} for A and B molecules respectively. \textsuperscript{45}
Figure 2.21 Stick representation of the X-ray crystal structure of 4k dimers with intermolecular hydrogen bonds indicated (dashed orange lines). Blue, grey, white and red correspond to nitrogen, carbon, hydrogen and oxygen atoms, respectively.

<table>
<thead>
<tr>
<th>D···A</th>
<th>d XH···Y (Å)</th>
<th>d XH···Y (Å)</th>
<th>∠ XH···Y (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1A-H15A···N4B</td>
<td>3.1270 (4)</td>
<td>2.2624 (3)</td>
<td>167.324 (21)</td>
</tr>
<tr>
<td>N1A-H15A···N6B</td>
<td>2.9725 (4)</td>
<td>2.4707 (3)</td>
<td>116.745 (19)</td>
</tr>
<tr>
<td>N1A-H14A···N7B</td>
<td>3.2790 (4)</td>
<td>2.5618 (3)</td>
<td>139.222 (20)</td>
</tr>
<tr>
<td>C3A-H3A···πB</td>
<td>3.6757 (2)</td>
<td>2.8396 (2)</td>
<td>58.554 (4)</td>
</tr>
<tr>
<td>C17A-H17A···πB</td>
<td>3.6741 (2)</td>
<td>2.7363 (2)</td>
<td>80.817 (9)</td>
</tr>
<tr>
<td>N1B-H15B···N4A</td>
<td>3.0813 (4)</td>
<td>2.2218 (3)</td>
<td>165.374 (23)</td>
</tr>
<tr>
<td>N1B-H15B···N6A</td>
<td>2.9223 (4)</td>
<td>2.4405 (3)</td>
<td>114.912 (20)</td>
</tr>
<tr>
<td>N1B-H14B···N7A</td>
<td>3.2270 (4)</td>
<td>2.4895 (3)</td>
<td>141.760 (21)</td>
</tr>
<tr>
<td>C3B-H3B···πA</td>
<td>3.6362 (2)</td>
<td>2.7270 (2)</td>
<td>68.090 (6)</td>
</tr>
<tr>
<td>C17B-H17B···πA</td>
<td>3.7234 (2)</td>
<td>2.8697 (2)</td>
<td>63.976 (10)</td>
</tr>
</tbody>
</table>
A comparison of the intermolecular distances and heterocyclic ring planes angles of all the dimer arrays described in the preceding X-ray crystal structures are listed in Table 2.9. It is worth outlining the correlation between the hydrogen bond distances and dimer’s planarity in the crystal structure with the dimerization strength estimated in the dilution experiments. In this sense, the compound with the largest intermolecular distances shows the lowest dimerization constant, 4a. Dimer structures from derivatives 4d and 4f have similar intermolecular distances with small deviations from coplanarity between heterocyclic rings. Hence, it is not unexpected to note that their dimerization constants in CDCl₃ fall within the same range (36 and 32 M⁻¹ for 4d and 4f, respectively). Finally, 4k dimer has intermolecular distances slightly lower than those observed for 4d and 4f dimers. Particularly 4k dimer has the lowest N-Hb···Nc distance (3.2 Å, Table 2.9) which implies a stronger participation of the pyridyl nitrogen acceptor compared with 4a, 4d and 4f. This
might rationalize that from all compounds studied through X-Ray crystallography 4k has the highest dimerization constant in solution.

![Figure 2.23](image.png)

**Figure 2.23** Donor and acceptor sites assignment of 4a, 4d, 4f and 4k dimers.

**Table 2.9** Summary of hydrogen bond distances, intramolecular and intermolecular ring’s planes angles of 4a, 4d, 4f and 4k from their crystal structure data.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>N-Ha····Nc (Å)</th>
<th>N-Ha····Nd (Å)</th>
<th>N-Hb····Nc (Å)</th>
<th>Intramolecular Ring Plane Angles (°)</th>
<th>Intermolecular Ring Plane Angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>3.1551 (8)</td>
<td>3.0115 (7)</td>
<td>3.5477 (10)</td>
<td>44.576</td>
<td>44.576</td>
</tr>
<tr>
<td>4d</td>
<td>3.0436 (8)</td>
<td>2.9228 (6)</td>
<td>3.3159 (8)</td>
<td>11.357</td>
<td>11.357</td>
</tr>
<tr>
<td></td>
<td>3.1785 (8)</td>
<td>3.0158 (5)</td>
<td>3.3145 (7)</td>
<td>3.830</td>
<td>20.285</td>
</tr>
<tr>
<td></td>
<td>3.1199 (8)</td>
<td>2.9262 (6)</td>
<td>3.2669 (7)</td>
<td>7.637</td>
<td>26.896</td>
</tr>
<tr>
<td></td>
<td>3.1140 b</td>
<td>2.9549 b</td>
<td>3.2991 b</td>
<td>7.608 b</td>
<td>19.513 b</td>
</tr>
<tr>
<td>4f</td>
<td>3.1500 (3)</td>
<td>2.9500 (4)</td>
<td>3.2831 (3)</td>
<td>0.912</td>
<td>0.912</td>
</tr>
<tr>
<td>4k</td>
<td>3.1270 (4)</td>
<td>2.9725 (4)</td>
<td>3.2790 (4)</td>
<td>9.096</td>
<td>21.076</td>
</tr>
<tr>
<td></td>
<td>3.0813 (4)</td>
<td>2.9223 (4)</td>
<td>3.2270 (4)</td>
<td>4.468</td>
<td>24.592</td>
</tr>
<tr>
<td></td>
<td>3.1042 b</td>
<td>2.9474 b</td>
<td>3.2530 b</td>
<td>6.782 b</td>
<td>22.834 b</td>
</tr>
</tbody>
</table>

^a Angle between least squares triazine and pyridine ring planes, ^b Average values from all dimers present in the crystal structure
2.4 Summary and Conclusion

A range of self-complementary hydrogen bond DDAAA arrays (4a-p) were designed, synthesized and characterized. The novelty of the system proposed lies in the inclusion of a photochromic group in the binding site’s array; utilizing an azo group as a hydrogen bond acceptor. Dimerization constants of derivatives 4a-p were obtained employing two different solvent systems: CDCl₃ and Toluene-d₈. In deuterated chloroform, dimerization constants varied from 8.4 to 180 M⁻¹. In deuterated toluene, dimerization constants ranged from 600 to 3700 M⁻¹. The difference in $K_{d}$ values in different solvents is consistent with a stronger interaction between chloroform and the monomers which competes with dimerization. Nevertheless, in both solvent systems, derivatives 4a-p with stronger electron withdrawing RX groups achieved larger dimerization constants (e.g. perfluorophenoxy derivative 4n displayed the highest dimerization constants). The dimer structures in the solid state were confirmed by single crystal X-ray diffraction of four derivatives: 4a, 4d, 4f, and 4k. The structures supported the existence of hydrogen bond interactions between amino group and triazine, azo and pyridine moieties as anticipated from the original design. Of all these interactions, the strongest one appeared to be between the amino group and triazine ring since in all dimer structures observed, it displayed N-H···N angles closest to 180°. Differences between intermolecular distances of derivatives 4a, 4d, 4f and 4k are in accordance with the dimerization strength observed for each derivative (e.g. derivative 4a has the smallest dimerization constant and showed the largest intermolecular distances).
Finally, the impact of the pyridine acceptor was examined through a comparison between 4c, 4f and 4k with compounds 5c, 5f and 5k. The energetic contribution of the pyridine acceptors in each solvent system was estimated at 4 and 8 kJ mol$^{-1}$ in chloroform and toluene respectively. According to literature, primary and secondary hydrogen bonds have energetic contributions in chloroform of 7.9 and 2.9 kJ mol$^{-1}$, respectively. In this sense, and based on the dimer structures obtained by X-ray diffraction, the pyridine acceptor site is located far enough away from the amino group that the hydrogen bond between these moieties falls somewhere between a primary and a secondary interaction. These observations leave room for improvement on the design proposed in this chapter. A design wherein the pyridine rings are replaced by another aromatic system with an acceptor site bonded ortho- to the azo group and closer to the amino group in a dimer structure will be considered in Chapter 4.

### 2.5 Experimental Methodology

#### 2.5.1 Generalities

All experiments were performed in ambient atmospheric conditions unless otherwise indicated. Chemicals were purchased from Alfa Aesar, Sigma-Aldrich, and Oakwood Products and used as received. Solvents (acetone, acetonitrile, butanol, chloroform, dichloromethane, diethyl ether, diisopropyl ether, dimethyl formamide, ethyl acetate, hexanes, methanol, tetrahydrofuran, and toluene) were obtained from Caledon Laboratories, Fisher Chemicals, Sigma-Aldrich and VWR Analytical. In the case of inert
Atmosphere conditions, solvents were dried using an Innovative Technology Inc. Controlled Atmospheres Solvent Purification System that utilizes dual alumina columns (SPS-400-5), or purchased from Sigma-Aldrich and used as received. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated TLC-sheets POLYGRAM®SIL G/UV₂₅₄. Column chromatography was performed with SiliCycle®SiliaFlash® F60, 40-63 µm 60 Å. Nuclear Magnetic Resonance spectra were recorded on Mercury 400 MHz, INOVA 400 MHz and INOVA 600 MHz spectrometers (¹H = 400.08 MHz, 399.77 MHz and 599.32 MHz; ¹³C {¹H} = 100.52 MHz and 150.78 MHZ respectively). ¹H and ¹³C spectra were referenced relative to Me₄Si using the residual non-deuterated NMR solvent signal (¹H: CHCl₃, δ = 7.26 ppm, (CHD₂)₂SO, δ = 2.50 ppm, (CHD₂)C₆D₅, δ = 2.09 ppm, ; ¹³C {¹H}: CHCl₃, δ = 77.0 ppm, (CHD₂)₂SO, δ = 39.5 ppm). Solvents for NMR spectroscopy (Chloroform-d, DMSO-d₆, and Toluene-d₈) were purchased from Cambridge Isotope Laboratories and Sigma-Aldrich. Mass spectra were recorded using an electron ionization Finnigan MAT 8200 spectrometer at an ionizing voltage of 70 eV. X-Ray diffraction data were collected on Bruker Apex II and Nonius Kappa CCD X-Ray diffractometers using graphite monochromatic Mo-Kα radiation (γ = 0.71073 Å) and Cu-Kα radiation (γ = 1.54178 Å), respectively.
2.5.2 Synthetic Methods

Synthesis of 4,6-dichlorotriazin-2-amine (1). Synthetic procedure as reported by Baliani and coworkers. In a round bottom flask with a stir bar, cyanuric chloride (20.0 g, 0.11 mol, 1 eq.) was dissolved in acetone (100 mL) and then a 1:1 ice and distilled water mixture (100 mL) was poured into the solution to make a thick slurry. The slurry was cooled down to a temperature below 5 °C and 2 eq. of aqueous ammonia 29% (30 mL, 0.22 mol, 2 eq.) was added dropwise without letting the reaction mixture exceed 5°C. The reaction mixture was stirred 30 minutes at a temperature below 5°C and then 30 minutes coming to room temperature. The product was filtered and dried by vacuum filtration. Yield = 14 g, 78%. EI-HRMS: Calc. for C₃H₂Cl₂N₄:163.9657, Found: 163.9658. ¹H NMR (400 MHz, DMSO-d₆): δ(ppm) 8.57 (bs, 2H). ¹³C NMR (100 MHz, DMSO-d₆): δ(ppm) 166.9, 169.1.

General procedures for synthesis of 4-chloro-1,3,5-triazin-2-amine derivatives (2a-p).

Method A: 2-amino-4,6-dichlorotriazine (5.0 g, 30.3 mmol, 1 eq.) was dissolved in THF. The solution was cooled down to -78°C and then K₂CO₃ (4.19 g, 30.3 mmol, 1 eq.) and reactant RXH (30.3 mmol, 1 eq.) were added sequentially. The reaction mixture was stirred overnight and allowed to slowly reach room temperature. The solvent was removed under reduced pressure and the crude was washed with distilled water and filtered by vacuum filtration. If necessary, further purification was performed by flash chromatography using 1:1 hexanes / diethyl ether as eluent.
**Method B:** Under an N\textsubscript{2} atmosphere, a round bottom flask, provided with a stir bar, was filled with 100 mL of dry THF and chilled to 0°C in an ice-water bath. NaH (60% dispersion in mineral oil, 1.45 g, 36.4 mmol, 1.2 eq.) was poured into the dry THF and stirred to generate a fine suspension. Fifteen minutes later reactant RXH (36.4 mmol, 1.2 eq.) was added dropwise over 30 minutes to the fine suspension and the reaction mixture was stirred 30 minutes (in the ice-water bath). Then the reaction mixture was gradually warmed to reflux for 4 hours and finally cooled down to room temperature. In a separated flask under N\textsubscript{2}, 4,6-dichlorotriazin-2-amine (5.86 g, 35.5 mmol, 1 eq.) was dissolved in 100 mL of dry THF and cooled to -78°C. Once the alkoxide reaction mixture had reached room temperature, it was added drop-wise to the 4,6-dichlorotriazin-2-amine solution. The resulting reaction mixture was stirred overnight and allowed to reach room temperature. The solvent was removed under reduced pressure and the crude was washed with distilled water and filtered. If necessary, further purification was performed by flash chromatography using 1:1 hexanes / diethyl ether as eluent.

**Method C:** In a round bottom flask provided with a stir bar, 4,6-dichlorotriazin-2-amine (5.00 g, 30.3 mmol, 1 eq.) was dissolved in 100 mL of acetone and then 100 mL of distilled water was poured into the solution to form a slurry. The reaction mixture was cooled down to 0°C. In a separate flask 50 mL of distilled water, reactant RXH (30.31 mmol, 1 eq.) and sodium hydroxide (1.21 g, 30.30 mmol, 1 eq.) were dissolved. To the 4,6-dichlorotriazin-2-amine suspension prepared before, the reactant RXH and sodium hydroxide solution was added dropwise keeping the temperature below 5°C. The product reaction mixture was stirred overnight allowing it to reach room temperature. The reaction mixture was filtered
and washed with distilled water. If necessary, further purification was performed by flash chromatography using 1:1 hexanes / diethyl ether as eluent.

Synthesis of 4-chloro-6-(piperidin-1-yl)-1,3,5-triazin-2-amine (2a). 4,6-dichlorotriazin-2-amine (5.00 g, 30.3 mmol, 1 eq.) was dissolved in 100 mL of THF in a round bottom flask provided with a stir bar; the solution was cooled to -78°C. In a separated flask piperidine (3.0 mL, 30.3 mmol, 1 eq.) and triethylamine (4.2 mL, 30.3 mmol, 1 eq.) were dissolved in 100 mL of THF and the resulting solution slowly added to the 4,6-dichlorotriazin-2-amine solution. The reaction mixture was stirred overnight allowing it to reach room temperature. The solvent was removed at reduced pressure and the crude was washed with distilled water and filtered. Yield = 3.70 g, 57% EI-HRMS: Calc. for C₈H₁₂ClN₅: 213.0781, Found: 213.0786. ¹H NMR (600 MHz, CDCl₃): δ(ppm) 5.19 (b, 2H), 3.74 (m, 4H), 1.62 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 169.6, 166.7, 164.2, 44.5, 25.8, 24.5.

Synthesis of 4-chloro-6-methoxy-1,3,5-triazin-2-amine (2b). In a round bottom flask 4,6-dichlorotriazin-2-amine (5.00 g, 30.3 mmol, 1 eq.) was dissolved in 100 mL of methanol. The solution was cooled down to -78°C and later added sodium methoxide salt
(1.64 g, 30.3 mmol, 1 eq.). The reaction mixture was stirred over 6 hours allowing it to reach room temperature. Later, the reaction mixture was poured into an ice-water mixture and the product was filtered and dried by vacuum filtration. Yield = 4.87 g, 81%. EI-HRMS: Calc. for C₄H₅ClN₄O: 160.0152, Found: 160.0154. ¹H NMR (400 MHz, DMSO-d₆) δ(ppm) 7.99 (bs, 2H), 3.85 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ(ppm) 170.8, 169.8, 168.0, 54.9.

Synthesis of 4-butoxy-6-chloro-1,3,5-triazin-2-amine (2c). Synthesis performed according to Method B; wherein reactant RXH corresponds to 1-butanol. Yield = 6.10 g, 99%. EI-HRMS: Calc. for C₇H₁₁ClN₄O: 202.0621, Found: 203.0703. ¹H NMR (400 MHz, CDCl₃) δ(ppm) 5.83 (b, 1H), 5.56 (b, 1H), 4.34 (t, 2H, J = 6.6 Hz), 1.74 (m, 2H, J = 7.8, 6.6 Hz), 1.46 (m, 2H, J = 7.8, 7.4 Hz), 0.95 (t, 3H, J = 7.4 Hz). ¹³C NMR (100 MHz, CDCl₃) δ(ppm) 171.4, 171.1, 168.1, 68.4, 30.6, 18.9, 13.7.

Synthesis of 4-chloro-6-(octyloxy)-1,3,5-traizin-2-amine (2d). Synthesis performed according to Method B; wherein reactant RXH corresponds to 1-octanol. The product was isolated by flash chromatographic column with a mixture 2:1 hexanes : diethyl Ether as eluent. Yield =3.31g, 36%. EI-HRMS: Calc. for C₁₁H₁₉ClN₄O: 258.1247, Found:
\[ ^1 \text{H NMR (400 MHz, DMSO-d}_6) = \delta(\text{ppm}) 7.97 \text{ (bs, 1H), 7.92 \text{ (bs, 1H), 4.23 (t, 2H, } J= 6.6 \text{ Hz), 1.65 (q, 2H, } J= 6.6 \text{ Hz), 1.48-1.22 (m, 10H), 0.85 (t, 3H, } J= 6.6 \text{ Hz).} \]

\[ ^{13} \text{C NMR (100 MHz, DMSO-d}_6) \delta(\text{ppm}) 170.3, 169.8, 168.0, 67.4, 32.5, 31.2, 28.6, 25.2, 22.0, 13.8. \]

**Synthesis of 4-chloro-6-(prop-2ynyloxy)-1,3,5-triazin-2-amine (2e).** Synthesis performed according to Method A; wherein reactant RXH is propargyl alcohol. The product was purified by flash chromatography with a mixture of 1:1 hexanes : diethyl ether as eluent. Yield = 5.26 g, 94%. EI-HRMS: Calc. for C\(_6\)H\(_5\)ClN\(_4\)O: 184.0152, Found: 185.0231. \[ ^1 \text{H NMR (400 MHz, DMSO-d}_6) \delta(\text{ppm}) 8.12 \text{ (bs, 2H), 4.95 (d, 2H, } J= 2.3 \text{ Hz), 3.64 (t, 1H, } J= 2.3 \text{ Hz).} \]

\[ ^{13} \text{C NMR (100 MHz, DMSO-d}_6) \delta(\text{ppm}) 169.9, 169.6, 167.9, 78.4, 78.2, 54.9. \]

**Synthesis of 4-chloro-6-(hexylthio)-1,3,5-triazin-2-amine (2f).** Synthesis performed according to Method C; wherein reactant RXH is 1-hexanethiol. Yield = 5.70 g, 76%. EI-HRMS: Calc. for C\(_9\)H\(_{15}\)ClN\(_4\)S: 246.0706, Found: 246.0707. \[ ^1 \text{H NMR (400 MHz, CDCl}_3) \delta(\text{ppm}) 5.40 \text{ (bs, 2H), 3.09 (t, 2H, } J= 7.4 \text{ Hz), 1.70 (q, 2H, } J= 7.8, 7.0 \text{ Hz), 1.47-1.39 (m,} \]

\[ \text{Synthesis of 4-chloro-6-(prop-2ynyloxy)-1,3,5-triazin-2-amine (2e).} \]

\[ \text{Synthesis of 4-chloro-6-(hexylthio)-1,3,5-triazin-2-amine (2f).} \]
2H), 1.33-1.29 (m, 4H), 0.90 (t, 3H, J = 7.0 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) δ(ppm) 184.0, 169.0, 165.4, 31.2, 30.4, 28.8, 28.4, 22.5, 14.0.

**Synthesis of 4,6-diiodotriazin-2-amine (2h).** Synthetic procedure based on procedure reported by Smith and coworkers$^{47}$. In a round bottom flask provided with a stir bar, 1 eq. of 4,6-dichlorotriazin-2-amine (5.00 g, 30.31 mmol) dissolved in CH$_2$Cl$_2$ and 2 eq. of hydroiodic acid 67% (12.73 mL, 60.67 mmol) were stirred overnight at room temperature. The reaction mixture was treated with a saturated aqueous solution of NaHCO$_3$ until pH=7. The product was filtered from the reaction mixture and washed with water. Yield = 4.38 g, 42%. EI-HRMS: Calc. for C$_3$H$_2$I$_2$N$_4$: 347.8369, Found: 347.8370. $^1$H NMR (400 MHz, DMSO-d$_6$) δ(ppm) 8.20.

**Synthesis of 4-chloro-6-phenoxy-1,3,5-triazin-2-amine (2i).** Synthesis performed according to Method C; wherein reactant RXH is phenol. Yield = 6.70 g, 99% EI-HRMS: Calc. for C$_9$H$_7$ClN$_4$O: 222.0308, Found: 222.0305. $^1$H NMR (400 MHz, CDCl$_3$) δ(ppm) 7.43 (m, 2H.), 7.30 (m, 1H), 7.16 (m, 2H), 5.68 (bs, 1H), 5.51 (bs, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ(ppm) 172.0, 171.2, 168.3, 151.5, 129.6, 126.2, 121.5.
Synthesis of 4-chloro-6-(4-nitrophenoxy)-1,3,5-triazin-2-amine (2j). Synthesis performed according to Method C; wherein reactant RXH is 4-nitrophenol. Yield = 7.26 g, 97%. EI-HRMS: Calc. for C9H6ClN5O3: 267.0159, Found: 267.0152. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\)(ppm) 8.32 (m, 2H), 8.17 (bs, 1H), 8.24 (bs, 1H), 7.56 (m, 2H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\)(ppm) 170.2, 169.9, 168.1, 156.4, 145.0, 125.4, 123.2.

Synthesis of 4-(4-tert-butylphenoxy)-6-chloro-1,3,5-triazin-2-amine (2k). Synthesis performed according to Method A; wherein reactant RXH is 4-tert-butylphenol. Yield = 4.98 g, 59%. EI-HRMS: Calc. for C\(_{13}\)H\(_{15}\)ClN\(_4\)O: 278.0934, Found: 278.0931. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\)(ppm) 7.42 (m, 2H), 7.07 (m, 2H), 5.91 (bs, 1H), 5.72 (bs, 1H), 1.34 (s, 9H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\)(ppm) 170.1, 168.2, 149.3, 148.0, 126.3, 121.0, 114.6, 34.2, 31.2.

Synthesis of 4-chloro-6-(3-(trifluoromethyl)phenoxy)-1,3,5-triazin-2-amine (2l). Synthesis performed according to Method A; wherein reactant RXH is 3-
(trifluoromethyl)phenol. Yield = 7.70 g, 87%. EI-HRMS: Calc. for C_{10}H_{6}ClF_{3}N_{4}O: 290.0182, Found: 290.0177. \(^1\)H NMR (600 MHz, DMSO-d\(_6\)) \(\delta\) (ppm) 8.16 (bs, 1H), 8.12 (bs, 1H), 7.70-7.65 (m, 3H), 7.59 (m, 1H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) (ppm) 170.3, 170.1, 168.1, 151.9, 131.0, 130.2, 126.3, 122.7, 122.3, 119.0. \(^{19}\)F NMR (376 MHz, DMSO-d\(_6\)) \(\delta\) (ppm) -60.99.

Synthesis of 4-(3,5-bis(trifluoromethyl)phenoxy)-6-chloro-1,3,5-triazin-2-amine (2m). Synthesis performed according to Method A; wherein reactant RXH is 3,5-bis(trifluoromethyl)phenol. Yield = 10.72 g, 96%. EI-HRMS: Calc. for C_{11}H_{5}ClF_{6}N_{4}O: 358.0056, Found: 358.0053. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) (ppm) 8.24 (bs, 1H), 8.16 (s, 1H), 7.97 (s, 2H), 7.93 (bs, 1H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) (ppm) 171.2, 170.2, 168.1, 167.1, 152.6, 131.5, 131.4, 124.1, 123.6, 121.4, 109.6. \(^{19}\)F NMR (376 MHz, DMSO-d\(_6\)) \(\delta\) (ppm) -61.31, -61.55.

Synthesis of 4-chloro-6-(perfluorophenoxy)-1,3,5-triazin-2-amine (2n). Synthesis performed according to Method A; wherein reactant RXH is perfluorophenol. Yield = 8.72 g, 92%. EI-HRMS: Calc. for C_{9}H_{2}ClF_{5}N_{4}O: 311.9837, Found: 311.9847. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 6.07 (bs, 1H), 5.76 (bs, 1H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\))
δ(ppm) 173.7, 170.3, 169.3, 165.8, 158.5, 154.2, 148.0. $^{19}$F NMR (376 MHz, CDCl$_3$) δ(ppm) -152.55 (d, 2H, $J = 17.2$ Hz), -157.48 (t, 1H, $J = 22.4$ Hz), -162.01 (dd, 2H, $J = 22.4, 17.2$).

Synthesis of 4-(benzyloxy)-6-chloro-1,3,5-triazin-2-amine (2o). Synthesis performed according to **Method B**; wherein reactant RXH corresponds to benzyl alcohol. Yield = 7.10 g, 99%. EI-HRMS: Calc. for C$_{10}$H$_9$N$_4$O: 236.0465, Found: 236.0463. $^1$H NMR (400 MHz, DMSO-d$_6$) δ(ppm) 8.03 (bs, 1H), 8.00 (bs, 1H), 7.45-7.35 (m, 5H), 5.33 (s,2H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ(ppm) 170.2, 170.0, 168.1, 135.7, 128.5, 128.3, 68.8.

Synthesis of 4-chloro-6-(4-tritylphenoxy)-1,3,5-triazin-2-amine (2p). Synthesis performed according to **Method A**; wherein reactant RXH is 4-tritylphenol. Yield = 10.0 g, 71%. EI-HRMS: Calc. for C$_{28}$H$_{21}$N$_4$O: 461.1546, Found: 461.1408. $^1$H NMR (400 MHz, DMSO-d$_6$) δ(ppm) 8.20 (bs, 2H), 7.34-7.16 (m, 19H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ(ppm) 168.1, 146.3, 131.6, 130.4, 127.8, 126.1, 120.7, 64.1.
Synthesis of 2-hydrazinylpyridine. Synthetic procedure as based on the procedure reported by Klingele and coworkers.\textsuperscript{48} A mixture of 2-fluoropyridine (8.86 mL, 103 mmol, 1 eq.) and hydrazine monohydrate (50.20 mL, 1030 mmol, 10 eq.) was refluxed for 6 hours. After cooling down the reaction mixture to room temperature 100 mL of NaOH 1M aqueous solution was added and the crude was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried with MgSO\textsubscript{4} and the solvent was removed under reduced pressure to get pure product. Yield = 10.5 g, 94%. EI-HRMS; Calc. for C\textsubscript{5}H\textsubscript{7}N\textsubscript{3}: 109.0640, Found: 109.0637. \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}): \(\delta\) (ppm) 8.12 (dd, 1H, 5.1, 0.8 Hz), 7.48 (ddd, 1H, 8.6, 7.0, 1.5 Hz), 6.69 (d, 1H, J=8.6 Hz), 6.67 (ddd, 1H, J=7.0, 5.1, 0.8 Hz), 5.82 (bs, 1H), 3.77 (bs, 2H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) (ppm) 161.1, 147.3, 137.1, 113.8, 106.6.

General procedure for synthesis of 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivatives (3a-p)

In a round bottom flask 4-chloro-1,3,5-triazin-2-amine derivative (2) (1 eq.), potassium carbonate (1 eq.) and 2-hydrazinopyridine (1 eq.) were dissolved in THF and the reaction mixture was refluxed overnight. The solvent was removed via reduced pressure and the crude was washed with distilled water to then filter the crude by vacuum filtration. The product was purified by flash chromatography using diethyl ether as eluent.
Synthesis of 4-(piperidin-1-yl)-6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3a). Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2a. Yield = 1.60 g, 32%. EI-HRMS: Calc. for C_{13}H_{18}N_{8}: 286.1654, Found: 286.1650. ¹H NMR (400 MHz, CDCl₃) δ(ppm) 8.14 (d, 1H, J = 4.7 Hz), 7.49 (dd, 1H, J = 8.2, 8.2 Hz), 6.89 (bs, 1H), 6.79 (d, 1H, J = 8.2 Hz), 6.74 (dd, 1H, J = 5.9, 5.9 Hz), 5.01 (bs, 2H), 3.60 (m, 4H), 1.91 (bs, 1H), 1.57-1.45 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ(ppm) 167.1, 164.8, 147.7, 137.9, 115.9, 110.0, 107.3, 44.1, 25.7, 24.8.

Synthesis of 4-methoxy-6-(2-(pyridine-2-yl)hydrazinyl)--1,3,5-triazin-2-amine (3b). Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2b. Yield = 3.20 g, 55%. EI-HRMS: Calc. for C_{9}H_{11}N_{7}O: 233.1025, Found: 233.1022. ¹H NMR (400 MHz, DMSO-d₆) δ(ppm) 8.90 (bs, 1H), 8.28 (bs, 1H), 8.01 (d, 1H, J = 4.3 Hz), 7.47 (dd, 1H, J = 7.8, 7.8 Hz), 6.85 (bs, 2H), 6.64 (dd, 1H, J = 6.0, 6.0 Hz), 6.50 (d, 1H, J = 7.8 Hz), 3.77 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ(ppm) 147.5, 137.3, 113.9, 105.7, 53.4.
Synthesis of 4-butoxy-6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3c). Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2c. Yield = 7.87 g, 95%. EI-HRMS: Calc. for C_{12}H_{17}N_{7}O: 275.1495, Found: 275.1487. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$(ppm) 8.19 (bs, 2H), 7.98 (d, 1H, $J$ = 3.9 Hz), 7.50 (dd, 1H, $J$ = 8.2, 7.4 Hz), 6.78 (d, 1H, $J$ = 8.2 Hz), 6.70 (dd, 1H, $J$ = 6.2, 6.2 Hz), 6.29 (bs, 2H), 4.10 (t, 2H, $J$ = 6.6 Hz), 1.53 (m, 2H), 1.29 (m, 2H), 0.84 (t, 3H, $J$ = 7.0 Hz). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$(ppm) 170.4, 169.3, 168.5, 160.0, 147.5, 137.3, 113.9, 105.7, 65.3, 30.4, 18.6, 13.6.

Synthesis of 4-(octyloxy)-6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3d). Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2d. Yield = 6.77 g, 58%. EI-HRMS: Calc. for C$_{16}$H$_{25}$N$_7$O: 331.2121, Found: 331.2122. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$(ppm) 8.02 (d, 1H, $J$ = 4.7 Hz), 7.48 (dd, 1H, $J$ = 7.0, 7.0 Hz), 6.69-6.74 (m, 2H), 5.89 (bs, 2H), 4.11 (t, 2H), 1.56 (m, 2H), 1.29 (m, 10H), 0.86 (t, 3H, $J$ = 7.0 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$(ppm) 176.0, 169.0, 159.6, 159.4, 138.7, 115.5, 115.4, 107.0, 67.3, 31.8, 29.2, 29.1, 28.6, 25.8, 22.6, 14.0.
Synthesis of 4-(prop-2-ynyloxy)-6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3e). Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2e. Yield = 6.38 g, 87 %. EI-HRMS: Calc. for C_{11}H_{11}N_{7}O: 257.1025, Found: 257.1033. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\)(ppm) 9.00 (bs, 1H), 8.32 (bs, 1H), 8.02 (d, 1H, J = 4.7 Hz), 7.48 (dd, 1H, J = 8.2, 8.2 Hz), 6.96 (bs, 2H), 6.64 (d, 1H, J = 5.9 Hz), 6.49 (d, 1H, J = 8.2 Hz), 4.88 (s, 2H), 4.75 (s, 1H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\)(ppm) 169.3, 168.5, 159.8, 147.4, 137.4, 114.0, 105.8, 79.8, 77.3, 53.2.

Synthesis of 4-(hexylthio)-6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3f). Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2f. Yield = 1.77 g, 24%. EI-HRMS: Calc. for C_{14}H_{21}N_{7}S: 319.1579, Found: 319.1578. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\)(ppm) 8.01 (bs, 1H), 7.96 (m, 1H), 7.42 (m, 1H), 7.35 (bs, 1H), 6.68 (m, 1H), 6.52 (m, 2H), 4.07 (t, 2H, J = 7.4 Hz), 1.64 (m, 2H), 1.37 (m, 2H), 1.27 (m, 4H), 0.86 (t, 3H, J = 7.0 Hz). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\)(ppm) 178.6, 169.3, 166.6, 159.8, 147.4, 137.4, 114.0, 105.8, 36.8, 30.9, 29.2, 27.9, 22.1, 13.9.
Synthesis of 4-chloro-6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3g). In a round bottom flask, 4,6-dichlorotriazin-2-amine (1) (5.00 g, 30.3 mmol, 1 eq.) was dissolved in THF. The solution was cooled down to -78°C and potassium carbonate (4.19 g, 30.3 mmol, 1 eq.) and 2-hydrazinopyridine (3.30 g, 30.3 mmol, 1 eq.) were added. The reaction mixture was stirred overnight allowing it to reach room temperature. The solvent was removed from the reaction mixture under reduced pressure and washed with distilled water. The product was filtered and dried by vacuum filtration. Yield = 7.13 g, 99%. EI-HRMS: Calc. for C_{8}H_{8}ClN_{7}: 237.0530, Found: 237.0526. ^1H NMR (400 MHz, DMSO-d$_{6}$) δ(ppm) 9.00 (bs, 1H), 8.60 (bs, 1H), 8.07 (dd, 1H, $J = 7.8$, 7.8 Hz), 7.99 (d, 1H, $J = 5.6$ Hz), 7.73 (bs, 2H), 7.29 (d, 1H, $J = 8.6$ Hz), 7.05 (t, 1H, $J = 6.6$ Hz). ^13C NMR (100 MHz, DMSO-d$_{6}$) δ(ppm) 174.4, 169.2, 168.0, 153.9, 147.4, 139.7, 127.9, 115.5.

Synthesis of 4-iodo-6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3h). 4,6-diiodotriazin-2-amine (2h) (4.38 g, 12.6 mmol, 1 eq.) was dissolved in THF. The solution was cooled down to -78°C and 2-hydrazinopyridine (1.37 g, 12.6 mmol, 1 eq.) and potassium carbonate (1.74 g, 12.6 mmol, 1 eq.) were added. The reaction mixture was stirred overnight allowing it to reach room temperature. The solvent was removed under
reduced pressure and the crude was washed with distilled water. The product was finally filtered and dried by vacuum filtration. Yield = 3.81 g, 92%. Intermediate 3h was not characterized since it was immediately taken into the oxidation step.

Synthesis of 4-phenoxy-6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3i).
Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2i. Yield = 5.19 g, 58%. EI-HRMS: Calc. for C_{14}H_{13}N_{7}O: 295.1182 Found: 295.1181. ^1H NMR (400 MHz, DMSO-d_{6}) δ(ppm) 9.06 (bs, 1H), 8.32 (bs, 1H), 8.02 (m, 1H), 7.00 – 7.50 (m, 9H), 6.64 (m, 1H), 6.52 (m, 1H). ^13C NMR (100 MHz, DMSO-d_{6}) δ(ppm) 170.4, 169.4, 168.7, 152.4, 147.5, 137.4, 129.4, 125.0, 122.0, 121.6, 114.0, 105.8.

Synthesis of 4-(4-nitrophenoxy)-6-(2-(pyridin-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3j). Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2j. Yield = 2.70 g, 42%. EI-HRMS: Calc. for C_{14}H_{12}N_{8}O_{3}: 340.1032 Found: 340.1028. ^1H NMR (400 MHz, DMSO-d_{6}) δ(ppm) 9.18 (bs, 1H), 8.29 (m, 2H), 8.09 (d, 1H, J = 9.0 Hz), 8.02 (1H, d, J = 4.7 Hz), 7.49 (m, 2H), 7.22
(d, 1H, \( J = 9.0 \) Hz), 7.13 (bs, 2H), 6.68 (m, 1H), 6.51 (d, 1H, \( J = 8.6 \) Hz). \(^{13}\)C NMR (400 MHz, DMSO-\( d_6 \)) \( \delta \) (ppm) 169.3, 168.6, 159.6, 157.6, 147.6, 144.3, 137.4, 125.2, 123.0, 114.0, 105.8.

Synthesis of 4-(4-tert-butylphenoxy)-6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3k). Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2k. Yield = 4.99 g, 99%. EI-HRMS: Calc. for C\(_{19}\)H\(_{22}\)N\(_7\)O: 351.1808 Found: 351.1808. \(^1\)H NMR (400 MHZ, DMSO-\( d_6 \)) \( \delta \) (ppm) 9.04 (bs, 1H), 8.33 (bs, 1H), 8.02 (m, 1H), 7.49 (m, 1H), 7.41 (m, 2H, \( J = 8.2 \) Hz), 7.08 (m, 2H), 6.99 (bs, 2H), 6.72-6.62 (m, 1H), 6.51 (m, 1H), 1.29 (s, 9H). \(^{13}\)C NMR (100 MHz, DMSO-\( d_6 \)) \( \delta \) (ppm) 170.6, 169.4, 168.0, 159.8, 150.0, 147.4, 137.4, 126.1, 125.8, 121.2, 120.8, 114.0, 113.9, 105.9, 105.8, 34.1, 31.2.

Synthesis of 4-(2-(pyridine-2-yl)hydrazinyl)-6-(3-(trifluoromethyl)phenoxy)-1,3,5-triazin-2-amine (3l). Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2l. Yield = 5.00 g, 80%. EI-HRMS: Calc. for C\(_{15}\)H\(_{12}\)F\(_3\)N\(_7\)O: 363.1055 Found: 363.1056. \(^1\)H NMR (400 MHZ, DMSO-
1H NMR (400 MHz, DMSO-d6) δ(ppm) 9.16 (bs, 1H), 8.37 (bs, 1H), 7.89-8.05 (m, 4H), 7.49 (dd, 1H, $J = 7.8, 7.8$ Hz), 7.25 (bs, 1H), 7.11 (bs, 1H), 6.64 (ddd, 1H, $J=7.0, 5.1, 0.8$ Hz) 6.50 (d, 1H, $J=8.2$ Hz). 13C NMR (100 MHz, DMSO-d6) δ(ppm) 170.7, 169.3, 159.7, 153.4, 147.6, 137.4, 131.6, 123.9, 121.6, 118.9, 114.0, 105.8. 19F NMR (376 MHz, DMSO-d6) δ(ppm) -61.18.

**Synthesis of 4-(3,5-bis(trifluoromethyl)phenoxy)-6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3m).** Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2m. Yield = 3.13 g, 52%. EI-HRMS: Calc. for C16H11F6N7O: 431.0929 Found: 431.0931. 1H NMR (400 MHz, DMSO-d6) δ(ppm) 9.16 (bs, 1H), 8.37 (bs, 1H), 7.89-8.05 (m, 4H), 7.49 (dd, 1H, $J = 7.8, 7.8$ Hz), 7.25 (bs, 1H), 7.11 (bs, 1H), 6.64 (ddd, 1H, $J=7.0, 5.1, 0.8$ Hz) 6.50 (d, 1H, $J=8.2$ Hz). 13C NMR (100 MHz, DMSO-d6) δ(ppm) 170.7, 169.3, 159.7, 153.4, 147.6, 137.4, 131.6, 123.9, 121.6, 118.9, 114.0, 105.8. 19F NMR (376 MHz, DMSO-d6) δ(ppm) -61.18.

**Synthesis of 4-(perfluorophenoxy)-6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3n).** Synthesis performed according to general procedure for intermediate 3;
wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2n. The product was filtered by vacuum filtration and isolated via flash chromatography starting from mixture of hexanes: diethyl ether 1:1 to 100% diethyl ether as eluent. Yield = 2.46 g, 40%. EI-HRMS: Calc. for C_{14}H_{8}F_{5}N_{7}O: 385.0710 Found: 385.0721. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\)(ppm) 9.32 (bs, 1H), 9.24 (bs, 1H), 8.39 (bs, 1H), 8.11 (bs, 1H), 8.02 (d, 1H, \(J = 4.0\) Hz), 7.92 (d, 1H, \(J = 4.0\) Hz), 7.41-7.51 (m, 3H), 7.20-7.30 (m, 3H), 6.64 (q, 2H, \(J = 12.1, 5.5\) Hz), 6.50 (d, 1H, \(J = 8.2\) Hz), 6.38 (d, 1H, \(J = 8.2\) Hz). \(^1^9\)F NMR (376 MHz, DMSO-d\(_6\)) \(\delta\)(ppm) -153.94 (d, 1F, \(J = 20.6\) Hz), -154.42 (d, 1F, \(J = 20.6\) Hz), -160.03 (t, 1/2F, \(J = 22.4, 20.6\) Hz), -160.72 (t, 1/2F, \(J = 22.4, 20.6\) Hz), -163.38 (t, 2F, \(J = 22.4\) Hz).

Synthesis of 4-(benzyloxy)-6-(2-(pyridin-2-yl)hydrazinyl)-1,3,5-triazin-2-amine (3o).

Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2o. The product was filtered by vacuum filtration and purified via flash chromatography using a mixture of ethyl acetate and 10% methanol as eluent. Yield = 5.20 g, 56%. EI-HRMS: Calc. for C\(_{15}\)H\(_{15}\)N\(_7\)O: 309.1338 Found: 309.1337. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\)(ppm) 8.94 (bs, 1H), 8.28 (m, 1H), 8.03 (m, 1H), 7.48-7.26 (m, 5H), 6.87 (m, 1H), 6.65 (bs, 1H), 5.32 (s, 2H), 5.29 (bs, 1H), 5.14 (bs, 1H). \(^1^3\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\)(ppm) 171.5, 169.3, 168.5, 147.5, 137.3, 136.4, 128.4, 128.0, 127.8, 113.9, 105.7, 66.9.
Synthesis of 4-(2-(pyridin-2-yl)hydrazinyl)-6-(4-tritylphenoxy)-1,3,5-triazin-2-amine (3p). Synthesis performed according to general procedure for intermediate 3; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is (2p). The product was filtered by vacuum filtration and purified via flash chromatography using a mixture of ethyl acetate and 10% methanol as eluent. Yield = 4.93g, 38%. EI-HRMS: Calc. for C_{33}H_{27}N_{7}O: 537.2277 Found: 537.2266. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$(ppm) 9.05(bs, 1H), 8.31 (m, 1H), 8.02 (m, 1H), 6.45-7.49 (m, 24H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$(ppm) 170.3, 169.4, 168.7, 168.2, 147.5, 146.4, 137.3, 131.4, 130.5, 127.8, 126.0, 120.9, 120.2, 113.9, 106.2, 105.8, 64.1.

General procedure for synthesis of (E)-4-(pyridin-2-yldiazenyl)-1,3,5-triazin-2-amine derivatives (4a-p)

Synthetic procedure based on a report by Iranpoor and coworkers 49. In a round bottom flask, intermediate 3 (1 eq.) was dissolved in 50 mL of THF and stirred at room temperature. Iodobenzene diacetate (1 eq.) was added at once and the solution was stirred for 6 hours at room temperature. The solvent was removed under reduced pressure and the crude was washed with 50 mL of distilled water. The product was purified by flash chromatography starting with diethyl ether and ending with ethyl acetate as eluents. Note: The chemical shift of the amino protons of derivatives 4a-p are concentration sensitive.
The amino protons chemical shift reported below correspond to the average values of the monomer shift, dimer shift obtained from three separate dilution experiments obtained using an iterative fitting procedure.

Synthesis of \((E)-4\text{-}(\text{piperidin-1-yl})\text{-}6\text{-}(\text{pyridin-2-yl)diazenyl})\text{-}1,3,5\text{-triazin-2-amine}\) (4a). Synthesis performed according to the general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3a. Yield = 1.36 g, 73%. EI-HRMS: Calc. for C\(_{13}\)H\(_{18}\)N\(_8\) (M+2H): 286.1654 Found: 286.1645. \(^1\)H NMR (400 MHz, CDCl\(_3\)) = \(\delta\) (ppm) 8.78 (dd, 1H, \(J = 4.7, 1.6\) Hz), 7.87-7.94 (m, 2H), 7.47 (ddd, 1H, \(J = 6.6, 4.7, 2.0\) Hz), 6.92 (bs, 2H)**, 5.14 (bs, 2H)*, 3.88-3.82 (m, 4H), 1.70-1.60 (m, 6H) *NH\(_2\) of free monomer, **NH\(_2\) of dimer. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) = \(\delta\) (ppm) 174.0, 168.0, 165.5, 162.6, 149.7, 138.3, 126.5, 116.0, 44.6, 25.8, 24.7. Melting Point = 206.9 - 209.1 C.

Synthesis of \((E)-4\text{-}\text{methoxy-6-(pyridin-2-yl)diazenyl})\text{-}1,3,5\text{-triazin-2-amine}\) (4b). Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3b. Yield = 2.88 g, 90%. EI-
HRMS: Calc. for C_9H_{10}N_7O (M+1H): 232.0947 Found: 232.0952. ^1^H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.12 (ddd, 1H, J = 7.8, 7.4, 2.0 Hz), 7.99 (bs, 1H), 8.02 (bs, 1H), 7.78 (d, 1H, J = 7.8 Hz), 7.68 (ddd, 1H, J = 7.4, 4.7, 1.2 Hz), 3.92 (s, 1H). ^13^C NMR (100 MHz, DMSO-d_6) = δ (ppm) 175.9, 171.9, 169.0, 162.1, 149.8, 139.4, 127.3, 114.8, 54.7. Melting Point = 210.6 - 211.1 C.

Synthesis of (E)-4-butoxy-6-(pyridin-2-yldiazenyl)-1,3,5-triazin-2-amine (4c).

Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3c. Yield = 1.88 g, 38%. EI-HRMS: Calc. for C_{12}H_{17}N_7O (M+2H): 275.1495 Found: 275.1489. ^1^H NMR (400 MHz, CDCl_3) = δ (ppm) 8.82 (dd, 1H, J = 4.7, 1.6 Hz), 8.76 (bs, 1H)**, 7.89-7.97 (m, 2H), 7.52 (ddd, 1H, J = 7.0, 4.7, 1.6 Hz), 6.80 (bs, 1H)**, 5.49 (bs, 2H)*, 4.47 (t, 2H, J = 6.6 Hz), 1.79 (m, 2H, J = 6.6 Hz), 1.50 (m, 2H, J = 7.4 Hz), 0.97 (t, 3H, J = 7.4 Hz) *NH of free monomer, **NH of dimer. ^13^C NMR (100 MHz, CDCl_3) = δ (ppm) 175.1, 172.5, 169.3, 162.3, 149.9, 138.5, 127.0, 115.3, 68.2, 30.7, 19.0, 13.7. Melting Point = 131.4 - 134.7 C.
Synthesis of \((E)-4\text{-}(octyloxy)\text{-}6\text{-}(pyridin-2-yl)diazan}-1,3,5\text{-}triazin-2\text{-}amine \((4d)\). Synthesis performed according to general procedure for product \(4\); wherein the \(6\text{-}(2\text{-}(pyridine-2\text{-}yl)hydrazinyl)\text{-}1,3,5\text{-}triazin-2\text{-}amine\) derivative is \(3d\). Yield = 2.57 g, 38%. Ei-HRMS: Calc. for \(C_{16}H_{25}N_{7}O\) (M+2H): 331.2121 Found: 331.2111. \(^1\)H NMR (600 MHz, CDCl\(_3\)) = \(\delta\) (ppm) 8.80 (dd, 1H, \(J = 4.7, 1.8\) Hz), 8.78 (bs, 1H)**, 7.97-7.92 (m, 2H), 7.50 (ddd, 1H, \(J = 6.4, 4.7, 1.8\) Hz), 6.78 (bs, 1H)**, 5.54 (bs, 1H)*, 5.50 (bs, 1H)*, 1.80 (dd, 2H, \(J = 7.6, 6.4\) Hz), 1.45 (m, 2H, \(J = 7.6\) Hz), 1.35-1.25 (m, 8H), 0.88 (t, 3H, \(J = 7.6\) Hz) * NH of free monomer ** NH of dimer. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) = \(\delta\) (ppm) 174.5, 172.4, 169.2, 162.2, 149.9, 138.4, 127.0, 114.1, 68.3, 31.7, 29.2, 29.1, 28.6, 25.8, 22.6, 14.0. Melting Point = 121.6 - 123.2 C.

Synthesis of \((E)-4\text{-}(prop-2-ynyloxy)\text{-}6\text{-}(pyridin-2-yl)diazan}-1,3,5\text{-}triazin-2\text{-}amine \((4e)\). Synthesis performed according to general procedure for product \(4\); wherein the \(6\text{-}(2\text{-}(pyridine-2\text{-}yl)hydrazinyl)\text{-}1,3,5\text{-}triazin-2\text{-}amine\) derivative is \(3e\). Yield = 0.23 g, 23%. Ei-HRMS: Calc. for \(C_{11}H_{9}N_{7}O\): 255.0869 Found: 255.0862. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) = \(\delta\) (ppm) 8.78 (dd, 1H, \(J = 4.7, 2.0\) Hz), 8.13 (ddd, 1H, \(J = 7.8, 7.4, 2.0\) Hz), 8.11 (bs, 1H), 8.06 (bs, 1H), 7.79 (dd, 1H, \(J = 7.8, 1.2\) Hz), 7.70 (ddd, 1H, \(J = 7.4, 4.7, 1.2\) Hz), 5.04 (d,
2H, J = 2.3 Hz), 3.62 (t, 1H, J = 2.3 Hz). $^{13}$C NMR (100 MHz, DMSO-d$_6$) = δ (ppm) 175.9, 170.7, 169.0, 162.0, 149.8, 139.4, 127.4, 115.0, 78.2, 54.7.

**Synthesis of (E)-4-(hexylthio)-6-(pyridin-2-yldiazenyl)-1,3,5-triazin-2-amine (4f).**

Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3f. Yield = 1.36 g, 77 %. EI-HRMS: Calc. for C$_{14}$H$_{19}$N$_7$: 317.1423 Found: 317.1414. $^1$H NMR (600 MHz, CDCl$_3$) = δ (ppm) 8.80 (d, 1H, J = 4.7 Hz), 8.67 (bs, 1H)**, 7.96-7.91 (m, 2H), 7.51 (dd, 1H, J = 7.0, 4.7 Hz), 6.80 (bs, 1H)**, 5.48 (bs, 1H)*, 5.38 (bs, 1H)*, 3.20 (t, 2H, J = 7.6 Hz), 1.74 (m, 2H, J = 7.6 Hz), 1.45 (m, 2H, J = 7.0), 1.33-1.30 (m, 4H), 0.89 (t, 3H, J = 7.0 Hz) *NH of free monomer, **NH of dimer. $^{13}$C NMR (100 MHz, CDCl$_3$) = δ (ppm) 184.5, 171.7, 166.5, 162.3, 149.9, 138.5, 127.1, 114.6, 31.3, 30.4, 28.9, 28.4, 22.5. Melting Point = 131.1 - 132.5 C

**Synthesis of (E)-4-chloro-6-(pyridin-2-yldiazenyl)-1,3,5-triazin-2-amine (4g).**

Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3g. Yield = 1.22 g, 24 %. EI-
HRMS: Calc. for C₈H₇ClN₇ (M+1H): 236.0451 Found: 236.0460. ¹H NMR (400 MHz, DMSO-d₆) = δ (ppm) 8.80 (d, 1H, J = 4.7 Hz), 8.62 (bs, 1H), 8.60 (bs, 1H), 8.14 (m, 1H, J = 7.8, 2.0 Hz), 7.82 (d, 1H, J = 8.2 Hz), 7.72 (ddd, 1H, J = 7.4, 4.7, 1.2 Hz). ¹³C NMR (100 MHz, DMSO-d₆) = δ (ppm) 174.4, 170.5, 168.0, 161.9, 149.9, 139.5, 127.7, 115.4.

Synthesis of (E)-4-iodo-6-(pyridin-2-yldiazenyl)-1,3,5-triazin-2-amine (4h). Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3h. Yield = 0.74 g, 25%. EI-HRMS: Calc. for C₈H₅I₇N (M+2H): 328.9886 Found: 328.9887. ¹H NMR (400 MHz, DMSO-d₆) = δ (ppm) 8.79 (dd, 1H, J = 4.7, 1.6 Hz), 8.46 (bs, 1H), 8.37 (bs, 1H), 8.14 (ddd, 1H, J = 7.8, 7.4, 1.6 Hz), 7.80 (d, 1H, J = 8.2 Hz), 7.71 (ddd, 1H, J = 7.4, 4.7, 1.2 Hz). ¹³C NMR (100 MHz, DMSO-d₆) = δ (ppm) 165.7, 161.9, 154.9, 149.9, 142.9, 139.4, 127.6, 115.1. Melting Point = >300°C.

Synthesis of (E)-4-phenoxy-6-(pyridin-2-yldiazenyl)-1,3,5-triazin-2-amine (4i). Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3i. Yield = 4.20 g, 81%. EI-
HRMS: Calc. for C_{14}H_{13}N_{7}O (M+2H): 295.1182 Found: 295.1184. ^1^H NMR (400 MHz, CDCl3)= δ (ppm) 8.78 (d, 1H, J = 4.7 Hz), 8.05 (bs, 1H)**, 7.97-7.90 (m, 2H), 7.5 (ddd, 1H, J = 5.1, 4.7, 2.0 Hz), 7.45-7.41 (m, 2H), 7.30-7.23 (m, 3H), 6.77 (bs, 1H)**, 5.63 (bs, 1H)*, 5.55 (bs, 1H)* *NH of free monomer, **NH of dimer. ^13^C NMR (100 MHz, DMSO-d_6) = δ (ppm) 176.1, 171.7, 169.2, 162.0, 151.8, 149.8, 139.4, 129.7, 127.4, 125.7, 121.8, 115.1. Melting Point = 208 - 212 C.

**Synthesis of (E)-4-(4-nitrophenoxy)-6-(pyridin-2-yldiazenyl)-1,3,5-triazin-2-amine (4j).** Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3j. Yield = 2.38 g, 89%. EI-HRMS: Calc. for C_{14}H_{12}N_{8}O_{3} (M+2H): 340.1032 Found: 340.0991. ^1^H NMR (600 MHz, DMSO-d_6) = δ (ppm) 8.77 (dd, 1H, J = 4.7, 1.2 Hz) 8.33 (m, 2H), 8.26 (bs, 1H), 8.17 (bs, 1H), 8.12 (m, 1H, J = 7.6, 1.8 Hz), 7.62 (m, 2H), 7.78 (d, 1H, J = 7.6 Hz), 7.69 (ddd, 1H, J = 7.6, 4.7, 1.2 Hz). ^13^C NMR (100 MHz, DMSO-d_6) = δ (ppm) 178.5, 171.1, 169.1, 161.9, 156.7, 149.8, 144.9, 139.4, 125.4, 123.2, 115.2, 109.5.
Synthesis of (E)-4-(4-tert-butylyphenoxy)-6-(pyridin-2-yldiazenyl)-1,3,5-triazin-2-amine (4k). Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3k. Yield = 0.44 g, 11%. EI-HRMS: Calc. for C_{18}H_{21}N_{7}O (M+2H): 351.1808, Found: 351.1818. \(^1\)H NMR (600 MHz, CDCl\(_3\)) = \(\delta\) (ppm) 8.78 (d, 1H, \(J = 4.1\) Hz), 8.04 (bs, 1H)***, 7.94-7.89 (m, 2H), 7.50 (dd, 1H, \(J = 5.9, 5.3\) Hz), 7.42 (m, 2H), 7.16 (m, 2H), 6.70 (bs, 1H)***, 5.56 (bs, 1H)*, 5.53 (bs, 1H)*, 1.34 (s, 9H), *NH of free monomer, **NH of dimer. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) = \(\delta\) (ppm) 175.2, 172.6, 169.3, 162.2, 149.9, 149.5, 148.7, 138.5, 127.1, 126.4, 121.0, 115.1, 34.5, 31.4. Melting Point = 171.3 - 173.1 C.

Synthesis of (E)-4-(pyridin-2-yldiazenyl)-6-(3-(trifluoromethyl)phenoxy)-1,3,5-triazin-2-amine (4l). Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3l. Yield = 1.10 g, 22%. EI-HRMS: Calc. for C_{15}H_{12}F_{3}N_{7}O (M+2H): 363.1055, Found: 363.1049. \(^1\)H NMR (600 MHz, CDCl\(_3\)) = \(\delta\) (ppm) 8.67 (bs, 1H)**, 8.79 (d, 1H, \(J = 4.7\) Hz), 7.98-7.90 (m, 2H), 7.56-7.50 (m, 4H), 7.46-7.42 (m, 1H), 6.80 (bs, 1H)***, 5.57 (bs, 1H)*, 5.68 (bs, 1H)*, 1.34 (s, 9H), *NH of free monomer, **NH of dimer. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) = \(\delta\) (ppm)
175.4, 172.2, 169.4, 162.1, 151.9, 150.0, 138.6, 132.2, 131.9, 130.1, 127.3, 125.4, 122.7, 119.1, 115.5. \(^{19}\)F NMR (376.42 MHz, CDCl\(_3\)) = \(\delta\) (ppm) -62.6. Melting Point = 170.2 - 172.4 C.

Synthesis of (E)-4-(3,5-bis(trifluoromethyl)phenoxy)-6-(pyridin-2-yl)diazetyl)-1,3,5-triazin-2-amine (4m). Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3m. Yield = 1.94 g, 62%. EI-HRMS: Calc. for C\(_{16}\)H\(_{11}\)F\(_{6}\)N\(_7\)O (M+2H): 431.0929, Found: 431.0877.

\(^1\)H NMR (600 MHz, DMSO-d\(_6\)) = \(\delta\) (ppm) 8.78 (d, 1H, \(J = 4.7\) Hz), 8.26 (bs, 1H), 8.22 (s, 2H), 8.18 (bs, 1H), 8.13 (ddd, 1H, \(J = 7.8, 7.4, 1.9\)), 8.06 (s, 1H), 7.80 (d, 1H, \(J = 7.8\) Hz), 7.70 (ddd, 1H, \(J = 7.4, 4.7, 1.2\) Hz), * NH of free monomer, ** NH of dimer. \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) = \(\delta\) (ppm) 176.0, 171.3, 169.1, 162.0, 152.8, 149.8, 139.4, 131.6, 127.5, 124.0, 121.5, 119.6 115.3. \(^{19}\)F NMR (376 MHz, DMSO-d\(_6\)) = \(\delta\) (ppm) -61.22. Melting Point = 193.2 - 196.2 C

Synthesis of (E)-4-(perfluorophenoxy)-6-(pyridin-2-yl)diazetyl)-1,3,5-triazin-2-amine (4n). Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3n. Yield = 1.54 g, 62 %. EI-
HRMS: Calc. for C_{14}H_{8}F_{5}N_{7}O (M+2H): 385.0710 Found: 385.0710. \textsuperscript{1}H NMR (400 MHz, DMSO-d_{6}) = \delta (ppm) 8.78 (ddd, 1H, J = 4.7, 2.0, 0.8 Hz), 8.57 (bs, 1H), 8.40 (bs, 1H), 8.14 (ddd, 1H, J= 8.2, 7.4, 2.0 Hz), 7.82 (d, 1H, J= 8.2 Hz), 7.70 (ddd, 1H, J= 7.4, 4.7, 0.8 Hz). \textsuperscript{13}C NMR (100 MHz, DMSO-d_{6}) = \delta (ppm) 176.2, 170.0, 169.2, 161.8, 159.4, 149.9, 139.5, 127.7, 115.7, 109.5. \textsuperscript{19}F NMR (376 MHz, DMSO-d_{6}) = \delta (ppm) -153.6 (d, 2H, J= 19.9 Hz), -158.3 (dd, 1H, J = 23.9, 19.9Hz), -162.6 (t, 2H, J= 23.9 Hz).

**Synthesis of (E)-4-(benzyloxy)-6-(pyridin-2-yldiazenyl)-1,3,5-triazin-2-amine (4o).**

Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3o. Yield = 1.35 g, 26%. EI-HRMS: Calc. for C_{15}H_{15}N_{7}O (M+2H): 309.1338 Found: 309.1335. \textsuperscript{1}H NMR (400 MHz, CDCl_{3}) = \delta (ppm) 8.85 (bs, 1H)**, 8.82 (d, 1H, J= 4.3 Hz), 7.97-7.90 (m, 2H), 7.52 (ddd, 1H, J= 6.6, 4.7, 1.6 Hz), 7.48 (m, 2H), 7.39-7.31 (m, 3H), 7.08 (bs, 1H)**, 5.56 (bs, 1H)*, 5.54 (s, 2H), 5.54 (bs, 1H)*, *NH Free monomer, **NH dimer. \textsuperscript{13}C NMR (100 MHz, CDCl_{3})= \delta (ppm) 174.9, 172.3, 169.3, 162.3, 150.0, 138.5, 135.5, 128.5, 128.2, 128.1, 127.1, 114.9, 69.6.
Synthesis of \((E)-4-(pyridin-2-yl)diazene\)-6-(4-tritylphenoxy)-1,3,5-triazin-2-amine (4p). Synthesis performed according to general procedure for product 4; wherein the 6-(2-(pyridine-2-yl)hydrazinyl)-1,3,5-triazin-2-amine derivative is 3p. Yield = 1.38 g, 28%. El-HRMS: Calc. for C\(_{33}\)H\(_{27}\)N\(_7\)O (M+2H): 537.2277 Found: 537.2282. \(^1\)H NMR (400 MHz, CDCl\(_3\)) = \(\delta\) (ppm) 8.80 (d, 1H, J= 5.1 Hz), 8.01 (bs, 1H)**, 7.99-7.92 (m, 2H), 7.53 (ddd, 1H, \(J\) = 7.0, 5.1, 2.0 Hz), 7.30-7.19 (m, 17H), 7.15 (m, 2H), 6.68 (bs, 1H)**, 5.64 (bs,1H)*, 5.56 (bs, 1H)*, *NH free monomer, **NH dimer. \(^1^3\)C NMR (100 MHz, CDCl\(_3\))= \(\delta\) (ppm) 175.4, 172.4, 169.4, 162.2, 149.9, 146.6, 144.4, 138.6, 132.2, 131.1, 127.5, 127.2, 126.0, 120.4, 115.6, 110.0, 64.6.

**General procedure for synthesis of \((E)-6-(phenyldiazene)-1,3,5-triazin-2-amine derivatives (5)**

In a clean, dry round bottom flask 4-chloro-1,3,5-triazin-2-amine derivative (2) (1 eq.), phenylhydrazine (1 eq.) and potassium carbonate (1 eq.) were mixed with 100 mL of THF. The reaction mixture was refluxed for 5 hours, cooled and the solvent removed under reduced pressure. The crude material was poured into 50 mL of distilled water and the intermediate was extracted with 3 x 50 mL of dichloromethane. The organic phase was dried over sodium sulfate and the drying agent was removed by gravity filtration. One equivalent of (diacetoxy)iodobenzene was added to the intermediate solution and stirred
overnight at room temperature. Solvent was removed under reduced pressure and the product was purified by flash chromatography using a solvent mixture 1:1 hexanes : diethyl ether as eluent.

**Synthesis of (E)-4-butoxy-6-(phenyldiazenyl)-1,3,5-triazin-2-amine, 5c.** Synthesis performed according to general procedure for product 5; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2c. Yield = 1.00 g 21%. EI-HRMS: Calc. for C_{13}H_{18}N_{6}O (M+2H): 274.1542 Found: 274.1548. ¹H NMR (400 MHz, CDCl₃)= δ (ppm) 8.02 (m, 2H), 7.92 (bs, 1H)**, 7.59-7.52 (m, 3H), 6.89 (bs, 1H)**, 5.67 (bs, 1H)*, 5.52 (bs, 1H)*, 4.44 (t, 2H, J = 6.4 Hz), 1.78 (m, 2H, J = 7.6, 6.4 Hz), 1.48 (m, 2H, J = 7.6 Hz), 0.95 (t, 3H, J = 7.6 Hz), *NH free monomer, **NH dimer. ¹³C NMR (100 MHz, CDCl₃) = δ (ppm) 175.2, 172.3, 169.2, 152.1, 133.5, 129.2, 124.0, 68.1, 30.6, 19.0, 13.7.

**Synthesis of (E)-4-(hexylthio)-6-(phenyldiazenyl)-1,3,5-triazin-2-amine, 5f.** Synthesis performed according to general procedure for product 5; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2f. Yield = 0.25 g 15%. EI-HRMS: Calc. for C_{15}H_{22}N_{6}S (M+2H): 318.1627 Found: 318.1629. ¹H NMR (400 MHz, CDCl₃)= δ (ppm) 8.05 (m, 2H),
7.97 (bs, 1H)**, 7.61-7.52 (m, 3H), 5.70 (bs, 1H)**, 5.50 (bs, 1H)*, 5.49 (bs, 1H)*, 3.18 (t, 2H, $J = 7.4$ Hz), 1.73 (m, 2H), 1.45 (m, 2H), 1.32 (m, 4H), 0.89 (t, 3H, $J = 7.0$ Hz), *NH free monomer, **NH dimer. $^{13}$C NMR (100 MHz, CDCl$_3$) = $\delta$ (ppm) 184.5, 172.1, 166.6, 152.2, 133.5, 129.2, 124.0, 31.2, 30.0, 28.4, 22.4, 14.0.

**Synthesis of (E)-4-(4-(tert-butyl)phenoxy)-6-(phenyldiazenyl)-1,3,5-triazin-2-amine, 5k.** Synthesis performed according to general procedure for product 5; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2k. Yield = 0.35 g 22%. EI-HRMS: Calc. for C$_{19}$H$_{22}$N$_6$O (M+2H): 350.1855 Found: 350.1857. $^1$H NMR (400 MHz, CDCl$_3$) = $\delta$ (ppm) 8.06 (m, 2H), 7.59-7.53 (m, 3H), 7.43 (m, 2H), 7.40 (bs, 1H)**, 7.14 (m, 2H), 6.80 (bs, 1H)**, 5.65 (bs, 1H)*, 5.53 (bs, 1H)*, 1.34 (s, 9H), *NH free monomer, **NH dimer. $^{13}$C NMR (100 MHz, CDCl$_3$) = $\delta$ (ppm) 175.4, 172.5, 169.3, 152.0, 149.5, 148.8, 133.6, 129.2, 126.4, 124.0, 121.0, 34.4, 31.4.
2.5.3 $^1$H NMR Dilution Experiments

General Procedure for a Dilution Experiment.

Preparation of saturated solutions of $(E)$-4-(pyridin-2-yldiazenyl)-1,3,5-triazin-2-amine derivative (4). At least one day before the dilution experiment, a volume of 8 mL of saturated solution of the $(E)$-4-(pyridin-2-yldiazenyl)-1,3,5-triazin-2-amine derivative (4) in the selected solvent (CHCl$_3$ or Toluene) was prepared in a clean and dry vial. Separately, three clean and dry vials were labeled and weighed on a Sartorius Analytical Balance CPA124S. To each of the three vials, 2.0 mL of a previously prepared saturated solution of 4 was added, to later take them into a desiccator and remove the solvent under reduced pressure. Once all solvent was removed, the vials were weighed again to record the exact mass of 4 in each vial. Right before a dilution procedure, 2.0 mL of deuterated solvent (CDCl$_3$ or Toluene-$d_8$, consistent with the selected solvent) were added to each vial in order to dissolve 4.

Dilution Procedure. In a clean and dry eight inches NMR tube, 0.5 mL of the selected deuterated solvent (CDCl$_3$ or Toluene-$d_8$) was injected via syringe. A $^1$H NMR spectrum was recorded in order to ensure the purity of the same. Aliquots of the prepared saturated solution were added successively to the NMR tube with the selected deuterated solvent (4 $\mu$L x 5, 10 $\mu$L x 2, 20 $\mu$L x 3, 50 $\mu$L x 2, 100 $\mu$L, 200 $\mu$L, 500 $\mu$L x 2). The NMR tube was shaken between each addition and a $^1$H NMR spectrum was recorded right after. The chemical shifts of the N-H protons from 4 were identified and tracked during the experiment. The correlation between the concentration of 4 and the chemical shift of an N-H proton was fitted satisfactorily to the dimerization model using Origin Data Analysis.
Software. Dilution procedure was repeated twice more to ensure the reliability and reproducibility of the obtained values.

2.6 References


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Chapter 3

3  Photochemistry of Photoswitchable Self-Complementary DDAAA Hydrogen Bond Arrays

3.1  Introduction

The development of smart materials has encouraged the design and synthesis of novel and sophisticated molecules that are responsive to their environment. In this regard, photoswitches are some of the most attractive examples. Interest in these systems is often due to the fact that there is no extra chemical additive required in order to induce a change in the system, in contrast to stimuli such as pH, ions and solvent system.\(^1\)\(^2\)\(^3\) The only requirement is the irradiation of a specific wavelength which offers an effective and specific method of controlling the property one is interested in modifying.\(^4\) A common application of photoswitches in smart materials is control over their patterns of aggregation. The strategic inclusion of a photoswitch can generally either: (1) turn ON/OFF the formation of a supramolecular entity; or (2) increase/reduce the complexation strength between monomers forming aggregates (e.g. dimers or higher order complexes).

The first scenario is exemplified by Takeshita and co-workers’ report of a photoreversible supramolecular polymer.\(^5\)\(^6\) In this work, the supramolecular polymer binding sites were two quadruple hydrogen bond units (Meijer’s ureidopyrimidones) linked to a diarylethene moiety by phenyl groups (Scheme 3.1).\(^6\) The authors reported a significant increase in particle size once chloroform and tetrahydrofuran solutions were irradiated with
UV light. The reasoning behind this change is that the closed form of the diarylethene moiety fixes the two quadruple hydrogen bond units on opposing sides of the molecule. This configuration promotes intermolecular hydrogen bond interactions that lead to the formation of a supramolecular polymer. Once the system is exposed to visible light, the average particle size in solution decreased in value. This is due to the flexibility of the open form that allows weak intramolecular hydrogen bonding. When chloroform was employed as the solvent, besides visible light irradiation, heating was required in order to return the particle size to its initial value. On the other hand, when tetrahydrofuran was used, the particle size returned to its begining value without further assistance. These results are in accordance with the effect of the solvent polarity on the hydrogen bond strength: the more polar the solvent, the weaker the hydrogen bond interactions.

![Scheme 3.1 Takeshita’s photoreversible supramolecular polymer.](image-url)
On the other hand, photoswitches can also control the strength of non-covalent interactions between participating entities. In 2001, Yokoyama and coworkers reported an indolylfulgimide – bis(acylamino)pyridine ADA-DAD complex whose association constant can be controlled upon irradiation of a particular wavelength (Scheme 3.2). As outlined in Scheme 3.2, the complexation constant of 1E-3 (photoswitch open form) is significantly higher than the complexation constant of 1C-3 (photoswitch closed form); i.e. 885 ± 63 M⁻¹ and 156 ± 11 M⁻¹ respectively. The authors explained the drop in the complexation constant as due to a loss of planarity of the 1E-3 complex once switched to the 1C-3 complex. In the former complex, the bismethylenesuccinimide moiety in 1E is flexible, and therefore, it can rearrange to interact with 3 in a planar fashion. In the latter complex, the maleimide moiety in 1C is fixed which does not allow reorganization and reduces recognition between interacting sites.

Another example that outlines how the stability of a supramolecular complex can be modulated by a photochromic system is that reported by Hecht and coworkers (Scheme 3.3). In this example, the enhanced or diminished stability of the bis(thiazol-4-yl)maleimides – melamine complexes depends on changes in the electron-density of the maleimide moiety. The π conjugation in the closed forms (1b/2b) reduces the electron-density on the maleimide ring and polarizes the imide N-H bond turning it into a better donor compared with the imide N-H bond of the open form (1a/2a).
Scheme 3.2 Yokoyama’s indolylfulgimide – bis(acylamino)pyridine complex.

Scheme 3.3 Photoswitchable triple hydrogen bond motif studied by Hecht and coworkers.
In these examples, the control over complexation via photoswitching is based on the premise that one of the isomers is particularly designed to be part of a supramolecular array. Meanwhile, the other isomer is expected either to be unable to interact or to form a weaker complex due to structural changes peripheral to the array itself. In this sense, the photoswitchable self-complementary DDAAA hydrogen bond arrays reported in Chapter 2 differ significantly. Here, the array’s structure itself is changed by photoisomerization to an inherently less complementary arrangement.

Compounds 4a-p were designed to dimerize as trans isomers, now referred as (t)-4a-p. In these compounds, the location of the acceptor sites in the pyridine moiety and the azo group were tailored to match the donor sites from the amino group. Likewise, the planarity of these isomers contributes to the alignment between binding sites. Once (t)-4a-p are transformed into the cis-isomeric form (referred to as (c)-4a-p) the change in the geometric disposition of the aromatic rings and the concurrent loss of molecular planarity9,10 cause a reduction in the number of sites available to interact in a putative dimer; i.e. 4a-p change from DDAAA arrays to DA arrays (Scheme 3.4).

![Scheme 3.4 Photoisomerization of derivatives 4a-p.](image)

Assuming a 100% interconversion from trans to cis (and vice versa), the equilibria would be simplified to a comparison between the dimerization strengths of each isomeric
form (as exemplified in Yokoyama’s complexes). Conversely, if both isomeric forms are present at the photostationary state (PSS), the study of the distribution of all species present would be represented by the different equilibria taking place at the same time (Scheme 3.5).

Scheme 3.5 illustrates how a trans to cis interconversion with a yield less than 100% results in the presence of several (t)-4a-p and (c)-4a-p species in solution. The trans-isomer would be able to dimerize (tt) as reported in Chapter 2 (Section 2.3.2). On the other hand, the existence of cis-isomer in solution allows for two further complexation options: the dimerization of (c)-4a-p (c·c in Scheme 3.5); and, the complexation of (c)-4a-p with (t)-4a-p (tc in Scheme 3.5).

As noted in Chapter 2 (and Scheme 3.5) the design of (t)-4a-p provides an effective molecular recognition in the sense that only one spatial arrangement of the monomeric units results in the desired stable dimer structure. Conversely, (c)-4a-p is able to form tc complexes with two different relative geometries. This is due to the isomerization that discards two hydrogen bond acceptors (the nitrogen atoms on the azo and pyridyl moieties). This change results in two edges of the triazine ring with the same hydrogen bond array (AD) where molecular recognition can take place. For the same reason, there are three potential c·c dimer structures (c·c (1), c·c (2) and c·c (3) in Scheme 3.5). As a result, the observed (c)-4a-p dimerization constant (K_{c·c}) will be the sum of all c·c dimer equilibria present. Similarly the observed complexation constant of (c)-4a-p with (t)-4a-p (K_{t·c}) will be the summation of the two complexation processes in solution. Therefore, the real microscopic K_{c·c} and K_{t·c} values for each complex will be lower than those calculated. However, since all c·c dimer structures and tc complex structures contribute to the
equilibria in solution, the composite $K_{c-c}$ and $K_{t-c}$, are most useful to describe the response of our derivatives $4a-p$. Regardless, it is likely impossible to deconvolute the contributions from the different individual $c\cdot c$ and $t\cdot c$ equilibria anyway. This is similar to the contribution of Watson-Crick and non-Watson-Crick base pairing in solution.$^{50,51,52}$

The aim of this chapter is to discuss the photochemical properties of derivatives $4a-p$ since the intended functionality of them depends on these properties. Likewise, it is our intention to elucidate the stabilities of the supramolecular species present in solution after photoisomerization where possible. The study of the stability of these complexes

Scheme 3.5 Hypothetical complexation equilibria present in mixed cis/trans solutions of derivatives $4a-p$ in non-polar solvents.
compared with the trans-trans dimerization is desirable in order to understand the impact (and control) of the external stimulus (light) over the solution equilibria. Finally, an analysis of the thermal stability of the cis isomer of derivatives 4c, 4f and 4k in toluene-\textit{d}_8 solution is presented.

3.2 Results and Discussion

3.2.1 UV-Vis Characterization

The absorption spectra of all derivatives 4a-p in their thermally stable trans-isomeric form (i.e. (\textit{t})-4a-p) were obtained from 10^{-5} to 10^{-4} M acetonitrile solutions at room temperature (Figure 3.1).

As expected for aromatic azo derivatives, (\textit{t})-4a-p displayed two characteristic absorption bands corresponding to n→π* and π→π* transitions (Table 3.1), where the latter transition showed higher absorption coefficients. The UV-Vis absorption spectra of (\textit{t})-4a-p showed a hypsochromic shift of the π→π* band in comparison with azobenzene and 2,2’-azopyridine (π→π* maximum of 313 and 306 nm respectively).\textsuperscript{11,12} This effect can be attributed to the triazine ring and its lower electron density that increases the π→π* energy gap. Regarding the n→π* band, all derivatives (\textit{t})-4a-p showed maximum absorptions similar to those observed in azobenzene and 2,2’-azopyridine (n→π* maximum of 436 and 466 nm respectively)\textsuperscript{11,12}. 
Figure 3.1 Normalized UV-Vis absorption spectra of (t)-4a-p in acetonitrile at 298 K.

Attempts to perform dilution experiments using UV-Vis absorption spectroscopy with chloroform and toluene as solvent systems were carried out. However, these efforts revealed no useful measurable changes.
Table 3.1 Characteristic n→π* and π→π* transition bands of derivatives \((t)-4a-p\) from UV-Vis spectroscopy in acetonitrile at 298 K.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>RX</th>
<th>n→π* Transition</th>
<th>π→π* Transition</th>
</tr>
</thead>
<tbody>
<tr>
<td>((t)-4a)</td>
<td>piperidin-1-yl</td>
<td>449 702</td>
<td>286 11100</td>
</tr>
<tr>
<td>((t)-4b)</td>
<td>methoxy</td>
<td>451 125</td>
<td>290 7930</td>
</tr>
<tr>
<td>((t)-4c)</td>
<td>n-butoxy</td>
<td>428 761</td>
<td>290 11600</td>
</tr>
<tr>
<td>((t)-4d)</td>
<td>n-octyloxy</td>
<td>438 402</td>
<td>289 12400</td>
</tr>
<tr>
<td>((t)-4e)</td>
<td>prop-2-ynyloxy</td>
<td>435 253</td>
<td>290 7140</td>
</tr>
<tr>
<td>((t)-4f)</td>
<td>hexylthio</td>
<td>435 175</td>
<td>284 9380</td>
</tr>
<tr>
<td>((t)-4g)</td>
<td>chloro</td>
<td>448 41</td>
<td>295 5870</td>
</tr>
<tr>
<td>((t)-4h)</td>
<td>iodo</td>
<td>452 107</td>
<td>290 8420</td>
</tr>
<tr>
<td>((t)-4i)</td>
<td>phenoxy</td>
<td>441 245</td>
<td>290 9320</td>
</tr>
<tr>
<td>((t)-4j)</td>
<td>4’-nitrophenoxy</td>
<td>444 1009</td>
<td>280 22800</td>
</tr>
<tr>
<td>((t)-4k)</td>
<td>4’-tert-butylphenoxy</td>
<td>426 403</td>
<td>289 7530</td>
</tr>
<tr>
<td>((t)-4l)</td>
<td>3-(trifluoromethyl)phenoxy</td>
<td>426 236</td>
<td>289 8850</td>
</tr>
<tr>
<td>((t)-4m)</td>
<td>3,5-bis(trifluoromethyl)phenoxy</td>
<td>430 458</td>
<td>289 8340</td>
</tr>
<tr>
<td>((t)-4n)</td>
<td>perfluorophenoxy</td>
<td>407 292</td>
<td>291 5730</td>
</tr>
<tr>
<td>((t)-4o)</td>
<td>benzyloxy</td>
<td>440 636</td>
<td>288 10000</td>
</tr>
<tr>
<td>((t)-4p)</td>
<td>4-tritylphenoxy</td>
<td>413 459</td>
<td>290 10500</td>
</tr>
</tbody>
</table>

On the other hand, UV-Vis absorption spectra of \((c)-4c\), \((c)-4f\), and \((c)-4k\) and were obtained from \(10^{-4}\) M acetonitrile solutions (Figures 3.2 to 3.4). Details of the experimental procedure followed to obtain cis-isomer are outlined in the Experimental section at the end.
of this chapter. The absorption spectra of derivatives \((c)\)-4c, \((c)\)-4f and \((c)\)-4k displayed more intense \(n\rightarrow\pi^*\) bands; conversely, the \(\pi\rightarrow\pi^*\) band decreased in intensity compared to the \textit{trans}-isomeric derivatives (Table 3.2).

\textbf{Table 3.2} Characteristic \(n\rightarrow\pi^*\) and \(\pi\rightarrow\pi^*\) transition bands of derivatives \((c)\)-4 from UV-Vis spectroscopy in acetonitrile at 298 K.

| Compound | RX                  | \(n\rightarrow\pi^*\) Transition | \(\pi\rightarrow\pi^*\) Transition | Isosbestic Point
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>((c))-4c</td>
<td>(n)-butoxy</td>
<td>(\lambda_{\text{max}}) (nm)</td>
<td>(\varepsilon) (M(^{-1}) cm(^{-1}))</td>
<td>(\lambda_{\text{max}}) (nm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>432</td>
<td>853</td>
<td>283</td>
</tr>
<tr>
<td>((c))-4f</td>
<td>Hexylthio</td>
<td>436</td>
<td>538</td>
<td>284</td>
</tr>
<tr>
<td>((c))-4k</td>
<td>4'-\textit{tert}-butylphenoxy</td>
<td>433</td>
<td>919</td>
<td>287</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>370</td>
</tr>
</tbody>
</table>

It is important to outline that the \textit{cis}-isomers obtained from \textit{4a-p} were stable in the solid state at low temperature \(< 0 \, ^\circ\text{C}\) and protected from visible light. In all cases, \textit{cis} to \textit{trans} thermal reversion was observed to take place immediately after dissolution at room temperature. The gradual transition from \textit{cis} to \textit{trans} is observed in the changes in the absorption spectra: the \(n\rightarrow\pi^*\) band decreases while the \(\pi\rightarrow\pi^*\) band increases in intensity (Figures 3.2 to 3.4). Likewise, isosbestic points are observed during the course of each thermal reversion. The presence of these points in the UV-Vis spectra confirm the presence of only two species during these reversions: \textit{cis} and \textit{trans}. It is important to point out that since acetonitrile was the solvent system used during these UV-Vis absorption characterizations, no complexation is possible due to hydrogen bond competition by the solvent.
Figure 3.2 UV-Vis absorption spectra of (c)-4c and its thermal reversion to (t)-4c in acetonitrile at 298 K (4c total concentration =1.71 x 10^{-4} M). Inset figure: isosbestic point at 375 nm.
Figure 3.3 UV–Vis absorption spectra of (c)-4f and its thermal reversion to (t)-4f in acetonitrile at 298 K (4f total concentration =1.67x10^{-4} M). Inset figure: isosbestic point at 391 nm.
Figure 3.4 UV-Vis absorption spectra of (c)-4k and its thermal reversion to (t)-4k in acetonitrile at 298 K (4k total concentration = 3.72x10^-5 M). Inset figure: isosbestic point at 370 nm.

3.2.2 Photoisomerization Trans to Cis.

Photoisomerization experiments were carried out irradiating solutions of derivatives (t)-4a-p with UV light centered at 360 nm. These experiments were performed employing three different solvent systems: CDCl₃, toluene-d₈, and CD₃CN. The selection of the first two solvents was made in order to replicate the dilution experiments of derivatives 4a-p in Chapter 2 (Section 2.3.2). On the other hand, photoisomerization experiments in CD₃CN were carried out in order to observe whether or not there is a
difference using a polar solvent that prevents self-complexation. Deuterated solvents were used in order to verify the photoisomerization through $^1$H NMR spectroscopy.

The presence of the cis-isomer after UV irradiation was corroborated by the presence of a new set of signals in the $^1$H NMR spectrum. These signals were generally located upfield in reference to the trans-isomer (Figure 3.5 and 3.6). The changes in the chemical shift are in agreement with the disposition of the cis isomer wherein the proximity of the heteroaromatic rings locates most of the pyridyl hydrogen atoms in the shielding cone of the facing triazine heterocycle. The trans- to cis- interconversion yield was calculated from the cis/trans integration ratio of two signals that represent the same proton in (t)-4a-p and (c)-4a-p isomers. Table 3.3 shows the trans- to cis- interconversion yields of all derivatives 4a-p tested at their PSS.

![Figure 3.5](image)

**Figure 3.5** $^1$H NMR spectra displaying derivative 4p at PSS in CDCl$_3$ at 298 K. RX = 4'-tritylphenoxy.
Figure 3.6 $^1$H NMR spectra displaying derivative 4d at (i) PSS, and (ii) after complete cis- to trans- thermal reversion in CD$_3$CN at 298 K. RX = n-octyloxy.
The *trans*- to *cis*- interconversion yields for derivatives 4a-p at their PSS in CDCl$_3$ range from 9 to 28 percent. The lowest yield corresponded to the *n*-octyloxy 4d and the benzyloxy 4o; meanwhile the highest yield was achieved by the phenoxy derivative 4i. When toluene-*d$_8$* was employed as solvent system, of the four derivatives tested (4c, 4f, 4k and 4n) the only ones that contained *cis*-isomer in solution after UV irradiation were the

**Table 3.3** *Trans* to *cis* interconversion yields at PSS after irradiation with UV Light (360 nm) at 298 K.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>RX</th>
<th><em>trans to cis</em> conversion in CDCl$_3$ (%)</th>
<th><em>trans to cis</em> conversion in Toluene-*d$_8$ (%)</th>
<th><em>trans to cis</em> conversion in CD$_3$CN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>piperidin-1'-yl</td>
<td>22</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>4b</td>
<td>Methoxy</td>
<td>-</td>
<td>-</td>
<td>22</td>
</tr>
<tr>
<td>4c</td>
<td><em>n</em>-butoxy</td>
<td>12</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>4d</td>
<td><em>n</em>-octyloxy</td>
<td>9</td>
<td>-</td>
<td>26</td>
</tr>
<tr>
<td>4f</td>
<td>Hexylthio</td>
<td>18</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>4g</td>
<td>Chloro</td>
<td>-</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>4h</td>
<td>Iodo</td>
<td>-</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>4i</td>
<td>Phenoxy</td>
<td>28</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>4k</td>
<td>4'-<em>tert</em>-butylphenoxy</td>
<td>15</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>4l</td>
<td>3’-(trifluoromethyl)phenoxy</td>
<td>17</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>4m</td>
<td>3’,5’-bis(trifluoromethyl)phenoxy</td>
<td>16</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td>4n</td>
<td>Perfluorophenoxy</td>
<td>17</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>4o</td>
<td>Benzyloxy</td>
<td>9</td>
<td>-</td>
<td>21</td>
</tr>
<tr>
<td>4p</td>
<td>4’-tritylphenoxy</td>
<td>24</td>
<td>-</td>
<td>33</td>
</tr>
</tbody>
</table>

- Compound non soluble in the solvent system used.
derivatives \(4c\) (\(n\)-butoxy) and the \(4f\) (hexylthio) with 22 and 20 percent yields, respectively. Finally, the photoisomerization of derivatives \(4a-p\) dissolved in CD\(_3\)CN provided interconversions from 14 to 35 percent. In this case, the highest yield corresponded to the phenoxy derivative \(4i\) again and the lowest yield to the derivative \(4g\) (chloro). Comparing the results obtained from the different solvent systems examined it can be observed that photoisomerization yields were generally slightly higher in CD\(_3\)CN than in CDC\(_3\). One important thing to point out from the use of CD\(_3\)CN as solvent is the repercussion in the dimerization of the derivatives \(4a-p\); i.e. due to the polar nature of this solvent, derivatives \(4a-p\) do not dimerize. This is supported by the observed concentration independence of the amino proton chemical shifts upon thermal relaxation to the trans-starting material (Figure 3.6).

Another important feature to evaluate in our systems was the fatigue or photodegradation after the repetitive use of their photochromic properties. In this sense, a toluene-\(d_8\) solution of \(4c\) ([\(4c\]) = 9.10 x 10\(^{-4}\) M) was submitted to 5 cycles of alternate irradiation of UV light (centered at 360 nm for 1h) and visible light (\(\lambda > 400\) nm for 10 minutes) in order to observe the consistency in the system response (Figure 3.7). The response observed was the chemical shift of an amino proton of the trans-isomer in the \(^1\)H NMR spectra after each UV/Vis light irradiation. The average response after UV light irradiation of the \(4c\) solution corresponded to an N-H chemical shift of 5.45 ppm; meanwhile the average response after visible light irradiation corresponded to 5.55 ppm. In both cases, the larger deviation from the average value corresponds to 0.03 ppm. It is remarkable that after irradiation of visible light, the system did not recover to its trans-isomeric form in 100%; and therefore, it was not observed the initial chemical shift prior
trans- to cis- photoisomerization. Likewise, once the alternate irradiation was stopped and the system was allowed to cis- to trans- thermal reversion, it was noted that the N-H amino proton chemical shift was lower than the observed before UV/Vis irradiation without traces of cis-isomer or other side product observed at the $^1$H NMR spectrum. This final chemical shift corresponds to a solution with a concentration 6% lower than at the beginning of the experiment (i.e. $6 \times 10^{-5}$ M); which might not be detected by the NMR spectrometer resolution at the range of concentrations employed.

**Figure 3.7** Cyclization plot of 4c ($[4c] = 9.1 \times 10^{-4}$ M). Purple areas correspond to the N-H chemical shift change after UV light irradiation (centered at 360 nm for 1h). White areas correspond to the N-H chemical shift change after visible light irradiation ($\lambda > 400$ nm for 10 minutes). Yellow area correspond to the N-H chemical shift observed after thermal reversion of the solution over 72h.
Since the *trans*- to *cis*- interconversions of the derivatives 4a-p are lower than 100%, the model that describes the distribution of species after photoisomerization involves multiple complexation equilibria taking place at the same time in solution (Scheme 3.5). In addition, since thermal reversion to the *trans*-isomer takes places immediately after UV light irradiation is stopped, the distribution of species changes as the *cis/trans* ratio does. The following sections describe the approach we followed to mitigate these difficulties and evaluate the effect of the light induced isomerization on the distribution of species in solution.

3.2.3 Complexation Constants in Solution After Photoisomerization

The main challenge in determining the distribution of monomeric and dimeric species for mixed solutions of *cis* - and *trans*-4a-p is the determination of complexation constants involving the *cis*-isomer. Since (c)-4a-p are not thermally stable in solution, the determination of $K_{cc}$ and $K_{tc}$ are not possible by standard procedures such as dilution and titration.\textsuperscript{11,12} Therefore, it was necessary to take a different approach in order to determine or estimate these unknown constants.

In a mixed solution of *cis*- and *trans*- 4a-p, the *trans*-isomer in solution participates in the two equilibria illustrated in Scheme 3.6.
Based on Scheme 3.6, the total concentration of *trans*-isomer in solution ([*t*]₀) can be expressed as:

\[
[t]₀ = [t] + 2 \cdot [t \cdot t] + [t \cdot c]
\]  
*Equation 1*

Wherein

- [*t*] is the concentration of free *trans*-isomer;
- [*t* ∙ *t*] is the concentration of the *trans*-isomer dimer; and
- [*t* ∙ *c*] is the concentration of *trans-cis* complex.

The dimerization constant \( K_{t \cdot t} \) and complexation constant \( K_{t \cdot c} \) that characterize the equilibria illustrated in Scheme 3.5 are outlined in Equations 2 and 3.

\[
K_{t \cdot t} = \frac{[t \cdot t]}{[t]^2}
\]  
*Equation 2*

\[
K_{t \cdot c} = \frac{[t \cdot c]}{[t] \cdot [c]}
\]  
*Equation 3*

Where
[\text{c}] is the concentration of free cis-isomer;

Solving Equations 2 and 3 for \([t \cdot t]\) and \([t \cdot c]\) allow us to express Equation 1 in terms of \([t]\) and \([c]\):

\[
[t]_0 = [t] + 2 \cdot K_{tt} \cdot [t]^2 + K_{tc} \cdot [t] \cdot [c] \quad \text{Equation 4}
\]

In a similar manner to the trans-isomer, the total concentration of cis-isomer in solution (\([c]_0\)) that participates in the complexation equilibria illustrated in Scheme 3.7 is expressed in Equation 5 as a solution of free trans-isomer ([t]) and cis-isomer ([c]).

\[
[c]_0 = [c] + 2 \cdot K_{cc} \cdot [c]^2 + K_{tc} \cdot [t] \cdot [c] \quad \text{Equation 5}
\]

Where

\([c]\) is the concentration of free cis-isomer;

\(K_{cc}\) is the dimerization constant that describes the equilibrium between free cis-isomer and the dimer of cis-isomer; and,

\(K_{tc}\) is the complexation constant as described in Equation 3.

\textbf{Scheme 3.7} Complexation equilibria involving the 4a-p cis-isomer.
To sum up, all derivatives 4a-p in solution can be present in five different forms: free trans ([t]), free cis ([c]), trans-trans dimer ([t · t]), cis-cis dimer ([c · c]) and a trans-cis complex ([t · c]). The distribution of these species is dependent on three dimerization/association constants: $K_{tt}$, $K_{cc}$, and $K_{tc}$.

$K_{tt}$ has already been determined for each of the soluble (t)-4a-p in Chapter 2 (Section 2.3.2). In contrast, estimation of $K_{cc}$ had as a limitation that once in solution, pure cis-isomer immediately begins reverting thermally to the trans-isomer which makes difficult the execution of a dilution experiment.

An important thing to note is the effect of the solvent system where all the species previously described are present. That is, how significant is the change in the physical property going to be studied in different solvents. In our case, the physical property studied is the drop in the stability of derivates 4a-p as dimers by reducing the number of binding sites available, which is observed in the differences between $K_{tt}$ with $K_{cc}$ and $K_{tc}$. Since $K_{tt}$ represents the dimerization constant of the most stable complex, $K_{cc}$, and $K_{tc}$ values are within the range from 0 to $K_{tt}$. The larger the $K_{tt}$ the more significant is going to be the difference observed with the other constants. Therefore, we decided to study the distribution of monomer, dimer and complex structures in toluene-$d_8$ since, as reported in Chapter 2 (Section 2.3.2), $K_{tt}$ values in toluene-$d_8$ were much higher than those in CDCl$_3$.

In order to have an approximation of the expected values for $K_{cc}$, we looked back at the dimerization of 5c, 5f and 5k. Since the hydrogen bond array for these systems does not include the nitrogen acceptor located on the pyridine ring, it is reasonable to infer that the $K_{cc}$ values for (c)-4c, (c)-4f and (c)-4k will be equal to or lower than the dimerization constants of 5c, 5f and 5k, respectively. Moreover, 5c, 5f and 5k are likely overestimations
of the real $K_{cc}$ since dilution experiments of intermediates 1 and 2b (Figure 3.8) in toluene-$d_8$ presented maximum changes in the chemical shift of 0.12 and 0.04 ppm which are below the minimum $\Delta \delta$ to consider the $^1$H NMR dilution method employed reliable ($\Delta \delta_{\text{max}} = 0.5$ ppm, Chapter 2, Section 2.3.2). Plots of the chemical shift of the amino protons vs. concentration implied dimerization constant values less than 1 M$^{-1}$ and could not be fitted to the dimerization model due to lack of curvature.

![Chemical structures of intermediates 1 and 2b.](image)

**Figure 3.8** Chemical structures of intermediates 1 and 2b.

Based on this hypothesis $K_{tt}$ would be at least 20 times larger than $K_{cc}$ (Table 2.3) in toluene-$d_8$. For this reason, the $K_{cc}$ contribution can be eliminated without significant consequences in the calculation of the complexation distribution (vide infra). Equation 5 is thus reduced to Equation 6:

$$[c]_0 = [c] + K_{tc} \cdot [t] \cdot [c] \quad \text{Equation 6}$$

Solving Equation 6 for $[c]$, and substituting $[c]$ in Equation 4:

$$[t]_0 = [t] + 2 \cdot K_{tt} \cdot [t]^2 + \frac{K_{tc} \cdot [t] \cdot [c]_0}{1 + K_{tc} \cdot [t]} \quad \text{Equation 7}$$
Equation 7 is important due to the fact that \([\mathbf{t}]_0\) is described in terms of only one variable ([\(t\)]) and the only constant to be determined is \(K_{t,c}\). Regarding the total concentration of \(\text{trans}\) and \(\text{cis}\)-isomers in solution ([\(t\]) and [\(c\)]), these concentrations can be calculated through the integration of their signals in the \(^1\)H NMR spectra (in the same way as the determination of the PSS in Section 3.3).

Besides the calculation of the total amount of each isomer in solution using integration, \(^1\)H NMR spectroscopy provides an observable property whose change is proportional to the concentration of each specie in solution; e.g. the chemical shift of the amino protons of the \(\text{trans}\)-isomer. In this case, the chemical shift observed for an amino proton (\(\delta_{\text{obs}}\)) is the weighted average of all the chemical species wherein this isomer is participating (Equation 8).

\[
\delta_{\text{obs}} = \delta_m \cdot \frac{[\mathbf{t}]}{[\mathbf{t}]_0} + \delta_d \cdot \frac{2 \cdot [\mathbf{t} \cdot \mathbf{t}]}{[\mathbf{t}]_0} + \delta_{tc} \cdot \frac{[\mathbf{t} \cdot \mathbf{c}]}{[\mathbf{t}]_0} \quad \text{Equation 8}
\]

Where

\(\delta_m\) and \(\delta_d\) are the chemical shifts of the \(\text{trans}\)-isomer as a monomer and dimer, respectively (Chapter 2, Section 2.3.2); and

\(\delta_{tc}\) corresponds to the chemical shift of the \(\text{trans}\)-isomer in the \([\mathbf{t} \cdot \mathbf{c}]\) complex.

Similarly to the solution of Equation 1 into Equation 7, Equation 8 can be transformed in order to be expressed in terms of \([\mathbf{t}]\) (Equation 9).

\[
\delta_{\text{obs}} = 2 \cdot K_{tt} \cdot (\delta_d - \delta_{tc}) \cdot \frac{[\mathbf{t}]^2}{[\mathbf{t}]_0} + (\delta_m - \delta_{tc}) \cdot \frac{[\mathbf{t}]}{[\mathbf{t}]_0} + \delta_{tc} \quad \text{Equation 9}
\]
Since Equations 7 and 9 share the same variable \([t]\), it is possible to establish a relationship between \(K_{tc}\) and \(\delta_{tc}\) once the value of \([t]\) is known. This relationship provided a strategy where through the assignment of a range of values to \(\delta_{tc}\) a set of \(K_{tc}\) values are obtained for a \(\delta_{obs}\) in a \(^1\text{H}\) NMR spectrum at a specific cis/trans ratio. For this purpose Equation 9 was rearranged as a second order polynomial (Equation 10) and Equation 7 was rearranged to solve \(K_{tc}\) (Equation 11). The relationship between \(\delta_{tc}\) and \(K_{tc}\) is illustrated in Figure 3.9 at a specific total concentration of 4a-p ([4]) and ratio of cis/trans isomer.

\[
2 \cdot K_{tt} \cdot (\delta_d - \delta_{tc}) \cdot [t]^2 + (\delta_m - \delta_{tc}) \cdot [t] + (\delta_{tc} - \delta_{obs}) \cdot [t]_0 = 0 \quad \text{Equation 10}
\]

Where

\[
[t] = \frac{-(\delta_m - \delta_{tc}) \pm \sqrt{(\delta_m - \delta_{tc})^2 - 8 \cdot K_{tt} \cdot (\delta_d - \delta_{tc}) \cdot (\delta_{tc} - \delta_{obs}) \cdot [t]_0}}{4 \cdot K_{tt} \cdot (\delta_d - \delta_{tc})}
\]

\[
K_{tc} = \frac{[t]_0 - [t] - 2 \cdot K_{tt} \cdot [t]^2}{2 \cdot K_{tt} \cdot [t]^3 + [t]^2 + ([c]_0 - [t]_0) \cdot [t]} \quad \text{Equation 11}
\]

And we assume the boundary conditions:

\(\delta_m < \delta_{tc} < \delta_d\)
Figure 3.9 Relationship between $K_{tc}$ and $\delta_{tc}$, when $\delta_{Obs} = 5.61$ ppm at a cis/trans ratio $r = 1.85$ for a total $[4c] = 3.42 \times 10^{-3}$ M.

The solution of the real $K_{tc}$ and $\delta_{tc}$ values comes after applying this strategy to a set of $\delta_{Obs}$ at different cis/trans ratios when the total concentration of a derivative 4a-p is held constant. These data were obtained from a reversion experiment which consisted in following the chemical shift of an amino proton of the trans-isomer while the cis to trans thermal reversion takes place (Figure 3.10). The experiment was carried out from mixed cis/trans isomeric solutions in toluene-$d_8$ at known total concentrations of each of the derivatives 4c, 4f and 4k. An example of the change in the chemical shift observed ($\delta_{Obs}$) as total trans-isomer concentration increases in a reversion experiment ($[t]_0$) is illustrated in Figure 3.11. It is important to note that as the reversion experiment was carried out, the amino protons of the cis-isomer shift downfield significantly as the concentration of $[t]_0$...
increases. This behavior supports the assumption that $K_{tc}$ is significantly higher than $K_{cc}$.

![Chemical Structures](image)

Figure 3.10 $^1$H NMR spectra displaying the concentration-dependent behavior of 4c in toluene-$d_8$ at 298 K. Total concentration $[4c] = 3.27 \times 10^{-3}$ M, (i) $[c]_0/[t]_0 = 1.73$, (ii) $[c]_0/[t]_0 = 0.93$, (iii) $[c]_0/[t]_0 = 0.59$, (iv) $[c]_0/[t]_0 = 0.33$, (v) $[c]_0/[t]_0 = 0.22$, and (vi) $[c]_0/[t]_0 = 0$. 
Figure 3.11. Relationship between $\delta_{\text{Obs}}$ vs $[t]_0$ during a thermal reversion experiment of derivative 4c. Red corresponds to a reversion experiment ($[4c] = 2.90 \times 10^{-3}$ M). Solid line corresponds to the theoretical dilution curve obtained from the average of three separate dilution experiments with (t)-4c.

From each chemical shift observed at a specific cis/trans ratio evaluated in a reversion experiment, a relationship curve of $K_{tc}$ vs $\delta_{tc}$ (as observed in Figure 3.9) is obtained. Since it is impossible to observe the same $K_{tc}$ vs. $\delta_{tc}$ relationship (curve) for each $\delta_{\text{Obs}}$ in a reversion experiment, the point where all these curves converge represents the real pair of values for $K_{tc}$ and $\delta_{tc}$ (Figure 3.12). In our case, errors in the real data render the plot less visually accurate and required a method of determining the point of best fit to the data (Figure 3.13). Hence, we used a statistical procedure to determine these values.
Figure 3.12 Top Plot: Theoretical $K_{tc}$ vs $\delta_{tc}$ curves for the set of $\delta_{obs}$ from the least squares line that describes third reversion experiment of derivative $4c$ (green dots at Figure 3.14, $[4c] = 3.42 \times 10^{-3}$ M). Bottom Plot: Theoretical $CV$ vs $\delta_{tc}$ curve for the set of $K_{tc}$ calculated from the third reversion experiment of derivative $4c$ (Green dots at Figure 3.8, $[4c] = 3.42 \times 10^{-3}$ M).
Figure 3.13 Top Plot: $K_{t-c}$ vs $\delta_{tc}$ curves for the set of $\delta_{obs}$ from the third reversion experiment of derivative 4c (green dots at Figure 3.14, [4c] = 3.42 x 10^{-3} M). Bottom Plot: $CV$ vs $\delta_{tc}$ curve for the set of $K_{t-c}$ calculated from the third reversion experiment of derivative 4c (Green dots at Figure 3.8, [4c] = 3.42 x 10^{-3} M).

The convergence point of each set of $K_{t-c}$ vs $\delta_{tc}$ curves was determined through the coefficient of variation ($CV_{\delta_{tc}}$) from all $K_{t-c}$ obtained at a constant $\delta_{tc}$ (i.e. a vertical slice in Figure 3.13 plot, Equations 12 to 14). The coefficient of variation is defined as a standardized measure of the dispersion of a distribution.\(^\text{13}\) In the present case, each set of $K_{t-c}$ values (at a constant $\delta_{tc}$ value) is a distribution. Hence, the distribution that shows the value of minimum dispersion (i.e. minimum $CV_{\delta_{tc}}$ value) over a range of $\delta_{tc}$ represents the point where all curves converge closest to one another.
\[ \bar{K}_{t,c} = \frac{1}{n} \sum_{i=1}^{n} K_{t,c(i)} \]  

*Equation 12*

\[ S_{t,c} = \sqrt{\frac{1}{n-1} \sum_{i=1}^{n} (K_{t,c(i)} - \bar{K}_{t,c})^2} \]  

*Equation 13*

\[ CV_{\delta_{t,c}} = \frac{S_{t,c}}{\bar{K}_{t,c}} \]  

*Equation 14*

Where

- \( K_{t,c(i)} \) is the \( K_{t,c} \) calculated at a specific \( \delta_{tc} \);

- \( \bar{K}_{t,c} \) is the average value from all \( K_{t,c(i)} \) at a constant \( \delta_{tc} \) value;

- \( n \) is the number of \( \delta_{obs} \) values in a reversion experiment;

- \( S_{K_{t,c}} \) is the sample standard deviation at constant \( \delta_{tc} \) value; and,

- \( CV_{\delta_{t,c}} \) is the coefficient of variation at constant \( \delta_{tc} \) value.

This way, from each reversion experiment \( \bar{K}_{t,c} \) and \( \delta_{tc} \) were obtained at the convergence point. In total, three reversion experiments at different total concentrations ([4]) were carried out for each derivative 4 studied under this model. The \( \bar{K}_{t,c}, \Delta G_{t,c} \) and \( \delta_{tc} \) values obtained for derivatives 4c, 4f and 4k are listed in Table 3.4. Likewise, Figures 3.14 - 3.16 illustrate the predicted \( \delta_{obs} \) vs \([t]_0\) plots compared with the experimental data obtained for all reversion experiments carried out for derivatives 4c, 4f and 4k.
Table 3.4 Complexation constants, free energies of complexation and chemical shifts of the \textit{trans}-isomer in the complex $\delta_{tc}$ studied in Toluene-\textit{d}_8 (at 298 K).

<table>
<thead>
<tr>
<th>Derivative</th>
<th>RX</th>
<th>$K_{tc}$ (M$^{-1}$)</th>
<th>$\Delta G_{tc}$ (kJ mol$^{-1}$)</th>
<th>$\delta_{tc}$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4c</td>
<td>n-butoxy</td>
<td>160 ± 15</td>
<td>-12.57 ± 0.24</td>
<td>5.14 ± 0.11</td>
</tr>
<tr>
<td>4f</td>
<td>Hexylthio</td>
<td>172 ± 8</td>
<td>-12.76 ± 0.12</td>
<td>5.38 ± 0.13</td>
</tr>
<tr>
<td>4k</td>
<td>4'-tert-butylphenoxy</td>
<td>931 ± 123</td>
<td>-16.94 ± 0.33</td>
<td>5.01 ± 0.39</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Average values obtained using Equation 12 and three separate reversion experiments. Errors calculated from twice the standard deviation to give a 95\% confidence interval.

Figure 3.14 Relationship between $\delta_{\text{Obs}}$ vs $[t]_0$ for three reversion experiments of derivative 4c. Blue, red and green dots correspond to first, second and third separate reversion experiments, respectively. Blue, red and green dashed lines correspond to the calculated $\delta_{\text{Obs}}$ vs $[t]_0$ plots for the first, second and third reversion experiments with the $K_{tc}$ and $\delta_{tc}$ values with minimum CV (sample standard deviations of 0.003, 0.003 and 0.008 ppm, respectively). Solid line corresponds to the dilution curve obtained for (t)-4c from the average of three separate dilution experiments.
Figure 3.15 Relationship between $\delta_{\text{Obs}}$ vs $[t]_0$ for three reversion experiments of derivative 4f. Blue, red and green dots correspond to first, second and third separate reversion experiments, respectively. Blue, red and green dashed lines correspond to the calculated $\delta_{\text{Obs}}$ vs $[t]_0$ plots for the first, second and third reversion experiments with the $\bar{K}_{tc}$ and $\delta_{tc}$ values with minimum $CV$ (sample standard deviations of 0.01, 0.005 and 0.02 ppm, respectively). Solid line corresponds to the dilution curve obtained for $(t)$-4f from the average of three separate dilution experiments.
Figure 3.16 Relationship between $\delta_{\text{obs}}$ vs $[t]_0$ for three reversion experiments of derivative 4k. Blue, red and green dots correspond to first, second and third separate reversion experiments, respectively. Blue, red and green dashed lines correspond to the calculated $\delta_{\text{obs}}$ vs $[t]_0$ plots for the first, second and third reversion experiments with the $K_{tc}$ and $\delta_{tc}$ values with minimum CV (sample standard deviations of 0.03, 0.02 and 0.04 ppm, respectively). Solid line corresponds to the dilution curve obtained for (t)-4k from the average of three separate dilution experiments.
The *trans-cis* complexation constants obtained through this method for 4c, 4f and 4k were 160, 172 and 931 M⁻¹, respectively. Comparing *trans-trans* dimerization with *trans-cis* complexation, the energy differences between the two arrays for 4c, 4f and 4k are 4.46, 3.05 and 0.68 kJ mol⁻¹. Regarding derivatives 4c and 4f, $\tilde{K}_t$ and $\Delta G_t$ values are in agreement with the expectancy that the *trans-cis* complex stability should likely be an average of the *trans-trans* and *cis-cis* dimer stabilities. The reasoning behind this expectation is that in a *trans-cis* complex the *trans*-isomer donors participate as the *cis*-isomer donors do in a *cis-cis* complex; the *cis* donors interact similarly as the *trans* donors do in a *trans-trans* complex (Figure 3.17). In other words, the *trans-trans* dimer has six hydrogen bond interactions, *cis-cis* dimer would exhibit two and the *trans-cis* complex would thus contain four hydrogen bonds; i.e. the average number of interactions of the two dimer structures.

![Figure 3.17 Structural similarities between trans-trans, cis-cis dimers and the trans-cis complex in mixed solution of 4a-p.](image)
If the $\Delta G_{tt}$ values of butoxy 5c and hexylthiol 5f (-7.16 and -8.13 kJ mol$^{-1}$, respectively) were taken as $\Delta G_{cc}$ approximations for butoxy 4c and hexylthiol 4f, the average $\overline{\Delta G}$ for 4c and 4f are -12.00 and -11.97 kJ mol$^{-1}$, respectively. These values differ from the calculated $\Delta G_{tc}$ values by less than 1 kJ mol$^{-1}$ (0.57 and 0.79 kJ mol$^{-1}$ for 4c and 4f, respectively); therefore, trans-cis complexations for these systems are in accordance with the predicted model.

On the other hand, 4’-tert-butylphenoxy derivative 4k deviates from the expected complexation values since the average $\overline{\Delta G}$ is -13.54 kJ mol$^{-1}$; i.e. 3.4 kJ mol$^{-1}$ higher than the calculated $\Delta G_{tc}$. This difference from the predicted $\overline{\Delta G}$ and the estimated $\Delta G_{tc}$ is obvious visually when comparing the expected $\delta_{obs}$ vs $[t]_0$ plots from the reversion experiments with the experimental data obtained (Figure 3.18).

The explanation of why the derivative 4k deviates from the model proposed is not clear from our data. It could be that either there are more complex structures in solution than those proposed at the beginning; or, there are other factors we are not aware of that enhance trans-cis complexation stability. In this sense, after a careful observation of the particularities of compound 4k, we noticed that a trans-cis complex might provide an N-H/$\pi$ interaction that could increase the stability of the complex in comparison to complexes 4c and 4f complexes (Figure 3.19 (A)).
Figure 3.18 Relationship between $\delta_{\text{Obs}}$ vs $[t]_0$ through three reversion experiments of the derivative 4k. Blue, red and green dots correspond to first, second and third separated reversion experiments, respectively. Blue, red and green dashed lines correspond to the predicted $\delta_{\text{Obs}}$ vs $[t]_0$ plots for the first, second and third reversion experiments with the expected $\Delta G$ values (sample standard deviations of 0.05, 0.12, 0.11 ppm, respectively). Solid line corresponds to the dilution curve obtained from the average of three separated dilution experiments.

(A) 4k trans-cis complex structure; and (B) 5k dimer structure.
The N-H/π interaction is well known and reported in the literature.\textsuperscript{14-15} One of the main characteristics of this interaction is its effect over the chemical shift of the proton involved. That is, since the participating proton is shielded by the magnetic anisotropy of the aryl ring there is generally an observed upfield shift;\textsuperscript{16} contrary to a conventional hydrogen bond interaction. If this interaction were playing a significant energetic contribution in the \textit{trans-cis} complexation, an upfield shift should have been observed at higher concentrations of \textit{cis} isomer; which was not observed. Likewise; similar behavior should have been observed in the dilution of the derivative 5k, since 5k monomers can be arranged to allow N-H/π interactions (Figure 3.19 (B)). Therefore, due to the lack of evidence that supports the possible contribution of an N-H/π interaction, the reasoning behind the strength of the 4k \textit{trans-cis} complex remains unclear.

Finally, the calculation of $K_{\text{cc}}$ allow us to obtain a complete representation of the distribution of all species in solution at different \textit{cis/trans} ratios at a specific concentration; i.e. a speciation diagram. Calculated speciation diagrams for 4c, 4f and 4k taking two scenarios into account: 1) when \textit{cis} dimerization is not present in solution ($K_{\text{cc}} = 0$); and, 2) when \textit{cis} dimerization is present in solution ($K_{\text{cc}} > 0$). The $K_{\text{cc}}$ values employed for the second scenario corresponded to the dimerization constants of 5c, 5f and 5k. The purpose behind the comparison between these two scenarios is to estimate the impact that \textit{cis-cis} dimerization has over the distribution of the species when both (c)-4 and (t)-4 are present (Figures 3.20 - 3.22).
Figure 3.20 Theoretical speciation diagram of derivative 4c at the third reversion experiment (green dots at Figure 3.14, [4c] = 3.42 x 10^{-3} M) at 298 K. Solid lines correspond to the first scenario ($K_{cc} = 0$) and dotted-star marked lines correspond to the second scenario ($K_{cc} = 18$ M^{-1}) respectively. Blue, red, orange, yellow and brown colors correspond to [t], [t · t], [t · c], [c], and [c · c], respectively. Black dotted line corresponds to maximum cis/trans ratio in reversion experiment. Grey dotted line corresponds to cis/trans ratio at PSS.
Figure 3.21 Theoretical speciation diagram of derivative 4f at the third reversion experiment (green dots at Figure 3.15, $[4f] = 2.35 \times 10^{-3}$ M) at 298 K. Solid lines correspond to the first scenario ($K_{cc} = 0$) and dotted-star marked lines correspond to the second scenario ($K_{cc} = 26$ M$^{-1}$) respectively. Blue, red, orange, yellow and brown colors correspond to $[t]$, $[t \cdot t]$, $[t \cdot c]$, $[c]$, and $[c \cdot c]$, respectively. Black dotted line corresponds to maximum cis/trans ratio in reversion experiment. Grey dotted line corresponds to cis/trans ratio at PSS.
Figure 3.22 Theoretical speciation diagram of derivative 4k at the third reversion experiment (green dots at Figure 3.16, [4k] = 1.84 x 10^{-3} M) at 298 K. Solid lines correspond to the first scenario ($K_{cc} = 0$) and dotted-star marked lines correspond to the second scenario ($K_{cc} = 46 \text{ M}^{-1}$) respectively. Blue, red, orange, yellow and brown colors correspond to $[t]$, $[t \cdot t]$, $[t \cdot c]$, $[c]$, and $[c \cdot c]$, respectively. Black dotted line corresponds to maximum cis/trans ratio in reversion experiment.

Figures 3.20 to 3.22 illustrate the differences in concentration of all the species when cis-cis dimerization is assumed as nonexistent (solid lines) or present (dotted-star marked lines). From all the systems studied, derivative 4f showed the highest difference in concentration between both scenarios ($K_{cc} = 0$ and $K_{cc} = 26 \text{ M}^{-1}$). This is, approximately 13% in trans-cis complex concentration ($[t \cdot c]$) between both scenarios over the total amount of trans-isomer ($[t]_0$). This difference is observed in a solution with an excess of cis-isomer (i.e. 90% of (c)-4f, or $\chi = 0.1$ in Figure 3.20), and decreases as the total concentration of cis-isomer also decreases; e.g. at 50% of (c)-4f, or $\chi = 0.5$ in Figure 3.20.
the difference in \([t \cdot c]\) between the two cases is 5%. Since nearly all the reversion experiments started at a cis/trans ratio \(\leq 1\) (i.e. 50\% of \((c)-4\), or \(\chi = 0.5\)), the differences in \([t \cdot c]\) did not surpass the 5\% over the total concentration of trans-isomer. Therefore, it can be said that the mathematical model used to calculate the trans-cis complexation constant \((K_{t,c})\) is reliable since it provides a good description of the species distribution at the observed concentrations.

### 3.2.4 Cis to Trans Reversion Kinetics

One of the major difficulties during the study of the photochemistry of derivatives 4a-p was the cis to trans reversion that takes place immediately once the cis isomer is in solution at room temperature. We also observed during the reversion experiments that the rate of cis to trans reversion was different for each derivative. Therefore, parallel to the trans-cis complexation study, the cis/trans ratios obtained from each reversion experiment at specific times were useful to estimate the kinetics of the cis to trans thermal reversion. The thermal cis to trans reversions of derivatives 4c, 4f and 4k in toluene-\(d_8\) at room temperature corresponded to a first order reaction model (Equations 15 and 16). This is in agreement with the cis to trans thermal reversion of azobenzene documented by Cammenga and coworkers.\(^2\) The rate constants for each derivative tested are displayed in Table 3.5; and, the decay profiles of the cis-isomer of derivatives 4c, 4f and 4k are presented in Figures 3.23 to 3.25, respectively.

\[
Rate = -\frac{d[A]}{dt} = k[A] \quad \text{Equation 15}
\]
\[
\ln[A] - \ln[A]_0 = -kt
\]

\textit{Equation 16}

Table 3.5 Rate constants calculated for \textit{cis} to \textit{trans} thermal reversion of 4c, 4f and 4k studied in Toluene-\textit{d}_8 at 298 K.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>RX</th>
<th>(k \times 10^4 \text{ (s}^{-1})</th>
<th>(^\text{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>4c</td>
<td>\textit{n}-butoxy</td>
<td>3.36 ± 0.43</td>
<td></td>
</tr>
<tr>
<td>4f</td>
<td>Hexylthio</td>
<td>2.74 ± 0.40</td>
<td></td>
</tr>
<tr>
<td>4k</td>
<td>4’-\textit{tert}-butylphenoxy</td>
<td>6.02 ± 1.12</td>
<td></td>
</tr>
</tbody>
</table>

\(^\text{a}\) Average values obtained using the first order reaction model and three separate reversion experiments. Errors calculated from twice the standard deviation to give a 95\% confidence interval.

\textbf{Figure 3.23} Decay profiles of (c)-4c isomer in toluene-\textit{d}_8 at 298 K. Blue, red and green dots correspond to first, second and third separate reversion experiments (\(r = -0.9973, -0.9982\) and -0.9981) respectively. Blue, red and green dashed lines correspond to the calculated values obtained by linear least squares regression of the first, second and third separate reversion experiments, respectively.
Figure 3.24 Decay profiles of (c)-4f isomer in toluene-$d_8$ at 298 K. Blue, red and green dots correspond to first, second and third separate reversion experiments ($r = -0.9995$, -0.9981 and -0.9987) respectively. Blue, red and green dashed lines correspond to the calculated values obtained by linear least squares regression of the first, second and third separate reversion experiments, respectively.
Figure 3.25 Decay profiles of (c)-4k isomer in toluene-$d_8$ at 298 K. Blue, red and green dots correspond to first, second and third separate reversion experiments ($r = -0.9954$, -0.9907 and -0.9962) respectively. Blue, red and green dashed lines correspond to the calculated values obtained by linear least squares regression of the first, second and third separate reversion experiments, respectively.

An interesting observation from the thermal reversion rates observed is how the derivative with the lowest $K_{tt}$ value has the lowest cis- to trans- reversion rate (i.e. hexylthiol 4f); meanwhile, the system with the highest $K_{tt}$ has the highest thermal reversion rate (i.e. tert-butylphenoxy 4k). The unimolecular nature of the kinetics in 4c, 4f and 4k indicates that the complexation equilibria have no impacted the reversion. Hence, there is no template effect accelerating the reversion as observed in complementary designs (Wisner and Pleizier unpublished results).
3.3 Summary and Conclusions

The photophysical properties of derivatives 4a-p were evaluated. The UV-Vis absorption spectra of all derivatives 4a-p in their trans-isomeric form are similar to azobenzene and 2,2’-azopyridine UV-Vis absorption spectra. This is, the maximum absorptions for the n→π* band are approximately 440 nm, and for the π→π* band are approximately 290 nm (hypsochromic shift). On the other hand, the cis-isomers of derivatives 4c, 4f and 4k have UV-Vis absorption spectra wherein the n→π* band showed higher absorptivity and the π→π* band showed lower absorptivity compared with the trans-isomers. The presence of an isosbestic point during the cis to trans thermal reversion of 4c, 4f and 4k confirms that during this transition there are only two species involved: the cis and trans-isomers. The percentages of interconversion from trans to cis at the photostationary state for all derivatives 4a-p ranged from 9 - 28, 20 - 22 and 14 - 35 percent in CDCl₃, toluene-d₈ and CD₃CN, respectively. Since the photoisomerization yields obtained were lower than 100%, the presence of two more complexation equilibria in solution was assumed; i.e. the cis-cis dimerization and trans-cis complexation. The cis-cis dimerization strength was assumed to be equal to or lower than the dimerization constant values obtained for derivatives 5c, 5f and 5k. Therefore, since these constants are at least 20 times lower than their derivatives 4 counterparts in toluene-d₈, the effect of these complexes in the distribution of the total amount cis-isomer was disregarded. The trans-cis complexes of derivatives 4c, 4f and 4k stabilities were examined. The calculated K_{t,c} complexation constants for 4c and 4f are 160 and 172 M⁻¹; which are in accordance with expected values. On the other hand, the derivative 4k shows a complexation constant
higher than the anticipated value. The reasoning behind the enhance stability of the 4k trans-cis complex is unclear. The speciation diagrams of 4c, 4f and 4k at different trans-isomer molar fractions corroborate the minimal impact that cis dimer has over the species distribution in solution after photoisomerization. Finally, the stability of the 4c, 4f and 4k cis-isomers in solution were studied. In this sense, thermal reversions back to the trans-isomer proceeded as first order reactions wherein the rate constants for derivatives 4c, 4f and 4k are 3.36 x 10^{-4}, 2.74 x 10^{-4} and 6.02 x 10^{-4} s^{-1}, respectively.

3.4 Experimental Methodology

3.4.1 Generalities

All experiments were performed in ambient atmospheric conditions unless otherwise indicated. Solvents (dichloromethane, diethyl ether and hexanes) were obtained from Caledon Laboratories, Fisher Chemicals, Sigma-Aldrich and VWR Analytical. In the case of inert atmosphere conditions, solvents were dried using an Innovative Technology Inc. Controlled Atmospheres Solvent Purification System that utilizes dual alumina columns (SPS-400-5), or purchased from Sigma-Aldrich and used as received. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated TLC-sheets POLYGRAM®SIL G/UV254. Flash chromatography was performed with SiliCycle®SiliaFlash® F60, 40-63 μm 60 Å. Nuclear Magnetic Resonance spectra were recorded on INOVA 400 MHz spectrometer (^{1}H = 399.77 MHz; ^{13}C \{^{1}H\} = 100.52 MHz). ^{1}H spectra were referenced relative to Me$_4$Si using the residual non-deuterated NMR
solvent signal (\(^1\text{H}: \text{CHCl}_3, \delta = 7.26 \text{ ppm}, (\text{CHD}_2)\text{C}_6\text{D}_5, \delta = 2.09 \text{ ppm}, \text{CHD}_2\text{CN} \delta = 1.94 \text{ ppm}). Solvents for NMR spectroscopy (Chloroform-d, Acetonitrile-d\textsubscript{3} and Toluene-d\textsubscript{8}) were purchased from Cambridge Isotope Laboratories and Sigma-Aldrich. All photoisomerization experiments were carried out at a photoreactor unit LZC 4V from Luzchem Research Inc. with a complete set of low-pressure blue lamps with a radiation centered at 360 nm. UV-Vis absorption spectra were obtained from a CARY 300 UV-Visible spectrometer employing quartz curvette (chamber volume 300 mL, pathlength 10 mm, limit 200 – 2500 nm spectral range).

3.4.2 Photostationary State Experiments

Photoisomerization experiments were carried out by irradiating UV light to solutions of derivatives (\(t\))-4a-p in CDCl\textsubscript{3}, toluene-d\textsubscript{8} and CD\textsubscript{3}CN. In a typical photostationary state experiment 2 mL of a derivative 4a-p solution in the selected solvent system was prepared at concentrations of approximately \(10^{-3}\) M. For each derivative, 1 mL of the prepared solution was poured into a Wilmar ® quartz NMR tube (Limit = 400 MHz, Cutoff wavelength = 265 nm). The solution was purged with N\textsubscript{2} in order to avoid side reactions with O\textsubscript{2} present in solution. The UV light source employed in all photoisomerizations was a photoreactor unit LZC 4V from Luzchem Research Inc. with a complete set of low-pressure blue lamps with a radiation peak at 360 nm. Each sample was irradiated for one hour at room temperature and immediately placed into an ice bath and taken to the NMR Spectrometer INOVA 400 MHz. The \textit{cis/trans} ratio was calculated from
the integration of the signals corresponding to the ortho- pyridine proton of (c)-4a-p and (t)-4a-p in the $^1$H NMR spectrum recorded immediately.

3.4.3 Synthesis of (Z)-4-(pyridin-2-ylidazeyl)-1,3,5-triazin-2-amine derivatives ((c)-4c, (c)-4f and (c)-4k).

Approximately 160 mL of a $10^{-2}$ M solution of a derivative 4 in dichloromethane was prepared and distributed between 16 test tubes. Each test tube containing the derivative 4 solution was purged with N$_2$ in order to avoid side reactions with O$_2$ present in solution. The 16 test tubes were placed in the photoreactor and irradiated using lamps with radiation centered at 360 nm for 3 hours. After irradiation, the solution was cooled down to -78º and the solvent was removed employing a constant air flow to yield a mixture of cis and trans isomers. The cis-isomer was isolated through flash chromatography with diethyl ether as eluent. Once the first fraction (cis isomer) was obtained, it was cooled down to -78º to remove the diethyl ether with the aid of a constant air flow. In all cases, the cis-isomer was a yellow powder that was stored in a vial wrapped with black tape in the freezer to prevent thermal and photochemical reversion.

3.4.4 $^1$H NMR Reversion Experiments

In a clean and dry eight inches NMR tube, 0.5 mL of toluene-$d_8$ was injected via syringe. Locking and shimming of pure toluene-$d_8$ was carried out in order to speed up the acquisition of the first $^1$H NMR spectrum of the cis/trans mixture in solution. Apart, a freshly prepared toluene-$d_8$ solution of the cis-isomer was filtered and poured into a
separate empty NMR tube. A $^1$H NMR spectrum was recorded immediately in order to obtain the maximum cis/trans ratio. Then, a $^1$H NMR spectrum was recorded every 3 to 5 minutes until the signal to noise ratio of the cis-isomer signals were lower than 4. The cis/trans ratio and chemical shifts of the N-H protons of (c)-4 and (t)-4 were identified and tracked during the experiment. For each derivative 4 tested, the reversion procedure was repeated at least twice to ensure the reliability and reproducibility of the data. Data processing was performed off-line using the commercial software package MATLAB R2015b (The MathWorks Inc. 1984-2015).

### 3.5 References


Chapter 4


In the second and third chapters, the design, synthesis and analysis of a system which dimerizes thanks to the presence of amino, triazine, azo and pyridine moieties was presented; i.e. derivatives 4a-p. Based on the number and the nature of hydrogen bond interactions present in those arrays, it was expected that dimerization constants higher than $10^2 \text{M}^{-1}$ would be observed in CDCl$_3$. Unfortunately, this was not the case. This unexpected poor performance led us to consider what improvement might be made to the design in order to achieve higher complex stability in the trans-form of the arrays.

In this sense, the X-ray crystal structures were useful since they allowed us to observe the dimer structure in the solid state. More specifically, it let us measure the intermolecular distances and angles between interacting sites. From this analysis, we noted that the pyridine nitrogen atom lone pair is not colinear with the N-H bond of the amino group. The calculated average of the N-H···N(pyridine) angles measured in all dimers of 4
in the solid state averaged 138° (Figure 4.1). Therefore, the dimerization constants obtained were in agreement with a system stabilized by only one strong (or primary) hydrogen bond interaction and two weaker (or secondary) hydrogen bond interactions.

![Diagram](image)

**Figure 4.1** Average N-H···N(pyridine) angle in dimer structures of 4 observed in the solid state.

From this observation and the results of molecular modeling, it was concluded that the pyridine ring could be replaced by a fragment containing an aromatic ring wherein the acceptor site would be *bonded* *ortho* to the azo group (instead of *located* *α* to the azo group). This way the lone pair participating in the hydrogen bond interaction would be lined up with the N-H bond and hopefully lead to an improved photoswitchable self-complementary **DDAAA** hydrogen bond array (Figure 4.2).
In this sense, our first proposed change to the original design was to replace the pyridine ring by the quinoline group. The quinoline ring was a good option since it would provide an sp² nitrogen atom ortho- to the azo group to participate in a strong hydrogen bond interaction with an amino proton.\textsuperscript{1,2} Likewise, the planarity and aromaticity of this moiety could contribute to dimer stability through conjugation. Following the synthetic strategy employed for the synthesis of derivatives 4a-p, the quinoline ring was planned to be inserted at the third step as 8-hydrazinylquinoline; i.e., similarly to the addition of 2-hydrazinylpyridine in the synthesis of derivatives 4a-p (Scheme 4.1). However, the 8-hydrazinylquinoline is unstable at the temperatures needed to achieve the third addition to the triazine ring.

Scheme 4.1 Synthetic strategy to add quinoline ring as acceptor at the third step.
On the other hand, when the 8-hydrazinylquinoline is added at the second step, the addition of the RX group at the third step (or after oxidation of the hydrazinyl- derivative) attempted did not precede (Scheme 4.2). Therefore, the inclusion of a quinoline ring as a hydrogen bond acceptor was discarded.

![Scheme 4.2](image)

**Scheme 4.2** Synthetic strategy to add quinoline ring at the second step.

After a survey of alternative acceptor groups that could be incorporated into the aromatic ring, an alkoxy group was identified as a feasible alternative; i.e. an sp\(^3\) oxygen atom as hydrogen bond acceptor. Jeffrey and coworkers reported an extensive analysis of the crystal structure of barbiturates, purines, pyrimidines, nucleosides and nucleotides (45 barbiturates, 214 purines and pyrimidines, and 119 nucleosides and nucleotides crystal structures, respectively).\(^3,4\) In these studies, there was a particular attention to the hydrogen bond lengths of different pairs of donor and acceptor groups. The data analyzed provide a guide to indicate the relative donor and acceptor strength. In this sense, the relative acceptor strength of an ether group is slightly lower compared with an sp\(^2\) nitrogen atom, such as the acceptor site in the proposed quinoline ring (Table 4.1).\(^5\) However, the hydrogen bond distances reported for the alkoxy group as an acceptor are smaller in comparison with the hydrogen bond distances observed for the 4a, 4d, 4f and 4k dimer structures in the solid state reported in Chapter 2 (section 2.3.3). Therefore, it would be reasonable to expect an
improvement in the strength of the hydrogen bond interaction between the amino N-H site
and the alkoxy group for our photoswitchable self-complementary DDAAA arrays.

Table 4.1 Ranges and mean values of the lengths (Å) and angles (º) of hydrogen bonds in
crystal structures of purines and pyrimidines, nucleosides, and nucleotides.a

<table>
<thead>
<tr>
<th>Donors</th>
<th>Acceptors</th>
<th>N-H</th>
<th>O</th>
<th>N-N_b</th>
</tr>
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<tr>
<td></td>
<td>N-H</td>
<td>47</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.73</td>
<td>179</td>
<td>1.77</td>
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<td></td>
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<td>144</td>
<td>2.25</td>
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<td>168</td>
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<tr>
<td></td>
<td>-N(H)H</td>
<td>69</td>
<td>9</td>
<td>4</td>
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<td></td>
<td></td>
<td>1.85</td>
<td>179</td>
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<tr>
<td></td>
<td></td>
<td>2.76</td>
<td>119</td>
<td>2.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.04</td>
<td>163</td>
<td>2.26</td>
</tr>
</tbody>
</table>

a For each entry, row one is the number of data, row two is the minimum value, row three is the maximum value and row four the mean value; column one is the hydrogen bond length (Å) and column two is the two centered hydrogen bond angle (º). b Values obtained from crystal structures of derivatives 4a, 4d, 4f and 4k in Chapter 2 (Table 2.9).

Hence, we proposed the synthesis of (E)-4-((2-methoxyphenyl)diazinyl)-1,3,5-triazin-2-amine derivatives (7). These derivatives fulfill the main improvement proposed for our photoswitchable self-complementary array; i.e. the location of an acceptor group bonded ortho- to the azo group that would improve the trans-trans dimer stability (Scheme 4.3).
Scheme 4.3 Improved photoswitchable self-complementary AAADD hydrogen bond array.

Since the main purpose of the systems designed is to trigger a change in their molecular recognition through a light stimulus, it is important to note that, regardless of the alteration proposed, it is still expected that a trans- to cis- structural change should cause a reduction in the number of hydrogen bond interacting sites as assumed for derivatives 4a-p (Scheme 4.4).

Scheme 4.4 Amended photoswitchable self-complementary AAADD hydrogen bond array and its idealized function.

The remaining sections of this chapter present the synthesis and characterization of an amended photoswitchable self-complementary system. The dimer stability of the
proposed array in solution and the structure in the solid state will be discussed with a comparison to the derivatives 4a-p reported in Chapter 2 and 3. Likewise, the photochemical properties and the complexation pattern before and after photoisomerization of these new derivatives will be presented.

4.2 Results and Discussion.

4.2.1 Synthesis of Second Generation Photoswitchable Self-Complementary Hydrogen Bond Arrays.

Since the main alteration to our proposed system replacing pyridine ring for an methoxyphenyl group, the syntheses of these systems followed the same synthetic pathway established for derivatives 4a-p in Chapter 2 (Section 2.3.1). The only modification to the procedure corresponded to the use of the (2-methoxyphenyl)hydrazine hydrochloride salt instead of 2-hydrazinopyridine at the third stage of the triazine ring substitution (Scheme 4.5). Based on the results obtained from 4a-p, the RX groups employed were those that provided the highest dimerization constants and where soluble in toluene (Table 4.2).

Table 4.2 Reactants and overall yields of photoswitchable self-complementary hydrogen bond arrays 7.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>RXH</th>
<th>Base&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>7c</td>
<td>n-butanol</td>
<td>NaH</td>
<td>12</td>
</tr>
<tr>
<td>7f</td>
<td>hexanethiol</td>
<td>NaOH</td>
<td>38</td>
</tr>
<tr>
<td>7g&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
<td>NH&lt;sub&gt;4&lt;/sub&gt;OH&lt;sup&gt;d&lt;/sup&gt;</td>
<td>12</td>
</tr>
<tr>
<td>7i</td>
<td>phenol</td>
<td>NaOH</td>
<td>78</td>
</tr>
<tr>
<td>7k</td>
<td>4′-tert-butylphenol</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>8</td>
</tr>
<tr>
<td>7m</td>
<td>3,5-bis(trifluoromethyl)phenol</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>20</td>
</tr>
<tr>
<td>7n</td>
<td>perfluorophenol</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>46</td>
</tr>
</tbody>
</table>

<sup>a</sup> One equivalent added at 0 ºC.  
<sup>b</sup> Percent yield over 3 synthetic steps starting from intermediate 1.  
<sup>c</sup> Chloro is already in place in intermediate 1.  
<sup>d</sup> Two equivalents of base added.

The overall chemical yields obtained for derivatives 7 ranged from 8 to 78% starting from intermediate 1. These yields are similar to the range of the chemical yields
obtained for derivatives 4a-p. Based on those observations it can be concluded that the reactivity of (2-methoxyphenyl)hydrazine is similar to the 2-hydrazinopyridine.

4.2.2 $^1$H NMR Dilution Experiments: Stability of trans-trans dimers.

Dilution experiments of all derivatives 7 were carried out in CDCl$_3$. Table 4.3 displays the (most stable) trans-isomer dimerization constants ($K_{t-t}$) with the calculated chemical shifts of the amino protons when 7 are in solution as free monomers ($\delta_m$) and in a dimer structure ($\delta_d$).

Table 4.3 Dimerization constants, free energies of dimerization, chemical shifts of monomer ($\delta_m$) and dimer ($\delta_d$) species studied, and the total change in the chemical shift ($\Delta\delta_{max}$) in CDCl$_3$ at 298 K.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>RX</th>
<th>$K_{t-t}$ in CDCl$_3$ (M$^{-1}$)</th>
<th>$\Delta G_{t-t}$ (kJ mol$^{-1}$)</th>
<th>$\delta_m$ (ppm)</th>
<th>$\delta_d$ (ppm)</th>
<th>$\Delta\delta_{max}$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7c</td>
<td>-O(n-C$_4$H$_9$)</td>
<td>36 ± 5</td>
<td>-8.86 ± 0.32</td>
<td>5.47</td>
<td>6.53</td>
<td>1.07</td>
</tr>
<tr>
<td>7f</td>
<td>-S(n-C$<em>6$H$</em>{13}$)</td>
<td>57 ± 1</td>
<td>-10.02 ± 0.03</td>
<td>5.46</td>
<td>6.56</td>
<td>1.11</td>
</tr>
<tr>
<td>7g</td>
<td>-Cl</td>
<td>310 ± 140</td>
<td>-14.21 ± 1.09</td>
<td>5.72</td>
<td>6.46</td>
<td>0.74</td>
</tr>
<tr>
<td>7i</td>
<td>-OC$_6$H$_5$</td>
<td>210 ± 20</td>
<td>-13.29 ± 0.24</td>
<td>5.48</td>
<td>6.55</td>
<td>1.06</td>
</tr>
<tr>
<td>7k</td>
<td>-OC$_6$H$_4$-4'-C(CH$_3$)$_3$</td>
<td>120 ± 30</td>
<td>-11.75 ± 0.74</td>
<td>5.49</td>
<td>6.55</td>
<td>1.06</td>
</tr>
<tr>
<td>7m</td>
<td>-OC$_6$H$_3$-3',5'-bis(CF$_3$)</td>
<td>130 ± 50</td>
<td>-12.03 ± 1.00</td>
<td>5.54</td>
<td>6.37</td>
<td>0.83</td>
</tr>
<tr>
<td>7n</td>
<td>-OC$_6$F$_5$</td>
<td>80 ± 1</td>
<td>-10.88 ± 0.04</td>
<td>5.56</td>
<td>6.44</td>
<td>0.88</td>
</tr>
</tbody>
</table>

$^a$ Average values obtained using Equation 5 (Chapter 2) and three separate dilution experiments. Errors calculated from twice the standard deviation to give a 95% confidence interval $^b$ Resonance used in fitting process assigned to H$_a$ hydrogen atom in Figure 2.8.
In CDCl$_3$, derivatives 7 showed dimerization constant values from 36 to 309 M$^{-1}$; wherein the lowest constant corresponds to the butoxy derivative 7c (Figure 4.3); and the highest constant corresponds to the chloro derivative 7g (Figure 4.4).

![Chemical Structure of 7c](image)

**Figure 4.3** Dimerization isotherm of 7c with $K_{tt}$ value and free energy calculated from fitting of the data to a 1:1 dimerization model. Blue, green and red dots correspond to first, second and third separate dilution experiments, respectively. Solid line corresponds to the theoretical dilution curve obtained from the average $K_{tt}$ of three separate dilution experiments.
When the free energy of dimerization ($\Delta G_{t-t}$) was associated with the difference between the monomer and dimer calculated chemical shift, it was observed a roughly linear relationship between these two values ($r = 0.8595$, Figure 4.5). That is, as the free energy of dimerization decreases, the difference in the chemical shift between dimer and monomer also decreases.

On the other hand, the free energies of dimerization in CDCl$_3$ ($\Delta G_{t-t}$) of the derivatives 7c, 7g and 7i were plotted against the $\sigma_m$ values for their RX moieties (Figure 4.6). To this plot it was also added the $\Delta G_{t-t}$ values of the 7f and 7k with approximations to the $\sigma_m$ value for the hexylthiol and 4’- tert -butylphenoxy groups. Similarly to 4a-p, there is a correlation ($r = -0.91784$) between these two values. Hence, as $\sigma_m$ increases $\Delta G_{t-t}$
decreases. Likewise, a looser correlation between the $\Delta G_{t\cdot t}$ values with the inductive effect contribution (-$I$) (Figure 4.7) is observed.

**Figure 4.5** Correlation plot of $\ln(K_{t\cdot t})$ vs $\Delta \delta_{\text{max}}$ for all derivatives 7 in CDCl$_3$ at 298 K ($r = 0.8595$).
Figure 4.6 Correlation plot of $\Delta G_{tt}$ vs $\sigma_m$ of derivatives 7c, 7f, 7g, 7i, and 7k in toluene-$d_8$ at 298 K. Dotted line corresponds to the least squares correlation line ($r = -0.91784$).

Figure 4.7 Correlation plot of $\Delta G_{tt}$ vs $I$ of derivatives 7c, 7f, 7g, 7i, and 7k in CDCl$_3$ at 298 K. Dotted line corresponds to the least squares correlation line ($r = -0.86027$).
Regarding the effect of the \textit{ortho}-methoxyphenyl acceptor, it can be observed that dimerization constants of the derivatives 7 are generally higher than those obtained for corresponding derivatives 4. The only exception to this trend was the perfluorophenoxy derivative 7n, whose dimerization constant is half that of perfluorophenoxy derivative 4n. From those systems where derivatives 7 showed higher dimerization values than their derivatives 4 counterparts, dimerization free energy differences were from 0.25 kJmol$^{-1}$ to 3.19 kJmol$^{-1}$. In general, the total contribution of the \textit{ortho}-methoxyphenyl group acceptor site to the dimer stability can be estimated through the comparison of derivatives 7c, 7f and 7k with their counterparts derivatives 5 ($\Delta G_{t,t} = -4.43$ kJ mol$^{-1}$ for 5c, $\Delta G_{t,t} = -3.90$ kJ mol$^{-1}$ for 5f, and $\Delta G_{t,t} = -5.85$ kJ mol$^{-1}$ for 5k in CDCl$_3$). The energetic contribution of both \textit{ortho}-methoxyphenyl acceptor sites to the dimerization is approximately 5 kJ mol$^{-1}$ in CDCl$_3$ ($\Delta\Delta G_{\text{Butoxy}} = -4.43$ kJ mol$^{-1}$, $\Delta\Delta G_{\text{Hexylthiol}} = -6.12$ kJ mol$^{-1}$, and $\Delta\Delta G_{4'-\text{tert}-\text{butylphenoxy}} = -5.90$ kJ mol$^{-1}$); or 2.5 kJ mol$^{-1}$ per \textit{ortho}-methoxyphenyl moiety.

Alternatively, the dimerization constants obtained for derivatives 7c, 7f and 7n in toluene-$d_8$ are summarized in Table 4.4. Surprisingly, the 4'-\textit{tert}-butylphenoxy derivative 7k was not soluble in toluene-$d_8$, contrary to its pyridyl counterpart; 4k. As occurred for derivatives 4c, 4f and 4n, 7c, 7f and 7n displayed much higher dimerization constants in toluene-$d_8$ than those observed in CDCl$_3$. The highest dimerization constant corresponded to perfluorophenoxy derivative 7n with a value of 5640 M$^{-1}$ (Figure 4.8); meanwhile, the butoxy 7c and hexylthiol 7f displayed dimerization constants of 2740 and 2420 M$^{-1}$, respectively (Figures 4.9 and 4.10).
Table 4.4 Dimerization constants, free energies of dimerization, chemical shifts of monomer (δ<sub>m</sub>) and dimer (δ<sub>d</sub>) species studied, and the total change in the chemical shift (Δδ<sub>max</sub>) in toluene-d<sub>8</sub> at 298 K.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>RX</th>
<th>K&lt;sub&gt;tt&lt;/sub&gt; in Toluene-d&lt;sub&gt;8&lt;/sub&gt; (M&lt;sup&gt;-1&lt;/sup&gt;)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ΔG&lt;sub&gt;tt&lt;/sub&gt; (kJ mol&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>δ&lt;sub&gt;m&lt;/sub&gt; (ppm)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>δ&lt;sub&gt;d&lt;/sub&gt; (ppm)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Δδ&lt;sub&gt;max&lt;/sub&gt; (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7c</td>
<td>-O(n-C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;)</td>
<td>2740 ± 590</td>
<td>-19.62 ± 0.53</td>
<td>4.17</td>
<td>6.70</td>
<td>2.53&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7f</td>
<td>-S(n-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;)</td>
<td>2420 ± 760</td>
<td>-19.30 ± 0.77</td>
<td>4.04</td>
<td>6.66</td>
<td>2.62&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7n</td>
<td>-OC&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;5&lt;/sub&gt;</td>
<td>5640 ± 930</td>
<td>-21.40 ± 0.42</td>
<td>3.88</td>
<td>6.76</td>
<td>2.88&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Average values obtained using Equation 5 and three separate dilution experiments. Errors calculated from twice the standard deviation to give a 95% confidence interval.

<sup>b</sup> Resonance used in fitting process.

The dimerization constants obtained for derivatives 7 in toluene-d<sub>8</sub> at room temperature display a correlation with the electron withdrawing character of the RX substituent. Thus, the perfluorophenoxy derivative 7n with the strongest electron withdrawing RX moiety exhibits the highest dimerization constant. Meanwhile, the hexylthiol derivative 7f with the lowest electron withdrawing character had the lowest K<sub>tt</sub>. 
**Figure 4.8** Dimerization isotherm of 7n with $K_{t-t}$ value and free energy calculated from fitting of the data to a 1:1 dimerization model. Blue, green and red dots correspond to first, second and third separate dilution experiments, respectively. Solid line corresponds to the theoretical dilution curve obtained from the average $K_{t-t}$ of three separate dilution experiments.

**Figure 4.9** Dimerization isotherm of 7c with $K_{t-t}$ value and free energy calculated from fitting of the data to a 1:1 dimerization model. Blue, green and red dots correspond to first, second and third separate dilution experiments, respectively. Solid line corresponds to the theoretical dilution curve obtained from the average $K_{t-t}$ of three separate dilution experiments.
Figure 4.10 Dimerization isotherm of 7f with $K_{t-t}$ value and free energy calculated from fitting of the data to a 1:1 dimerization model. Blue, green and red dots correspond to first, second and third separate dilution experiments, respectively. Solid line corresponds to the theoretical dilution curve obtained from the average $K_{t-t}$ of three separate dilution experiments.

Overall, the differences in the dimerization free energy between derivatives 7c, 7f and 7n with their counterparts 4 ranged from 1.05 to 3.50 kJmol$^{-1}$. Likewise, the differences in the dimerization free energy between 7c and 7f with the counterparts 5 ($\Delta G_{t-t} = -7.16$ kJ mol$^{-1}$ for 5c, and $\Delta G_{t-t} = -8.13$ kJ mol$^{-1}$ for 5f in toluene-$d_8$) are at least 11 kJ mol$^{-1}$ ($\Delta \Delta G_{\text{Butoxy}} = -12.46$ kJ mol$^{-1}$, and $\Delta \Delta G_{\text{Hexylthiol}} = -11.17$ kJ mol$^{-1}$). In other words, the energetic contribution to the dimer stability is approximately 11 kJ mol$^{-1}$ in toluene-$d_8$ when both ortho-methoxyphenyl moieties participate, or 5.5 kJ mol$^{-1}$ per acceptor site. In conclusion, the improvement over the dimer strength provided by changing the pyridine ring to an ortho-methoxyphenyl group is larger in toluene-$d_8$ than in CDCl$_3$. This is in agreement with the effect of the solvent system wherein the intermolecular interactions take place, as previously discussed (Chapter 2, Section 2.3.2).
4.2.3 X-Ray Analysis of Self-Complementary Arrays

As described in Chapter 2, single crystal X-ray diffraction was helpful to substantiate our proposed dimer structure for derivatives 7c, 7f, 7k and 7n (Table 4.5). Crystal growth was carried out by slow evaporation or slow diffusion; in a similar manner to the process outlined for derivatives 4 (Chapter 2, Section 2.3.3).
Table 4.5 Crystallographic parameters for 7c, 7f, 7k and 7n crystals.

<table>
<thead>
<tr>
<th>Chemical Formula</th>
<th>7c</th>
<th>7f</th>
<th>7k</th>
<th>7n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight (g·mol⁻¹)</td>
<td>302.34</td>
<td>346.45</td>
<td>378.43</td>
<td>412.29</td>
</tr>
<tr>
<td>Crystal System</td>
<td>Monoclinic</td>
<td>Triclinic</td>
<td>Monoclinic</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space Group</td>
<td>C 2/c</td>
<td>P̅</td>
<td>P 2/n</td>
<td>P 2/n</td>
</tr>
<tr>
<td>a (Å)</td>
<td>10.9333 (17)</td>
<td>8.7724 (18)</td>
<td>12.5420 (52)</td>
<td>8.6611 (16)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>15.279 (2)</td>
<td>11.9917 (17)</td>
<td>11.1245 (36)</td>
<td>7.3759 (16)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>18.203 (2)</td>
<td>18.233 (3)</td>
<td>14.175 (6)</td>
<td>25.874 (4)</td>
</tr>
<tr>
<td>α (°)</td>
<td>90</td>
<td>73.554 (5)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>β (°)</td>
<td>107.366 (8)</td>
<td>76.971 (7)</td>
<td>101.2613 (15)</td>
<td>96.298 (11)</td>
</tr>
<tr>
<td>γ (°)</td>
<td>90</td>
<td>79.236 (7)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>V (Å³)</td>
<td>2902.1 (8)</td>
<td>1776.6 (5)</td>
<td>1939.66 (13)</td>
<td>1642.9 (5)</td>
</tr>
<tr>
<td>Z</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>F(000)</td>
<td>1280</td>
<td>736</td>
<td>800</td>
<td>832</td>
</tr>
<tr>
<td>T (K)</td>
<td>110</td>
<td>173</td>
<td>123</td>
<td>110</td>
</tr>
<tr>
<td>λ (Å)</td>
<td>1.54178</td>
<td>1.54178</td>
<td>0.71073</td>
<td>1.54178</td>
</tr>
<tr>
<td>ρ calc (g·cm⁻³)</td>
<td>1.384</td>
<td>1.295</td>
<td>1.296</td>
<td>1.667</td>
</tr>
<tr>
<td>μ (mm⁻¹)</td>
<td>0.804</td>
<td>1.748</td>
<td>0.088</td>
<td>1.359</td>
</tr>
<tr>
<td>Reflections Collected</td>
<td>27839</td>
<td>40537</td>
<td>42708</td>
<td>33039</td>
</tr>
<tr>
<td>Unique Reflections</td>
<td>2529</td>
<td>6090</td>
<td>3403</td>
<td>2841</td>
</tr>
<tr>
<td>Absorption Correction</td>
<td>multi-scan</td>
<td>multi-scan</td>
<td>multi-scan</td>
<td>multi-scan</td>
</tr>
<tr>
<td>Refinement on</td>
<td>F²</td>
<td>F²</td>
<td>F²</td>
<td>F²</td>
</tr>
<tr>
<td>Parameters Refined</td>
<td>271</td>
<td>586</td>
<td>315</td>
<td>298</td>
</tr>
<tr>
<td>R(F₀)/(&gt;2σ(I))</td>
<td>0.0333</td>
<td>0.0520</td>
<td>0.0468</td>
<td>0.0471</td>
</tr>
<tr>
<td>R_w(F₀²)/(&gt;2σ(I))</td>
<td>0.0865</td>
<td>0.1359</td>
<td>0.1180</td>
<td>0.1348</td>
</tr>
<tr>
<td>R(F₀)(all data)</td>
<td>0.0376</td>
<td>0.0617</td>
<td>0.0757</td>
<td>0.0536</td>
</tr>
<tr>
<td>R_w(F₀²)(all data)</td>
<td>0.0902</td>
<td>0.1455</td>
<td>0.1375</td>
<td>0.1413</td>
</tr>
<tr>
<td>GOF on F²</td>
<td>1.078</td>
<td>1.051</td>
<td>1.022</td>
<td>1.06</td>
</tr>
</tbody>
</table>
Butoxy derivative 7c was crystallized by slow diffusion of dry pentane into a saturated toluene solution to yield red prisms suitable for single crystal X-ray diffraction analysis. The collected data from this analysis was solved in the \( C 2/c \) space group with eight molecules per unit cell. Two symmetry related molecules take up the expected dimer configuration wherein the self-complementary array is arranged in an antiparallel manner through six hydrogen bonds (Table 4.6 and Figure 4.11). The aminotriazine rings of both monomers are coplanar and participate in a symmetry related pair of hydrogen bonds (\( \text{N}_{6}\text{H}_{6\text{A}}\cdots\text{N}_{5} = 2.93 \ \text{Å}; \angle \text{N-H}\cdots\text{N} = 175^\circ \)) as observed for 4 in the solid state. Likewise, oblique hydrogen bond interactions between an amino N-H donor and the azo nitrogen acceptor are observed (\( \text{N}_{6}\text{H}_{6\text{A}}\cdots\text{N}_{1} = 3.12 \ \text{Å}; \angle \text{N-H}\cdots\text{N} = 110^\circ \)). The last type of hydrogen bond present in the dimer structure corresponds to the interaction between the amino proton with the oxygen atom of the methoxy group. The intermolecular distance and angle between the interacting sites (\( \text{N}_{6}\text{H}_{6\text{B}}\cdots\text{O}_{1} = 2.88 \ \text{Å}; \angle \text{N-H}\cdots\text{O} = 164^\circ \)) are in agreement with the anticipated improvement from the dimer structure obtained for 4 in the solid state; i.e. shorter distances and intermolecular angles closer to linearity. More specifically, in comparison with the octyloxy derivative 4d, the intermolecular distances between the interacting sites in butoxy derivative 7c are (generally) shorter; and, two of the three pairs of hydrogen bond interactions are less than 20° from linearity. The butoxy 7c dimer deviates from planarity since there is an angle of 16° between the least squares planes of all heavy atoms in the triazine and phenyl rings. This angle is observed in an intramolecular and intermolecular sense since the dimer contains an inversion centre. Lastly, no other notable non-covalent interactions are observed in the extended lattice structure between dimers.
Table 4.6 Hydrogen bond distances and angles of complex 7c-7c X-ray crystal structure data.

<table>
<thead>
<tr>
<th>D···A</th>
<th>d NH···X (Å)</th>
<th>d NH···X (Å)</th>
<th>∠ NH···X (º)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N6-H6A···N5'</td>
<td>2.9282 (4)</td>
<td>2.0282 (3)</td>
<td>174.896 (17)</td>
</tr>
<tr>
<td>N6-H6A···N1'</td>
<td>3.1230 (4)</td>
<td>2.2836 (4)</td>
<td>110.043 (14)</td>
</tr>
<tr>
<td>N6-H6B···O1'</td>
<td>2.8792 (4)</td>
<td>2.0194 (3)</td>
<td>163.785 (16)</td>
</tr>
</tbody>
</table>

Figure 4.11 Stick representation of the X-ray crystal structure of 7c dimer with intermolecular hydrogen bonds indicated (dashed orange lines). Blue, grey, white and red correspond to nitrogen, carbon, hydrogen and oxygen atoms, respectively.
X-ray quality crystals of hexylthiol derivative 7f were obtained by slow diffusion of heptane into a saturated ethyl acetate solution. The crystals obtained were red prisms in space group $P\bar{1}$ with four molecules per unit cell displayed in the crystal lattice as two separate dimer structures: A-A’ and B-B’ (Figures 4.12 and 4.13). In each dimer structure, the monomers are related by symmetry (i.e. there is an inversion center). However, the dimers are differentiated by the dispositions of the hexylthiol groups. That is, the hexylthiol groups in dimer B-B’ are disordered in comparison with dimer A-A’. The 7f dimer structures display similar hydrogen bond interactions to those observed in the preceding 7c dimer in the solid state; i.e. hydrogen bonds between amino N-H protons with the triazine, azo and methoxy heteroatoms (Table 4.7). Likewise, the hydrogen bond distances in 7f dimers are alike to the hydrogen bond distances reported for the 7c dimer in the solid state. This observation corroborates that the dimer strength of derivative 7f is comparable to the dimer strength of 7c as deduced from the dimerization constants obtained for the two derivatives (Section 4.2.2). Compared with the dimer structure of hexylthiol derivative 4f in the solid state, 7f dimers exhibit (generally) shorter intermolecular distances between donor and acceptor sites, and angles closer to linearity. The azoheteroaromatic core (i.e. without including the hexylthiol group) of both dimer structures can be considered planar since there are no deviations larger than 0.10 and 0.11 Å from the least squares planes of all the heavy atoms for dimers A-A’ and B-B’ respectively. In this sense, the coplanarity of both dimers is a result of the planarity of each monomer. The largest deviations from the least squares planes of all heavy atoms in the azoheteroaromatic cores are 0.09 and 0.07 Å for molecules A and B, respectively. In the extended crystal lattice, dimers are slip-stacked as layers through $\pi-\pi$ interactions with their symmetry related dimers in the
adjacent unit cells. The angle between these layers of A-A’ and B-B’ dimers is 69° (Figure 4.14). In addition to the expected hydrogen bond interactions in 7f, molecules A show C5A-H5A···N3A’ hydrogen bonds to the opposing edge to the DDAAA array, as observed in the crystal lattice of derivatives 4d and 4f (Figure 4.15, Table 4.7). Since in the course of the three dilution experiments of 7f in CDCl₃ and toluene-d₈ there were no observable changes in the chemical shift corresponding to the H5A proton, it is concluded that these hydrogen bond interactions are a result of crystal packing.

![Figure 4.12 Stick representation of the X-ray crystal structure of 7f dimer A-A’ with intermolecular hydrogen bonds indicated (dashed orange lines). Blue, grey, white, red and yellow correspond to nitrogen, carbon, hydrogen, oxygen and sulfur atoms, respectively.](image)
Figure 4.13 Stick representation of the X-ray crystal structure of 7f dimer B-B’ with intermolecular hydrogen bonds indicated (dashed orange lines). Blue, grey, white, red and yellow correspond to nitrogen, carbon, hydrogen, oxygen and sulfur atoms, respectively. Note: the alkyl chains are disordered.

Table 4.7 Hydrogen bond distances and angles of complex 7f-7f X-ray from the crystal structure data.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimer A-A’</td>
<td>N6A-H6A2···N5A’</td>
<td>2.8966 (4)</td>
<td>2.0557 (3)</td>
<td>173.526 (17)</td>
</tr>
<tr>
<td></td>
<td>N6A-H6A2···N1A’</td>
<td>3.0967 (4)</td>
<td>2.7139 (4)</td>
<td>109.236 (14)</td>
</tr>
<tr>
<td></td>
<td>N6A-H6A1···O1A’</td>
<td>2.8728 (6)</td>
<td>2.0721 (4)</td>
<td>161.168 (27)</td>
</tr>
<tr>
<td></td>
<td>C5A-H5A···N3A’</td>
<td>3.3715 (5)</td>
<td>2.4819 (3)</td>
<td>173.257 (15)</td>
</tr>
<tr>
<td>Dimer B-B’</td>
<td>N6B-H6B1···N5B’</td>
<td>2.9449 (3)</td>
<td>2.0431 (2)</td>
<td>176.753 (16)</td>
</tr>
<tr>
<td></td>
<td>N6B-H6B1···N1B’</td>
<td>3.1489 (4)</td>
<td>2.7088 (4)</td>
<td>111.132 (13)</td>
</tr>
<tr>
<td></td>
<td>N6B-H6B2···O1B’</td>
<td>2.9080 (5)</td>
<td>2.0128 (4)</td>
<td>158.980 (23)</td>
</tr>
</tbody>
</table>
**Figure 4.14** Selected molecules in the crystal lattice of 7f. Green and blue structures correspond to dimer A-A’ and dimer B-B’, respectively.

**Figure 4.15** Stick representation of the X-ray crystal structure of 7f with C-H···N interactions indicated (dashed orange lines). Blue, grey, white, red and yellow correspond to nitrogen, carbon, hydrogen, oxygen and sulfur atoms, respectively.
Single crystals from derivative 7k were obtained by slow diffusion of heptane into a saturated solution of ethyl acetate. The red plates obtained were suitable for X-ray diffraction and were solved in the monoclinic space group P 2/n with four molecules per unit cell. As observed in Figure 4.16, derivative 7k in the solid state differs significantly from 7c and 7f in the sense that the molecular conformation of 7k locates the amino group at the opposite side of the triazine ring from the methoxy group. This difference allows 7k to form a head-to-tail infinite hydrogen bonded chains where the amino group participates in three hydrogen bond interactions with the triazine (N6-H6B⋯N3’ = 3.00 Å; ∠N-H⋯N = 164°), azo (N6-H6B⋯N1’ = 3.08 Å; ∠N-H⋯N = 109°) and methoxy (N6-H6B⋯O1’ = 2.93 Å; ∠N-H⋯O = 176°) acceptors from another molecule symmetry related by a screw operation. Compared with the 4’-tert-butylphenoxy derivative 4k, the 4’-tert-butylphenoxy 7k has (generally) shorter intermolecular distances between the heteroatoms participating in the hydrogen bond interactions. Another important characteristic of 7k structure in the solid state is the lack of planarity of the molecule. The angle between the least squares planes of all heavy atoms in the triazine and ortho-methoxyphenyl rings is 44°. In addition, the least squares plane of the 4’-tert-butylphenyl ring is twisted 82° from the triazine ring plane. This particular twisted conformation of the 7k molecules results in a zigzag layout in the extended lattice wherein layers are stacked through π-π interactions between the triazine and ortho-methoxyphenyl ring (Figure 4.17).
Figure 4.16 Stick representation of the X-ray crystal structure of 7k array with intermolecular hydrogen bonds indicated (dashed orange lines). Blue, grey, white and red correspond to nitrogen, carbon, hydrogen and oxygen atoms, respectively. View perpendicular to ab plane. All C-H hydrogen atoms removed for clarity. Note: tert-butyl groups are disordered.

Figure 4.17 Stick representation of the X-ray crystal structure of 7k layout with intermolecular hydrogen bonds indicated (dashed orange lines). Blue, grey, white and red correspond to nitrogen, carbon hydrogen and oxygen atoms, respectively. View perpendicular to the bc plane. All C-H hydrogen atoms removed for clarity. Note: tert-butyl groups are disordered.
Table 4.8 Hydrogen bond distances and angles of the array 7k X-ray from the crystal structure data.

<table>
<thead>
<tr>
<th>D···A</th>
<th>d NH···X (Å)</th>
<th>d N···X (Å)</th>
<th>∠ NH···X (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N6-H6B···N3</td>
<td>3.0049 (7)</td>
<td>2.1908 (5)</td>
<td>163.627 (21)</td>
</tr>
<tr>
<td>N6-H6A···N1</td>
<td>3.0811 (7)</td>
<td>2.6677 (7)</td>
<td>109.189 (19)</td>
</tr>
<tr>
<td>N6-H6A···O1</td>
<td>2.9339 (11)</td>
<td>2.0367 (7)</td>
<td>175.754 (45)</td>
</tr>
</tbody>
</table>

The infinite hydrogen bond chain exhibited by 7k in the solid state raises the question of whether or not such structures are also present in solution. In this sense, it is improbable that this head-to-tail complex is present to any great extent in solution. Hydrogen bonded chains of this nature contain half of the interactions that stabilize the fully self-complementary dimer structure. Therefore, in solution such chains would be greatly out-competed by the formation of discrete dimers with all six hydrogen bonds interactions. The further association of a third molecule is thus even less likely statistically. Hence, the likelihood of an appreciable concentration of dimeric or even trimeric chain-like species can be ignored.

Finally, single crystals of the perfluoro derivative 7n were obtained by slow diffusion of diisopropyl ether into a saturated dichloromethane solution to produce red prisms suitable for X-ray analysis. The data obtained from such analysis was modeled in the monoclinic P 2/n with four molecules per unit cell. Two molecules form a dimer structure with inversion symmetry, in a similar manner as described for 7c and 7f (Figure 4.18). The self-complementary arrays pair up in an antiparallel manner through hydrogen bonds between the amino N-H protons with the triazine (N6-H6A···N5’ = 2.92 Å; ∠N-
H⋯N = 176°), azo (N6-H6A⋯N1’ = 3.12 Å; ∠N-H⋯N = 114°) and methoxy (N6-H6B⋯O1’ = 2.90 Å; ∠N-H⋯O = 159°) acceptors. The intermolecular distances between donor and acceptor sites are within the range observed for 7c and 7f dimers in the solid state. The azoheterocyclic core of 7n dimer can be considered planar since the larger deviation from least squares plane of all heavy atoms is no larger than 0.28 Å. In other words, the angle between the triazine and ortho-methoxyphenyl ring planes (least squares planes of all heavy atoms) is 7° in an intramolecular and intermolecular sense. The perfluorophenoxy group of 7n in the solid state is twisted from the triazine ring by 70° (angle between least squares planes from all heavy atoms).

Figure 4.18 Stick representation of the X-ray crystal structure of 7n dimer with intermolecular hydrogen bond indicated (dashed orange lines). Blue, grey, white, red and green correspond to nitrogen, carbon hydrogen oxygen and fluor atoms, respectively.
Table 4.9 Hydrogen bond distances and angles of complex 7n•7n X-ray from the crystal structure data.

<table>
<thead>
<tr>
<th>D···A</th>
<th>d NH···X (Å)</th>
<th>d N-H···X (Å)</th>
<th>∠ NH···X (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N6-H6A···N5'</td>
<td>2.9163 (4)</td>
<td>2.1058 (3)</td>
<td>175.540 (17)</td>
</tr>
<tr>
<td>N6-H6A···N1'</td>
<td>3.1174 (5)</td>
<td>2.6940 (5)</td>
<td>114.297 (15)</td>
</tr>
<tr>
<td>N6-H6B···O1'</td>
<td>2.8962 (4)</td>
<td>2.1236 (3)</td>
<td>158.768 (17)</td>
</tr>
</tbody>
</table>

In a summary, all the intermolecular distances and the angles between heterocyclic ring planes of derivatives 7c, 7f, 7k and 7n in the solid state are listed in Table 4.10. With the exception of 7k, there is a correlation between the hydrogen bond distances with the dimerization constants obtained in the dilution experiments in CDCl3; i.e. the shorter the intermolecular distances, the higher the dimerization constant in CDCl3.

Figure 4.19 Donor and acceptor sites assignment of 7c, 7f, 7k and 7n dimers.
Table 4.10 Summary of hydrogen bond distances, intramolecular and intermolecular ring’s planes angles of 7c, 7f, 7k and 7n from their crystal structure data.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>N-H_a⋯N_c (Å)</th>
<th>N-H_a⋯N_d (Å)</th>
<th>N-H_b⋯O (Å)</th>
<th>Intramolecular Ring’s Planes Angle (°) ^a</th>
<th>Intermolecular Ring’s Planes Angle (°) ^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>7c</td>
<td>2.9282 (4)</td>
<td>3.1230 (4)</td>
<td>2.8792 (4)</td>
<td>16.679</td>
<td>16.679</td>
</tr>
<tr>
<td>7f</td>
<td>2.8966 (4)</td>
<td>3.0967 (4)</td>
<td>2.8728 (6)</td>
<td>4.118</td>
<td>4.118</td>
</tr>
<tr>
<td></td>
<td>2.9449 (3)</td>
<td>3.1489 (4)</td>
<td>2.9080 (5)</td>
<td>4.655</td>
<td>4.655</td>
</tr>
<tr>
<td></td>
<td>2.9208 (^b)</td>
<td>3.1228 (^b)</td>
<td>2.8904 (^b)</td>
<td>4.3865 (^b)</td>
<td>4.3865 (^b)</td>
</tr>
<tr>
<td>7k</td>
<td>3.0049 (7)</td>
<td>3.0811 (7)</td>
<td>2.9339 (11)</td>
<td>43.578 (12)</td>
<td>8.336 (16)</td>
</tr>
<tr>
<td>7n</td>
<td>2.9163 (4)</td>
<td>3.1174 (5)</td>
<td>2.8962 (4)</td>
<td>7.461</td>
<td>7.461</td>
</tr>
</tbody>
</table>

\(^a\) Angle between least squares triazine and pyridine ring planes, \(^b\) Average values from all dimers present in the crystal structure

On the other hand, comparing derivatives 7 with 4 in the solid state, it can be noted that by changing the pyridine ring to ortho-methoxyphenyl the intermolecular distances between monomers were shortened. In this sense, intermolecular distances between the amino group and the methoxy acceptor site in derivatives 7 were at least 0.30 Å shorter than those observed between the amino group and the pyridine acceptor site in derivatives 4. In addition, the position of the methoxy group was more closely aligned with the N-H bond of the amino group and the hydrogen bond interaction is closer to linearity. Besides the improvement in the proximity of these binding sites, the intermolecular distances of the amino group to the triazine acceptor site were reduced by at least 0.10 Å. A good example of all these observations can be seen comparing hexylthiol derivatives 4f and 7f (Table 4.11).
Table 4.11 Comparison of intermolecular distances in 4f and 7f dimer structures in the solid state.

<table>
<thead>
<tr>
<th>D···A</th>
<th>4f dimer</th>
<th>7f dimer</th>
<th>4f dimer</th>
<th>7f dimer</th>
<th>4f dimer</th>
<th>7f dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-H···N(triazine)</td>
<td>3.1500 (3)</td>
<td>2.9208</td>
<td>2.2848 (2)</td>
<td>2.0494</td>
<td>177.961 (10)</td>
<td>175.140</td>
</tr>
<tr>
<td>N-H···N(azo)</td>
<td>2.9500 (4)</td>
<td>3.1228</td>
<td>2.4723 (3)</td>
<td>2.7114</td>
<td>115.468 (6)</td>
<td>110.184</td>
</tr>
<tr>
<td>N-H···X</td>
<td>3.2831 (3)</td>
<td>2.8904</td>
<td>2.5905 (3)</td>
<td>2.0424</td>
<td>137.388 (8)</td>
<td>160.074</td>
</tr>
</tbody>
</table>

a 4f: X = N(pyridine), 7b: X = O (methoxy). b Average values from all dimers present in the crystal structure.

4.2.4 UV-Vis Characterization

The absorption spectra of 7 in their thermally stable trans-isomeric form (i.e. (t)-7) were obtained from 10^{-5} to 10^{-4} M acetonitrile solutions at room temperature (Figure 4.20).

Figure 4.20 Normalized UV-Vis Absorption Spectra of derivatives (t)-7 in acetonitrile at 298 K.
At first sight, the UV-Vis spectra of derivatives 7 is characterized by two prominent absorption bands, at wavelengths lower than 400 nm. This observation is in accordance with the literature that reports the 2,2'-dimethoxyazobenzene's UV-Vis spectrum has two \( \pi \rightarrow \pi^* \) absorption bands at 310 and 366 nm.\(^8\) Similarly to derivatives 4a-p, the \( \pi \rightarrow \pi^* \) absorption bands of derivatives 7 are slightly shifted to lower wavelengths (hypsochromic shift). On the other hand, the \( n \rightarrow \pi \) absorption bands of the 2,2'-dimethoxyazobenzene is located at 454 nm. In the case of the UV-Vis spectra of 7, this band was difficult to identify since it blends with the base of a \( \pi \rightarrow \pi^* \) band. Nevertheless, the UV-Vis absorption profiles of the derivatives 7 is in accordance with the expected UV-Vis spectrum of azobenzene containing compounds.

### Table 4.12 Characteristic \( n \rightarrow \pi^* \) and \( \pi \rightarrow \pi^* \) transition bands of derivatives (t)-7 from UV-Vis spectroscopy in acetonitrile at 298 K.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>RX</th>
<th>( n \rightarrow \pi^* ) Transition</th>
<th></th>
<th>( \pi \rightarrow \pi^* ) Transition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(t)-7c</td>
<td>( n )-butoxy</td>
<td>( \lambda_{\text{max}} ) (nm) 486</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 347</td>
<td>( \lambda_{\text{max}} ) (nm) 349</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 4880</td>
</tr>
<tr>
<td>(t)-7f</td>
<td>hexylthio</td>
<td>( \lambda_{\text{max}} ) (nm) 496</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 242</td>
<td>( \lambda_{\text{max}} ) (nm) 349</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 5290</td>
</tr>
<tr>
<td>(t)-7g</td>
<td>chloro</td>
<td>( \lambda_{\text{max}} ) (nm) 481</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 498</td>
<td>( \lambda_{\text{max}} ) (nm) 363</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 4200</td>
</tr>
<tr>
<td>(t)-7i</td>
<td>phenoxy</td>
<td>( \lambda_{\text{max}} ) (nm) 484</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 520</td>
<td>( \lambda_{\text{max}} ) (nm) 350</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 5220</td>
</tr>
<tr>
<td>(t)-7k</td>
<td>4'-tert-butylphenoxy</td>
<td>( \lambda_{\text{max}} ) (nm) 450</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 783</td>
<td>( \lambda_{\text{max}} ) (nm) 352</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 5370</td>
</tr>
<tr>
<td>(t)-7m</td>
<td>3,5-bis(trifluoromethyl)phenoxy</td>
<td>( \lambda_{\text{max}} ) (nm) 494</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 25</td>
<td>( \lambda_{\text{max}} ) (nm) 357</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 5930</td>
</tr>
<tr>
<td>(t)-7n</td>
<td>perfluorophenoxy</td>
<td>( \lambda_{\text{max}} ) (nm) 478</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 453</td>
<td>( \lambda_{\text{max}} ) (nm) 361</td>
<td>( \varepsilon ) (M(^{-1}) cm(^{-1})) 4930</td>
</tr>
</tbody>
</table>
Additionally, the UV-Vis spectrum of the *cis*-isomer of the derivative 7c ((c)-7c) in acetonitrile was obtained (Figure 4.21). As expected, the UV-Vis spectrum of the *cis*-isomeric forms display $\pi \rightarrow \pi^*$ absorption bands with lower absorptivities in comparison with the *trans*-isomer UV-Vis spectrum. Meanwhile, the n→$\pi^*$ band of the *cis*-isomer show slightly higher absorptivities than those observed in the *trans*-isomer. The thermal reversion of the *cis*-isomer of derivative 7c to its *trans*-isomeric form was monitored recording the UV-Vis spectra until all derivative 7c was in solution as a *trans*-isomer. Two isosbestic points were identified at 262 and 427 nm ($\varepsilon = 3193$ and 585 M$^{-1}$ cm$^{-1}$, respectively).

**Figure 4.21** UV-Vis absorption spectra of (c)-7c and its thermal reversion to (t)-7c in acetonitrile at 298 K (7c total concentration = 1.26 x 10$^{-4}$ M). Inset figure: isosbestic point at 427 nm.
Table 4.13 Characteristic n→π* and π→π* transition bands of derivative (c)-7c from UV-Vis spectroscopy in acetonitrile at 298 K.

<table>
<thead>
<tr>
<th>Compound</th>
<th>RX</th>
<th>n→π* Transition</th>
<th>π→π* Transition</th>
<th>Isosbestic Point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>λ_{max} (nm)</td>
<td>ε (M⁻¹ cm⁻¹)</td>
<td>λ_{max} (nm)</td>
</tr>
<tr>
<td>(c)-7c</td>
<td>n-butoxy</td>
<td>445</td>
<td>456</td>
<td>348</td>
</tr>
<tr>
<td></td>
<td></td>
<td>291</td>
<td>3828</td>
<td>262</td>
</tr>
</tbody>
</table>

4.2.5 Photoisomerization Trans to Cis

The photoisomerization of the *trans* isomeric forms of derivatives 7 were carried out. The experiment conditions were the same ones employed during the photoisomerization of derivatives (t)-4a-p; i.e. UV light centered at 360 nm and three different solvent systems (CDCl₃, toluene-d₈, and CD₃CN). Similarly to derivatives 4a-p, the *cis*-isomers of derivatives 7 are differentiated from their *trans*-isomeric form by a new set of signals in the ¹H NMR spectrum located upfield (Figures 4.22 and 4.23). This upfield shift is in agreement with the location of most of the phenyl hydrogen atoms in the shielding cone of the triazine ring.
Figure 4.22 $^1$H NMR spectra displaying derivative 7c at PSS in toluene-$d_8$ at 298 K. RX = $n$-butoxy.
Figure 4.23 $^1$H NMR spectra displaying derivative $7c$ at PSS in toluene-$d_8$ at 298 K. RX = $n$-butoxy.

The trans- to cis- interconversion yields for derivatives $7$ were calculated from the cis/trans integration ratio of the methoxy moiety. Table 4.14 shows the trans- to cis- interconversion yields. It is important to note that contrary to derivatives $4a$-p, the photoisomerization of ($t$)-$7$ in CDCl$_3$ solution did not take place since the $^1$H NMR spectrum of all ($t$)-$7$ tested in this solvent did not change after continuous irradiation of UV light for a period of up to 3 h. On the other hand, from the three derivatives $7$ soluble in toluene-$d_8$ (butoxy $7c$, hexylthiol $7f$ and perfluorophenoxy $7n$) the butoxy derivative $7c$ was the only one that showed trans- to cis- interconversion with 26% yield. This interconversion yield is slightly higher than that reported for the butoxy derivative $4c$ in toluene-$d_8$ (22% yield). Lastly, with the exception of the chloro derivative $7g$, all derivatives $7$ dissolved in CD$_3$CN exhibited photochromism with trans- to cis-
interconversion yields from 7 to 32 % yield. The lowest photoisomerization yield corresponded to the perfluorophenoxy derivative \(7n\); and, the highest yield corresponded to the \(n\)-butoxy derivative \(7c\). Overall, the photoisomerization yields obtained in CD\(_3\)CN for 7 were comparable to the yields observed for 4 in the same solvent system.

**Table 4.14** Trans to cis interconversion yields at PSS after irradiation with UV Light (360 nm) at 298 K.

| Derivative | RX                        | \(\text{trans to cis conversion in CDCl}_3\) (%) | \(\text{trans to cis conversion in Toluene-d}_8\) (%) | \(\text{trans to cis conversion in CD}_3\)CN (%) |
|------------|---------------------------|-----------------------------------------------|-----------------------------------------------|
| \(7c\)     | \(n\)-butoxy              | 0                                             | 26                                             | 32                                             |
| \(7f\)     | Hexylthio                 | 0                                             | 0                                             | 26                                             |
| \(7g\)     | Chloro                    | 0                                             | -                                             | 0                                              |
| \(7i\)     | Phenoxy                   | 0                                             | -                                             | 15                                             |
| \(7k\)     | \(4'\)-tert-butylphenoxy | 0                                             | -                                             | 21                                             |
| \(7m\)     | 3',5'-bis(trifluoromethyl)phenoxy | 0                                             | -                                             | 24                                             |
| \(7n\)     | Perfluorophenoxy          | 0                                             | 0                                             | 7                                              |

- Compound not soluble in the solvent system used.

The response of derivatives 7 to alternating light stimuli was tested through a photodegradation experiment similar to that described in Chapter 3 (Section 3.2.2, Figure 3.7). A toluene-\(d_8\) solution of \(7c\) ([\(7c\] = \(9.11 \times 10^{-4}\) M) was exposed to UV light (centered at 360 nm for 1h) and visible light (\(\lambda > 400\) nm for 10 min) in an alternate manner. After each UV/Vis light irradiation, a \(^1\)H NMR spectrum was acquired to confirm the presence or absence of cis-isomer and to record the N-H chemical shift of the trans-isomer. Once 5 cycles of UV/Vis light irradiation were completed, the sample was exposed to natural light...
at room temperature for 72 h to latter record a last $^1$H NMR spectrum (cis- to trans- thermal reversion, Figure 4.24). The average response after UV light irradiation for 7c was an N-H chemical shift at 5.61 ppm; meanwhile, the average response after visible light irradiation was 5.66 ppm. In both cases, deviations from the average value were no larger than 0.01 ppm. In a similar manner as observed in the photodegradation experiment of 4c, the $^1$H NMR spectrum of 7c after thermal reversion showed an amino proton chemical shift lower than the chemical shift prior the experiment. Likewise, no traces of cis-isomer or side product(s) were observed in the last spectrum. The last chemical shift observed corresponds to a 7c solution which concentration decreased by 11% (i.e. 9.80 x 10^{-5} M). This difference falls in the limit of the NMR spectrometer resolution.
Figure 4.24 Cyclization plot of 7c ([7c] = 9.11 x 10^{-4} M). Purple areas correspond to the N-H chemical shift change after UV light irradiation (centered at 360 nm for 1h). White areas correspond to the N-H chemical shift change after visible light irradiation (λ > 400 nm for 10 minutes). Yellow area correspond to the N-H chemical shift observed after thermal reversion of the solution over 72h.
4.2.6 Complexation Constants in Solution After Photoisomerization

Once the photophysical properties of the derivatives 7 were evaluated (UV-Vis absorption spectra and trans- to cis- interconversion yields at the photostationary state) we turned to the study of the complex equilibria after photoisomerization takes place. In this sense, we recall all the possible monomers and dimers in solution once (c)-7 is present (Figure 4.25).

Figure 4.25 Hypothetical complexation equilibria present in mixed cis/trans solutions of derivatives 7 in non-polar solvents.
In the same way as 4a-p, a cis/trans mixture of 7 in solution is prone to organize into different dimer structures. The trans-isomer was conceived to show one (and only one) stable dimer structure (ttt dimer in Figure 4.25). However, once photoisomerization occurs the exclusion of two hydrogen bond acceptors provides to the cis-isomer two triazine ring edges with an AD array ((c)-7 in Figure 4.25). This particularity brings the possibility of more than one structural arrangement for the cis-cis dimer and the trans-cis complex. It is not possible to determine which of all cis-cis dimer and trans-cis complex structures are the most energetically favored. Neither is it possible to isolate the contribution of all equilibria to the composite cis-cis dimerization constant (\(K_{c-c}\)) and trans-cis complexation constant (\(K_{t-c}\)).

Based on the similarities with the 4a-p derivatives, we decided to employ the mathematical model described in Chapter 3 (Section 3.2.3). Again we presume that the cis-cis dimerization constants for 7 are no greater than the dimerization constant of their counterpart derivatives 5. Moving on to the sole soluble and photoswitchable example, butoxy derivative 7c has a free energy of trans-trans dimerization in toluene-\(d_8\) at room temperature of -19.62 kJ mol\(^{-1}\), meanwhile the butoxy derivative 5c has a free energy of dimerization in toluene-\(d_8\) of -7.16 kJ mol\(^{-1}\). The difference between both equilibria is large enough (at least 12 kJ mol\(^{-1}\)) to discard the cis-cis dimer contribution to the distribution of the total concentration of cis-isomer in solution at the concentrations we are examining.

Up to this point, it was assumed that the assessment method for the trans-cis complexation constant (\(K_{t-c}\)) for 7 would be similar to that employed for 4a-p. However,
7 exhibited a significant difference that forced us to perform the reversion experiments in a different way than that settled for 4a-p. This difference was the cis- to trans- thermal reversions observed for derivatives 7 in toluene-d₈ solution were approximately 10 fold faster than 4a-c (Sections 3.2.4 and 4.2.7). A more detailed discussion with the corresponding constant values of the cis- to trans- thermal reversion rate are part of the following section; however, it is important to outline that the reversion rate of 7 (more specifically 7c) did not allow us to obtain enough data for a reliable estimation of $K_{t,e}$. To overcome this inconvenience, it was necessary to carry out the reversion experiments at lower temperature since the reversion rate is thermally dependent. This strategy required the determination of the trans-trans dimerization constant at the same temperature that the reversion experiments would be performed. The chosen temperature to carry out the dilution and reversion experiments was -10 °C (or 263 K, Figure 4.26). The butoxy derivative 7c was the only derivative examined as it was the only one to switch in toluene-d₈.
Figure 4.26 Dimerization isotherm of 7c with $K_{t,t}$ value and free energy calculated from fitting of the data to a 1:1 dimerization model. Blue and green dots correspond to first and second separate dilution experiments, respectively. Solid line corresponds to the theoretical dilution curve obtained from the average $K_{t,t}$ of two separate dilution experiments.

Once the dimerization constant and the chemical shift values of derivative 7c as monomer and dimer in toluene-$d_8$ solution at -10 °C were determined, we performed reversion experiments. For this purpose we were able to isolate derivative 7c as approximately 50% cis-isomer in the solid state. This way, a freshly prepared cis/trans 7c solution was submitted to $^1$H NMR spectroscopy at -10 °C to record the chemical shift of the amino protons, as well as the cis/trans ratio in solution as the thermal reversion was taking place (Figure 4.27). As expected, the thermal reversion rate at -10 °C was lower than at room temperature (25 °C); therefore, we were able to obtain a large enough number of data points to employ in the $K_{t,c}$ calculation (Figure 4.28).
Figure 4.27 $^1$H NMR spectra displaying the concentration-dependent behavior of 7c in toluene-$d_8$ at 263 K. Total concentration $[7c] = 5.84 \times 10^{-3}$ M, (i) $[c]_0/[t]_0 = 1.11$ (ii) $[c]_0/[t]_0 = 0.33$.

Figure 4.28 Relationship between $\delta_{obs}$ vs $[t]_0$ during three thermal reversion experiments of derivative 7c. Blue dots correspond to a reversion experiment ($[7c] = 8.8 \times 10^{-4}$ M). Solid line corresponds to the theoretical dilution curve obtained from the average of two separate dilution experiments with (t)-7c.
The data collected from the reversion experiments were used in the mathematical model described in Chapter 3 (Section 3.2.3) in order to obtain $K_{tc}$ and $\delta_{tc}$. It is important to recall that this mathematical model is based on the interdependency of $K_{tc}$ and $\delta_{tc}$ values; therefore, for a set of $\delta_{obs}$ values at different cis/trans ratios with a fixed 7c total concentration in solution there must be only one pair of $K_{tc}$ and $\delta_{tc}$ values common to all date points (i.e. the convergence point at Figure 4.29). From our calculations, such values were obtained through the minimum CV (coefficient of variation) for each $\delta_{tc}$ value employed (i.e. a vertical slice in Figure 4.30 plot). Table 4.15 displays the calculated $K_{tt}$, $K_{tc}$, $\delta_m$, $\delta_d$ and $\delta_{tc}$ for butoxy derivative 7c at -10 °C. An important point to note in Table 4.15 is the free energy difference between the trans-trans dimer and the trans-cis dimer which is 4.41 kJ mol$^{-1}$. This difference is comparable to that reported for the butoxy derivative 4c in Chapter 3 (Section 3.2.3) which is 4.46 kJ mol$^{-1}$.

In order to have as complete as possible a description of all equilibria present in a cis/trans mixture toluene-$d_8$ solution of 7c at -10 °C, the dimerization constant of butoxy 5c was determinated under the same solvent and temperature conditions. It is important to recall that the $K_{tt}$ value of 5c is an approximation of the maximum value expected for the dimerization constant of the cis-isomeric form of butoxy derivative 7c, which is 68 M$^{-1}$ ($\Delta G_{tt} = -9.23$ kJ mol$^{-1}$). From this $K_{cc}$ approximation it can be assumed that the cis-cis dimer of 7c is at least 11 kJ mol$^{-1}$ less stable than the trans-trans isomer ($\Delta \Delta G = 11.06$ kJ mol$^{-1}$). Likewise, the calculated $\Delta G_{tc}$ for 7c at -10 °C via our mathematical model is in agreement with the expected stability of the trans-cis complex (i.e. the average of the $\Delta G_{tt}$ values of 7c and 5c at -10 °C, which is -14.76 kJ mol$^{-1}$), since the difference between the
calculated and the expected free energies of such complex is approximately 1 kJ mol\(^{-1}\) 
\((\Delta \Delta G_{\text{tc}} = 1.13 \text{ kJ mol}^{-1})\)

**Figure 4.29** Top Plot: Theoretical \(K_{\text{tc}}\) vs \(\delta_{\text{tc}}\) curves for the set of \(\delta_{\text{obs}}\) from the least squares curve that describes the third reversion experiment of derivative \(7c\) (red dots in Figure 4.31, \([7c] = 1.47 \times 10^{-3} \text{ M}\)). Bottom Plot: Theoretical \(CV\) vs \(\delta_{\text{tc}}\) curve for the set of \(K_{\text{tc}}\) calculated from the third reversion experiment of derivative \(7c\) (red dots at Figure 4.31, \([7c] = 1.47 \times 10^{-3} \text{ M}\)).
Figure 4.30 Top Plot: $K_{tc}$ vs $\delta_{tc}$ curves for the set of $\delta_{obs}$ from the third reversion experiment of derivative 7c (red dots in Figure 4.31, [7c] = 1.47 x 10^{-3} M). Bottom Plot: CV vs $\delta_{tc}$ curve for the set of $K_{tc}$ calculated from the third reversion experiment of derivative 7c (red dots at Figure 4.31, [7c] = 1.47 x 10^{-3} M).
Table 4.15 Dimerization constant ($K_{tt}$), complexation constant ($K_{tc}$), free energy of dimerization ($\Delta G_{tt}$), free energy of complexation ($\Delta G_{tc}$), calculated chemical shifts of monomer ($\delta_m$), dimer ($\delta_d$) and complex ($\delta_{tc}$) species studied in Toluene-$d_8$ at 263 K.

<table>
<thead>
<tr>
<th>$K_{tt}$ in Toluene-$d_8$ (M$^{-1}$) $^a$</th>
<th>$\Delta G_{tt}$ (kJmol$^{-1}$)</th>
<th>$\delta_m$ (ppm) $^a$</th>
<th>$\delta_d$ (ppm) $^a$</th>
<th>$K_{tc}$ in Toluene-$d_8$ (M$^{-1}$) $^a$</th>
<th>$\Delta G_{tc}$ (kJmol$^{-1}$)</th>
<th>$\delta_{tc}$ (ppm) $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10700 ± 1100</td>
<td>-20.29 ± 0.23</td>
<td>4.17$^b$</td>
<td>7.22$^b$</td>
<td>1430 ± 198</td>
<td>-15.88 ± 0.29</td>
<td>5.20 ± 0.02</td>
</tr>
</tbody>
</table>

$^a$ Average values obtained using Equation 5 from Chapter 2 (Section 2.3.2). Errors calculated from two times the standard deviation to give a 95% of confidence interval.

$^b$ Chemical shift of the amino proton located upfield at the $^1$H NMR spectra.

Figure 4.31 Relationship between $\delta_{O bs}$ vs $[t]_0$ through three reversion experiments of the derivative 7c. Blue, green and red dots correspond to first, second and third separate reversion experiments, respectively. Blue, green and red dashed lines correspond to the predicted $\delta_{O bs}$ vs $[t]_0$ plots for the first, second and third reversion experiments with the expected $\Delta G$ values (sample standard deviations of 0.006, 0.003, 0.01 ppm, respectively). Solid line corresponds to the dilution curve obtained from the average of two separate dilution experiments.
Finally, all the equilibrium constants displayed in Table 4.15 and the approximation of the $K_{cc}$ for derivative 7c allowed us to obtain a full picture of all the species involved in solution in a cis/trans mixture at different ratios; and create a speciation diagram (Figure 4.32). Similarly to derivatives 4c, 4f and 4k, the speciation diagram for derivative 7c was calculated on the basis of two scenarios: 1) when there is no cis-dimer in solution ($K_{cc} = 0$, solid lines) and, 2) when there is cis-dimer in solution ($K_{cc} = 68 \text{ M}^{-1}$, dotted-star marked lines).

**Figure 4.32** Theoretical speciation diagram of derivative 7c at the third reversion experiment (red dots at Figure 4.31, $[7c] = 1.47 \times 10^{-3} \text{ M}$) at 263 K. Solid lines correspond to the first scenario ($K_{cc} = 0$) and dotted-star marked lines correspond to the second scenario ($K_{cc} = 68 \text{ M}^{-1}$) respectively. Blue, red, orange, yellow and brown colors correspond to $[t]$, $[t \cdot t]$, $[t \cdot c]$, $[c]$, and $[c \cdot c]$, respectively. Black dotted line corresponds to maximum cis/trans ratio in reversion experiment. Grey dotted line corresponds to cis/trans ratio at PSS.
Figure 4.32 shows that there are no significant differences between the concentrations of each dimer and monomer in solution when both scenarios are compared. The largest difference in concentration is approximately 4 % in trans-cis complex concentration ([t ∙ c]) between both scenarios over the total concentration of trans-isomer ([t]₀). This difference is expected when there is 90% cis-isomer in solution (χ = 0.1 in Figure 4.32) and decreases as the total concentration of trans-isomer increases. This observation led us to conclude that discarding the cis-cis dimerization from the calculation of $K_{t\cdot c}$ does not have a significant impact in the full description of the species distribution at the employed concentrations. In other words, taking into account the starting cis/trans ratio during our reversion experiments was approximately 1 (black dotted line in Figure 4.32), the largest concentration difference between both scenarios is 0.96 % in the trans-cis complex concentration over the total concentration of trans-isomer ([t]₀) which is insignificant in the context of the total amount of derivative 7c in solution.

4.2.7 Cis to Trans Reversion Kinetics

As mentioned in the previous section, the thermal reversion rate of 7c in toluene-$d_8$ was considerably higher than those observed in the derivatives 4a-p tested at room temperature. A more detailed analysis of the cis/trans ratio change in solution as time passed allowed us to calculate the rate of the thermal reversion 7c at room temperature. In this sense, the cis- to trans- thermal reversion follows a first order reaction model (Equations 15 and 16 in Chapter 3, Section 3.2.4) with a $k$ value of $2.62 \pm 1.88 \times 10^{-3}$ s$^{-1}$ (Figure 4.33). Compared with the thermal reversion rates reported for the 4a-p derivatives
tested (4c, 4f and 4k) the calculated rate constant of derivative 7c is at least 5 times higher; and more specifically, compared with the butoxy derivative 4c, k value for butoxy 7c is 8 times higher.

The same kinetic study was performed for the cis- to trans- thermal reversion of derivative 7c at -10 °C (263 K). At this temperature the thermal reversion rate calculated from three separate reversion experiments is $8.47 \pm 1.54 \times 10^{-5}$ s$^{-1}$ (Figure 4.34). At -10 °C the thermal reversion of 7c has a slower rate than those observed for 4c, 4f and 4k derivatives at room temperature; i.e. butoxy 4c thermal reversion rate at room temperature is four times higher than butoxy 7c at -10 °C.

![Figure 4.33](image)

**Figure 4.33** Decay profiles of (c)-7c isomer in toluene-$d_8$ at 298 K. Blue, red and green dots correspond to first, second and third separate reversion experiments ($r = -0.9934$, -0.9966, -0.9981) respectively. Blue, red and green dashed lines correspond to the calculated values obtained by linear least squares regression of the first, second and third separate reversion experiments, respectively.
Figure 4.34 Decay profiles of (c)-7c isomer in toluene-$d_8$ at 263 K. Blue, green and red dots correspond to first, second and third separate reversion experiments ($r = -0.9816$, -0.9574 and -0.9885), respectively. Blue, green and red dashed lines correspond to the calculated values obtained by linear least squares regression of the first, second and third separate reversion experiments, respectively.
4.3 Summary and Conclusions

A new marginally improved library of self-complementary hydrogen bond DDAAA arrays (7) were synthesized and characterized. The improvement over 4a-p presented in Chapter 2 and 3 lies in the change of an acceptor group; the pyridyl ring in derivatives 4a-p was replaced by a 2-methoxyphenyl group. The reasoning behind this change was to provide an acceptor group in closer physical proximity to the amino protons than in 4a-p. It was anticipated that the hydrogen bond interaction between this acceptor site and the amino protons would provide more stable dimer structures. Dimerization constants of derivatives 7 were obtained at room temperature in two solvent systems: CDCl₃ and toluene-d₈. In the first solvent, dimerization constants ranged from 36 to 309 M⁻¹; meanwhile, in toluene-d₈ dimerization constants varied from 2400 to 5600 M⁻¹. In both solvents employed, derivatives 7 generally displayed $K_{tt}$ values higher than those obtained for derivatives 4a-p. This difference is more evident in toluene-d₈ (a non-competitive solvent) and supports the idea of a more stable dimer structure due to the change of the pyridyl ring for a 2-methoxyphenyl group. In addition, similarly to 4a-p, the presence of electron withdrawing RX groups in derivatives 7 resulted in larger dimerization constants. The energetic contribution of the methoxy acceptors in each solvent system employed was estimated at 5 and 11 kJ mol⁻¹ in CDCl₃ and toluene-d₈, respectively. This contribution is significantly higher than that estimated for derivatives 4a-p which is in accordance with the improved arrangement. It was possible to confirm the dimerization of 7c, 7f, and 7n in the solid state by single crystal X-ray diffraction. In all these structures, hydrogen bond interactions between the amino group and triazine, azo and methoxy moieties were observed as expected. A special case was the 4'-tert-butylphenoxy...
derivative 7k in the solid state since it was observed as an infinite hydrogen bonded chain. However, in this structure the hydrogen bond interactions present were the similar to those observed for 7c, 7f, and 7n dimers in the solid state. The intermolecular distances between the interacting sites in derivatives 7c, 7f, 7k and 7n complex structures were shorter than those noted in the dimer structures of derivatives 4a, 4d, 4f and 4k in the solid state. This observation is in agreement with the larger dimerization constants for derivatives 7 compared with derivatives 4a-p.

Regarding the photochemical properties, the trans-isomer UV-Vis absorption spectra of derivatives 7 are characterized by one n→π* band (maximum absorption ≈ 481 nm) and two π→π* bands (maximum absorptions at ≈ 354 nm and ≈ 295 nm). Conversely, the cis-isomer of butoxy derivative 7c has a UV-Vis absorption spectrum with a n→π* band higher in absorptivity and π→π* bands lower in absorptivity compared with the trans-isomer. The presence of an isosbestic point thru the cis- to trans- thermal reversion of derivative 7c confirms that no intermediates are involved during this isomerization. The percentages of interconversion from trans- to cis- at the photostationary state for all derivatives 7 were obtained in three different solvent systems: CDCl₃, toluene-d₈ and acetonitrile. In CDCl₃ no photoisomerization was noted and in toluene-d₈ the butoxy derivative 7c was the only one that showed trans- to cis- photoisomerization (26% yield). The acetonitrile solutions of all 7 displayed trans- to cis- photoisomerization with yields of interconversion that ranged from 7 to 32 %. In order to characterize the species distribution in a cis/trans mixture in solution the same mathematical model described in Chapter 3 was applied to butoxy derivative 7c at -10 °C. At this temperature, butoxy derivative 7c has a $K_{tt}$ value of 10700 M⁻¹ and a calculated $K_{tc}$ value of 1400 M⁻¹. The
free energy difference between the trans-trans dimer and the trans-cis complex is similar to that observed in the butoxy derivative 4c. Finally, the stability of (c)-7c in toluene-$d_8$ solution was studied at two temperatures: room temperature and -10 °C (263 K). The thermal reversion from cis- to trans-isomer proceeds as first order reaction with rate constants of $2.62 \times 10^{-3}$ s$^{-1}$ and $8.47 \times 10^{-5}$ s$^{-1}$ at 25 and -10 °C, respectively.

4.4 Experimental Methodology

4.4.1 Generalities

All experiments were performed in ambient atmospheric conditions unless otherwise indicated. Chemicals were purchased from Alfa Aesar, Sigma-Aldrich, and Oakwood Products and used as received. Solvents (acetone, acetonitrile, butanol, chloroform, dichloromethane, diethyl ether, diisopropyl ether, dimethyl formamide, ethyl acetate, hexanes, methanol, tetrahydrofuran, and toluene) were obtained from Caledon Laboratories, Fisher Chemicals, Sigma-Aldrich and VWR Analytical. In the case of inert atmosphere conditions, solvents were dried using an Innovative Technology Inc. Controlled Atmospheres Solvent Purification System that utilizes dual alumina columns (SPS-400-5), or purchased from Sigma-Aldrich and used as received. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated TLC-sheets POLYGRAM®SIL G/UV$^{254}$. Column chromatography was performed with SiliCycle®SiliaFlash® F60, 40-63 µm 60 Å. Nuclear Magnetic Resonance spectra were recorded on Mercury 400 MHz, INOVA 400 MHz and INOVA 600 MHz spectrometers.
(\textsuperscript{1}H = 400.08 MHz, 399.77 MHz and 599.32 MHz; \textsuperscript{13}C \textsuperscript{1}H) = 100.52 MHz and 150.78 MHz respectively). \textsuperscript{1}H and \textsuperscript{13}C spectra were referenced relative to Me\textsubscript{4}Si using the residual non-deuterated NMR solvent signal (\textsuperscript{1}H: CHCl\textsubscript{3}, \(\delta = 7.26 \text{ ppm}\), (CHD\textsubscript{2})\textsubscript{2}SO, \(\delta = 2.50 \text{ ppm}\), (CHD\textsubscript{2})C\textsubscript{6}D\textsubscript{5}, \(\delta = 2.09 \text{ ppm}\); \textsuperscript{13}C \textsuperscript{1}H): CHCl\textsubscript{3}, \(\delta = 77.0 \text{ ppm}\), (CHD\textsubscript{2})\textsubscript{2}SO, \(\delta = 39.5 \text{ ppm}\)). Solvents for NMR spectroscopy (Chloroform-\textit{d}, DMSO-\textit{d}\textsubscript{6}, and Toluene-\textit{d}\textsubscript{8}) were purchased from Cambridge Isotope Laboratories and Sigma-Aldrich. Mass spectra were recorded using an electron ionization Finnigan MAT 8200 spectrometer at an ionizing voltage of 70 eV. X-Ray diffraction data were collected on Bruker Apex II and Nonius Kappa CCD X-Ray diffractometers using graphite monochromatic Mo-K\alpha radiation (\(\gamma = 0.71073 \text{ Å}\)) and Cu-K\alpha radiation (\(\gamma = 1.54178 \text{ Å}\)), respectively. \textsuperscript{1}H NMR dilution experiments, photostationary state experiments and \textsuperscript{1}H NMR reversion experiments were performed as described in Chapters 2 and 3 (Sections 2.5.3, 3.4.2 and 3.4.4).

4.4.2 Synthetic Methods

\[ \text{Synthesis of (2-methoxyphenyl)hydrazine hydrochloride.} \] Synthetic procedure as reported by Li and coworkers.\textsuperscript{10} In a round bottom flask a suspension of \textit{o}-anisidine (2.46 g, 20 mmol) in concentrated hydrochloric acid (40 mL) is prepared and cooled down to -10 °C. To this suspension, a solution of NaNO\textsubscript{2} (1.39 g, 20.2 mmol) in distillated water (10 mL) was added dropwise keeping the suspension at a temperature below 0 °C. Once
all NaNO$_2$ solution was added, the reaction mixture was stirred for 30 minutes at 0 °C. In a separate flask, a solution of SnCl$_2$·H$_2$O (9.12 g, 40.4 mmol) in concentrated hydrochloric acid (15 mL) was prepared and added all at once to the reaction mixture. The reaction mixture was stirred overnight and allowed to warm to room temperature. The product was filtered, washed with 1M HCl solution and dichloromethane and dried by vacuum filtration and. Yield = 3.45 g, 99%. ESI-HRMS: Calc. for C$_7$H$_{10}$N$_2$: 138.0793, Found: 138.0793. $^1$H NMR (400 MHz, DMSO-d$_6$): δ(ppm) 10.04 (bs 3H), 7.57 (bs, 1H), 7.06 (m, 1H), 6.88-7.01 (m, 3H), 3.82 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$): δ(ppm) 147.8, 134.2, 122.4, 120.6, 114.6, 111.0, 55.7.

**General procedure for synthesis of (E)-4-((2-methoxyphenyl)diazenyl)-1,3,5-triazin-2-amine derivatives (7).** In a clean, dry round bottom flask 4-chloro-1,3,5-triazin-2-amine derivative (2) (1 eq.), (2-methoxyphenyl)hydrazine hydrochloride (1 eq.) and potassium carbonate (2 eq.) were mixed with 100 mL of THF. The reaction mixture was refluxed for 12 h, cooled and the solvent removed under reduced pressure. The crude material was poured into 50 mL of distilled water and the intermediate was extracted with 3 x 50 mL of dichloromethane. The organic phase was dried over sodium sulfate and the drying agent was removed by gravity filtration. One equivalent of (diacetoxy)iodobenzene was added to the intermediate solution and stirred overnight at room temperature. Solvent was removed under reduced pressure and the product was purified by flash chromatography using a solvent mixture 1:1 hexanes : diethyl ether as eluent.
Synthesis of (E)-4-butoxy-6-((2-methoxyphenyl)diazenyl)-1,3,5-triazin-2-amine, 7c.

Synthesis performed according to general procedure for product 7; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2c. Yield = 12%. EI-HRMS: Calc. for C_{14}H_{20}N_{6}O_{2} (M+2H): 304.1648 Found: 304.1644. $^1$H NMR (400 MHz, CDCl$_3$) = δ (ppm) 9.19 (bs, 1H)**, 7.82 (dd, 1H, $J = 8.2, 2.0$ Hz), 7.57 (ddd, 1H, $J = 8.2, 7.4, 2.0$ Hz), 7.13 (dd, 1H, $J = 7.4, 1.2$ Hz), 7.01 (ddd, 1H, $J = 7.4, 7.4, 1.2$ Hz), 6.53 (bs, 1H)**, 5.66 (bs, 1H)*, 5.47 (bs, 1H)*, 4.44 (t, 2H, $J = 6.2$ Hz), 4.08 (s, 3H), 1.78 (m, 2H, $J = 7.8, 6.2$ Hz), 1.49 (m, 2H, $J = 7.8, 7.4$ Hz), 0.97 (t, 3H, $J = 7.4$ Hz), *NH free monomer, **NH dimer. $^{13}$C NMR (100 MHz, CDCl$_3$) = δ (ppm) 174.6, 172.3, 169.2, 158.5, 141.4, 135.8, 120.9, 117.0, 112.8, 67.8, 56.0, 30.6, 19.0, 13.7.

Synthesis of (E)-4-(hexylthio)-6-((2-methoxyphenyl)diazenyl)-1,3,5-triazin-2-amine, 7f. Synthesis performed according to general procedure for product 7; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2f. Yield = 50%. EI-HRMS: Calc. for C_{16}H_{24}N_{6}O_{2} (M+2H): 348.1732 Found: 348.1723. $^1$H NMR (400 MHz, CDCl$_3$) = δ (ppm) 9.38 (bs, 1H)**, 7.84 (dd, 1H, $J = 8.2, 1.6$ Hz), 7.58 (ddd, 1H, $J = 8.6, 8.2, 1.6$ Hz), 7.15
(d, 1H, $J = 8.6$ Hz), 7.02 (dd, 1H, $J = 8.6$, 8.2 Hz), 6.56 (bs, 1H)**, 5.47 (bs, 1H)*, 5.46 (bs, 1H)*, 4.12 (s, 3H), 3.17 (t, 2H, $J = 7.4$ Hz), 1.74 (m, 2H, $J = 7.4$, 7.0 Hz), 1.31-1.47 (m, 6H), 0.89 (t, 3H, $J = 7.0$ Hz), *NH free monomer, **NH dimer. $^{13}$C NMR (100 MHz, CDCl$_3$) = $\delta$ (ppm) 184.1, 171.3, 166.5, 158.5, 141.5 135.8, 121.0, 117.1, 112.8, 55.9, 31.3, 30.3, 28.9, 28.5, 22.5, 14.0.

![Chemical Structure](image)

**Synthesis of (E)-4-chloro-6-((2-methoxyphenyl)diazenyl)-1,3,5-triazin-2-amine, 7g.**

Synthesis performed according to general procedure for product 7; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 1. Yield = 12 %. EI-HRMS: Calc. for C$_{10}$H$_{11}$N$_6$O (M+2H): 266.0683 Found: 266.0680. $^1$H NMR (400 MHz, CDCl$_3$)= $\delta$ (ppm) 7.82 (d, 1H, $J = 7.0$ Hz), 7.69 (bs, 1H)**, 7.61 (m, 1H), 7.14 (d, 1H, $J = 8.8$ Hz), 7.02 (m, 1H), 6.46 (bs, 1H)**, 5.77 (bs, 1H)*, 5.72 (bs, 1H)*, 4.09 (s, 3H), *NH free monomer, **NH dimer.

$^{13}$C NMR (100 MHz, CDCl$_3$) = $\delta$ (ppm) 174.4, 170.4, 168.1, 167.0, 140.8, 120.6, 116.0, 114.0, 102.4, 56.0.

![Chemical Structure](image)

**Synthesis of (E)-4-((2-methoxyphenyl)diazenyl)-6-phenoxy-1,3,5-triazin-2-amine, 7i.**

Synthesis performed according to general procedure for product 7; wherein the 4-chloro-
1,3,5-triazin-2-amine derivative is 2i. Yield = 78%. EI-HRMS: Calc. for C_{16}H_{16}N_{6}O_{2} (M+2H): 324.1335 Found: 324.1329. \(^1H\) NMR (400 MHz, CDCl\textsubscript{3})= \(\delta\) (ppm) 8.56 (bs, 1H)**, 7.82 (dd, 1H, \(J = 7.6, 1.8\) Hz), 7.57 (ddd, 1H, \(J = 8.2, 7.6, 1.8\) Hz), 7.43 (m, 2H), 7.27 (m, 1H), 7.23 (m, 2H), 7.12 (d, 1H, \(J = 8.2\) Hz), 7.01 (dd, 1H, \(J = 7.6, 7.6\) Hz), 6.55 (bs, 1H)**, 5.69 (bs, 1H)*, 5.48 (bs, 1H)*, 3.97 (s, 3H), \*NH free monomer, **NH dimer. \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}) = \(\delta\) (ppm) 175.4, 172.7, 169.3, 158.8, 152.1, 141.5, 136.0, 129.4, 125.7, 121.9, 120.9, 117.2, 112.8, 55.9.

\[
\begin{array}{c}
\text{Synthesis of } (E)-4-(4-(\text{tert-butyl)}\text{phenoxy})-6-(\text{2-methoxyphenyl)diazenyl)-1,3,5-
\text{triazin-2-amine, 7k. Synthesis performed according to general procedure for product 7;}
\end{array}
\]

wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2k. Yield = 14%. EI-HRMS: Calc. for C_{20}H_{24}N_{6}O_{2} (M+2H): 380.1961 Found: 380.1960. \(^1H\) NMR (400 MHz, CDCl\textsubscript{3})= \(\delta\) (ppm) 8.83 (bs, 1H)**, 7.81 (dd, 1H, \(J = 8.2, 1.6\) Hz), 7.56 (ddd, 1H, \(J = 8.6, 7.4, 2.0\) Hz), 7.42 (m, 2H), 7.14 (m, 2H), 7.11 (d, 1H, \(J = 8.6\) Hz), 7.01 (ddd, 1H, \(J = 8.2, 7.4, 1.6\) Hz), 6.55 (bs, 1H)**, 5.66 (bs, 1H)*, 5.49 (bs, 1H)*, 4.00 (s, 3H), 1.35 (s, 9H), \*NH free monomer, **NH dimer. \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}) = \(\delta\) (ppm) 175.4, 172.8, 169.3, 158.7, 149.7, 148.5, 141.5, 135.9, 126.3, 121.1, 120.9, 117.2, 112.8, 55.9, 34.5, 31.5.
Synthesis of (E)-4-(3,5-bis(trifluoromethyl)phenoxy)-6-((2-methoxyphenyl)diazenyl)-1,3,5-triazin-2-amine, 7m. Synthesis performed according to general procedure for product 7; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2m. Yield = 21%. EI-HRMS: Calc. for C\textsubscript{18}H\textsubscript{14}F\textsubscript{6}N\textsubscript{6}O\textsubscript{2}(M+2H): 460.1082 Found: 460.1081. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})= δ (ppm) 8.36 (bs, 1H)**, 7.82 (dd, 1H, J = 8.2, 2.0 Hz), 7.80 (s, 1H), 7.73 (s, 2H), 7.59 (ddd, 1H, J = 8.8, 8.8, 1.8 Hz), 7.13 (d, 1H, J = 8.8 Hz), 7.02 (dd, 1H, J = 7.6, 7.6 Hz), 6.38 (bs, 1H)**, 5.74 (bs, 1H)*, 5.54 (bs, 1H)*, 4.00 (s, 3H), *NH free monomer, **NH dimer. \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) = δ (ppm) 201.8, 190.2, 171.3, 169.2, 164.2, 158.1, 152.9, 140.8, 135.7, 131.7, 124.0, 120.6, 116.0, 114.0, 56.0. \textsuperscript{19}F NMR (376.42 MHz, DMSO-d\textsubscript{6}) = δ (ppm) -61.18.

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Synthesis of (E)-4-((2-methoxyphenyl)diazenyl)-6-(perfluorophenoxy)-1,3,5-triazin-2-amine, 7n. Synthesis performed according to general procedure for product 7; wherein the 4-chloro-1,3,5-triazin-2-amine derivative is 2n. Yield = 50%. EI-HRMS: Calc. for C\textsubscript{16}H\textsubscript{11}F\textsubscript{5}N\textsubscript{6}O\textsubscript{2}: 414.0864 Found: 414.0857. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})= δ (ppm) 8.78 (bs, 1H)**, 7.81 (dd, 1H, J = 8.2, 2.0 Hz), 7.60 (dd, 1H, J = 7.0, 1.6 Hz), 7.15 (d, 1H, J = 8.2 Hz), 7.03 (dd, 1H, J = 8.2 Hz), 6.44 (bs, 1H)**, 5.76 (bs, 1H), 5.56 (bs, 1H)*, 4.06 (s,
3H), *NH free monomer, **NH dimer. $^{13}$C NMR (100 MHz, CDCl$_3$) = $\delta$ (ppm) 175.4, 169.4, 159.0, 141.5, 136.6, 121.0, 117.2, 113.0, 56.0. $^{19}$F NMR (376.42 MHz, DMSO-d$_6$) = $\delta$ (ppm) -152.2 (d, 2H, $J = 17.2$ Hz), -158.42 (t, 1H, $J = 22.4$ Hz), -162.58 (dd, 2H, $J = 242.4, 17.2$ Hz).

4.4.3 Synthesis of (Z)-4-butoxy-6-((2-methoxyphenyl)diazanly)-1,3,5-triazin-2-amine, (c)-7c.

Approximately 160 mL of a $10^{-2}$ M solution of a derivative 7 in dichloromethane was prepared and distributed between 16 test tubes. Each test tube containing the derivative 7 solution was purged with N$_2$ in order to avoid side reactions with O$_2$ present in solution. The 16 test tubes were placed in the photoreactor and irradiated using lamps with radiation centered at 360 nm for 3 hours. After irradiation, the solution was cooled down to -78$^\circ$ and the solvent was removed employing a constant air flow to yield a mixture of cis and trans isomers. The cis-isomer was isolated through flash chromatography with 1:1 hexanes : diethyl ether mixture as eluent. Once the first fraction (cis isomer) was obtained, it was cooled down to -78$^\circ$ to remove the solvent mixture with the aid of a constant air flow. In all cases, the cis-isomer was a yellow powder that was stored in a vial wrapped with black in the freezer to prevent thermal and photochemical reversion.
4.5 References


Chapter 5

5 Conclusions and Outlook

5.1 Conclusions

Azoaromatic compounds are well-known photoswitches with a variety of applications in materials science. Conversely, the heteroaromatic counterparts have had less attention in this area, regardless that they exhibit similar photochromic properties. This allowed a niche of opportunity we have explored in this thesis. We were able to obtain azoheteroaromatic self-complementary hydrogen bond arrays, derivatives 4 and 7. The novelty of these arrays lies in the function of the azo group as a hydrogen bond acceptor, in addition to a means of structural change in the supramolecular array by UV-Vis light irradiation. Specifically, these systems were design to form a stable **DDAAA-AAADD** array when they are present as trans-isomers.

Through $^1$H NMR dilution experiments we observed the effect of solvent systems and the electronic influence of the substituents employed in the trans-dimer stability. In addition, thanks to the X-ray crystal structures of four derivatives from our first system proposed (piperidine 4a, octyloxy 4d, hexylthiol 4f and tert-butylphenoxy 4k derivatives) we were able to corroborate the dimer structure expected. From these dimer structures in the solid state we noted that the pyridyl nitrogen acceptor site was not optimally aligned with an amino group acceptor for a strong hydrogen bond interaction between these sites. Therefore, we changed the pyridyl ring for a methoxyphenyl group. The methoxy group ortho- to the azo moiety was anticipated to be closer to the amino group in the dimer
Comparing derivatives 7 with 4a-p we observed a marginal improvement in the stability of the trans-dimer structures in solution for the former systems; specifically in toluene-$d_8$ solution. In addition, the X-ray crystal structures of the dimers of butoxy 7c, hexylthiol 7f, tert-butylphenoxy 7k and perfluorophenoxy 7n confirmed intermolecular distances from the methoxy oxygen acceptor to an amino’s proton shorter than those observed for the pyridyl nitrogen acceptor to the same proton in derivatives 4 dimers in the solid state.

Regarding the photophysical properties of all these azoheteroaromatic self-complementary hydrogen bond arrays, trans- to cis- photoisomerizations proceed with interconversion yields lower than 35%. The presence of cis-isomer in a solution of 4 or 7 induces a change in the system through the addition of two further equilibria: cis-cis dimerization and trans-cis complexation. Based on the number of hydrogen bond interactions expected in the cis-cis dimer, it was assumed that the stability of this dimer would be significantly lower compared with the trans-trans dimer and the trans-cis complex; therefore, the contribution of the cis-cis dimerization equilibrium into the species distribution was discarded. In this way, we were able to calculate the trans-cis complexation constants of butoxy 4c, hexylthiol 4f, tert-butylphenoxy 4k and butoxt 7c (the first three at 298 K and the last one at 263 K). Thanks to these complexation constants it is possible to obtain the speciation diagrams of 4c, 4f, 4k and 7c as the cis/trans ratio in solution changes.
5.2 Outlook

The calculation of the trans-cis complexation constant \((K_{t\,c})\) of butoxy 7c at -10 °C was a good exercise that provided us the energetic differences between the tran-trans dimer and the trans-cis complex stabilities at low temperature. However, the impossibility to calculate this constant at room temperature is a disappointment since we are not able to compare with derivatives 4c, 4f and 4k at the same temperature. For this reason, it would be interesting to attempt the calculation of \(K_{t\,c}\) for 7c at room temperature by extrapolation. This is, to calculate the trans-cis complexation constant of this system at different temperatures below room temperature (0, 5 and 10 °C) where the thermal reversion rate would allow the collection of a larger and reliable amount of data. Through the Van’t Hoff equation (Equation 1) \(K_{t\,c}\) for 7c at 25 °C could be calculated.

\[
\ln K_{t\,c} = -\frac{\Delta H^0}{RT} + \frac{\Delta S^0}{R} \quad \text{Equation 1}
\]

As described in Chapter 1 (Section 1.6), the preorganization of the monomeric units that participate in a supramolecular structure have a positive effect improving the molecular recognition process. In this sense, the rotational freedom of the methoxy group in 7 is an important issue to consider since it can impede the access to the oxygen acceptor atom in a hydrogen bond interaction. Therefore, the ether group ortho- to the azo moiety should be fixed as a cyclic ether (or ester) in order to expose the oxygen acceptor site (Scheme 5.1). A six member cyclic ether \((n = 2)\) would be ideal considering that the ring constrains on the intermolecular distance and angle between the amino protons and the oxygen atom in the dimer structure. However, it would be also interesting to see if in a
five-member ring ether \((n = 1)\) the dimer stability is improved due to preorganization regardless of the possible deviation from linearity between the interacting sites.

![Scheme 5.1](image)

**Scheme 5.1** Preorganized photo-isomerizable self-complementary hydrogen bond arrays

\((n = 1 \text{ or } 2)\)

Finally, the synthesis of supramolecular polymers including these photo-isomerizable self-complementary hydrogen bond arrays would provide opportunities for further studies. As an example, the addition of these systems could be as terminal binding groups wherein the linkage could be a long chain diol (Scheme 5.2). The synthesis and characterization of the supramolecular polymers SP-4 and SP-7 in Scheme 5.1 is currently being developed in our group.

![Scheme 5.2](image)

**Scheme 5.2** Proposed inclusion of photo-isomerizable self-complementary hydrogen bond arrays.
Curriculum Vitae

Name: Iamnica Janic Linares Mendez

Post-secondary
Education and Degrees:

- Universidad Autonoma de San Luis Potosi
  San Luis Potosi, S.L.P, Mexico
  2003-2008 B.A.

- Universidad Nacional Autonoma de Mexico
  Mexico City, Mexico
  2008-2010 M.A.

- The University of Western Ontario
  London, Ontario, Canada
  2011-2016 Ph.D.

Honours and Awards:

- Western Graduate Research Scholarship Graduate Scholarship 2011-2016
- Graduate oral presentation (First Place). Organic: Advances in Molecular Recognition, CSC 2014
- International Summer Science Research UASLP 2007
- National Summer Research AMC 2006

Related Work Experience

- Teaching Assistant
  The University of Western Ontario
  2011-2016

Conference Presentations:

