

Hydrogen-, halogen-, and chalcogen-bond driven solid-state assembly of functional
supramolecular systems

by

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Abstract

The chalcogen bond (ChB) is relatively underexplored in the context of controlling supramolecular self-assembly. In order to improve our understanding of the structural influence and tunability of the ChB, a series of alkylselenoacetylene derivatives were devised, synthesized and characterized using multinuclear NMR and single crystal X-Ray diffraction (SC-XRD), Chapter 2. Density functional theory (DFT) calculations showed excellent tunability and correlation between the magnitude of the σ -hole potential and the interaction energies of the synthesized compounds. Molecular electrostatic potential maps (MEPs) accurately predicted the plausible synthon assembly and the directionality of the ChBs based on the donor-acceptor preference.

To further enhance control over the magnitudes on both σ -holes on bivalent chalcogen atoms, a series of ‘triply activated’ phenylchalcogenacetylene derivatives were synthesized, Chapter 3. The σ -hole potential and the ChB donor ability were ranked based on the MEPs and the structural outcomes were postulated. The ChB preference of the synthons were established using crystallography, and the resulting geometrical features were benchmarked against the reported literature examples extracted from the Cambridge Structural Database (CSD). Cell viability assays for the synthesized target compounds against HeLa cell lines showed that the atom-to-atom substitution of selenium with tellurium can significantly improve the chemotherapeutic properties of these compounds by an order of magnitude.

The structural influence of hydrogen, halogen, and chalcogen bonding was explored based on three series of 1,3,4-chalcogenadiazole derivatives in Chapter 4. The delicate balance between the intermolecular interactions present were clearly displayed in the two polymorphs of 5-(4-iodophenyl)-1,3,4-thiadiazol-2-amine (T1-S-I). The MEPs showed the influence of atom-to-atom

substitution on the σ -hole potentials, where substitution of S with Se led to bifurcated ChBs and activated halogens resulted in 100% probability of halogen bond (XB) expectation. MEPs also succeeded in predicting the preferred hydrogen bond (HB) synthon in the crystal structures of the 1,3,4-chalcogenadiazole derivatives.

In Chapter 5, we examined (i) the influence of hydrogen, halogen, and chalcogen-bond donors on cocrystal synthesis; (ii) the possibility of predicting whether salts or cocrystals would form in a series of 2-amino-1,3,4-chalcogenadiazole derivatives. Four 1,3,4-chalcogenadiazole derivatives were screened for co-crystallization with 38 carboxylic acid coformers with a 82% success rate. A total of 17 crystal structures were obtained, with 71% resulting in salts and 29% leading to cocrystals. The predictability of salt and cocrystal synthesis was explored based on FT-IR, ΔpK_a , ΔD_{C-O} which showed that FT-IR and ΔD_{C-O} worked best with these systems. We also demonstrated the usefulness of DFT calculations for predicting, a priori, whether a salt or a cocrystal would form.

To create a structural competition between XB and ChB we replaced the amino group of 2-amino-5-(4-halophenyl)-1,3,4-chalcogenadiazole with bromo/iodo substituents to obtain a library of five 2-halo-5-(4-halophenyl)-1,3,4-chalcogenadiazole derivatives, Chapter 6. This produced five crystal structures, all were isostructural and contained primarily chalcogen and halogen bonding interactions. Hirshfeld surface analysis and energy framework calculations showed that, collectively, a bifurcated chalcogen bond was stronger than a single halogen bond and thus more structurally influential.

The 1,3,4-chalcogenadiazole derivatives that can form all three hydrogen, halogen and chalcogen bonding noncovalent interactions could provide a promising design strategy for creating flexible crystal systems. Considering the novelty of the mechanically flexible systems we decided

to explore potential structural modifications of 1,3,4-chalcogadiazoles using amide substituents with varying chain lengths and explore the structure-property relationship in Chapter 7. Fourteen crystal structures were obtained including several polymorphic forms. All the crystals either showed elastic bending or brittleness and none showed plastic deformation. The presence of corrugation and interlocking resulted in elastic bending systems 64% of the time and the lack of corrugation, slip planes, and interlocking results in brittleness in 36% of the crystals.

Finally, in Chapter 8, three cavitands functionalized with chalcogen-bond donors on the upper rim were synthesized and characterized. The ^1H and ^{77}Se NMR titration experiments demonstrated that host-guest binding was facilitated by chalcogen bonding.

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Dedication

To my father

For your unconditional love and trust in me

Preface

Research carried out in Kansas State University for this dissertation led to the following publications in scientific journals:

1. De Silva, V.; Averkiev, B. B.; Sinha, A. S.; Aakeröy, C. A. The Balance between Hydrogen Bonds, Halogen Bonds, and Chalcogen Bonds in the Crystal Structures of a Series of 1,3,4-Chalcogenadiazoles. *Molecules* **2021**, 26 (14), 4125. <https://doi.org/10.3390/molecules26144125>. (Chapter 4)
2. De Silva, V.; Le Magueres, P.; Averkiev, B. B.; Aakeröy, C. A. Competition between chalcogen and halogen bonding assessed through isostructural species. *Acta Cryst.* **2022**, C78, 716-721. <https://doi.org/10.1107/S205322962201052X>. (Chapter 6)

Chapter 1 – Introduction

1.1 Structure relevance towards the property

“Structure dictates the property” is a powerful relationship that has been proven to be of great importance in not just chemistry but even for biological systems, polymers, medicine, and engineering (Figure 1.1). The chemical structure can determine not just the physiochemical properties of substances such as melting points¹, flash points², binding energies^{3,4}, non-linear optical properties⁵, and mechanical response of materials⁶⁻⁸, it can also affect pharmacological activity.^{9,10} Therefore, understanding structure-property relationships can help us to design molecules and materials with desired properties and responsive and adaptive functions.

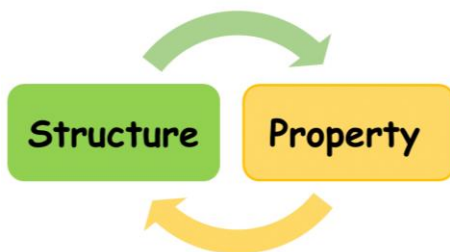


Figure 1.1 Structure property relationship.

The efforts towards identifying properties based on a simple chemical structure have progressed significantly over the past few decades partly owing to the advancement of quantum chemistry which can nowadays predict physical properties from crystal structures¹¹ to even waveguide properties¹². However, the design of novel materials with desired physiochemical properties still provides significant challenges due to lack of experimental evidence, limitation of irreversible covalent chemical synthesis and delicately balanced intermolecular forces. Kitaigorodsky pioneered the work of molecular crystal systems to control and finetune the properties of mixed crystals based on close-packing principles and overcame some of the previous

limitations.^{13,14} Controlling and finetuning bottom-up assembly of molecular crystals, however, still require an extensive understanding of the “chemistry beyond the molecule” also referred to as *Supramolecular chemistry*.¹⁵

Among many examples of structure property relationships, the correlation between the two at solid-state level can be found in the three polymorphs of 4-bromophenyl 4-bromobenzoate¹⁶ showing different mechanical response towards the external stimuli. The recognition of 3,5,3'-triiodothyroxine (T3) by human thyroid hormone receptor¹⁷ shows the significance of the less known intermolecular interactions in determining and controlling properties and functions in both at ligand-receptor supramolecular systems (Figure 1.2).

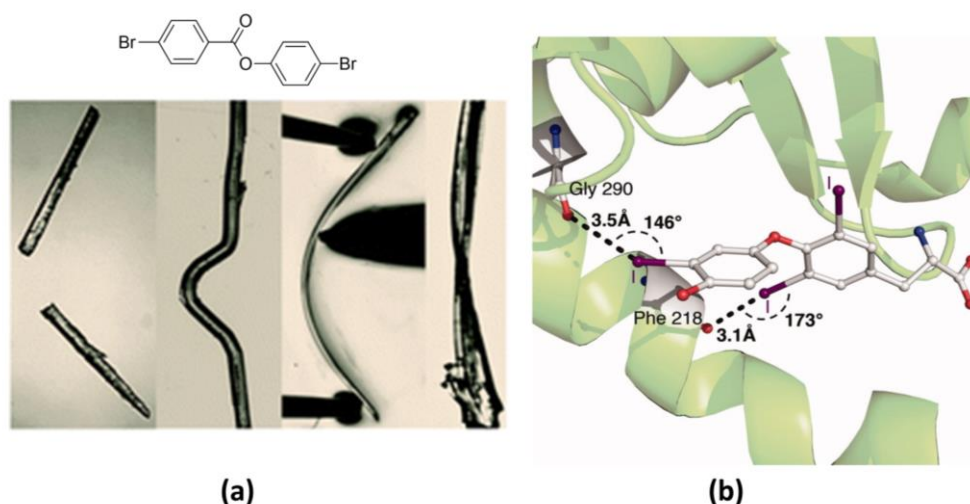


Figure 1.2 (a) Trimorphs of 4-bromophenyl 4-bromobenzoate showing different mechanical properties of brittle, plastic, and elastic¹⁶ **(b)** recognition of T3 by human thyroid receptor¹⁷.

1.2 Supramolecular Chemistry

Pioneering work on supramolecular chemistry was recognized in 1987 Nobel prize which was awarded to three scientists, Donald. J. Cram, Charles John Pederson and Jean-Marie Lehn. Supramolecular chemistry is recognized as the chemistry of noncovalent interactions (NCI) that

has a wide array of applications leading from host-guest chemistry to crystal engineering, all of which involve NCIs.

The area of research in supramolecular chemistry that is focused on manipulating the intermolecular interactions towards controlling the crystallization and molecular self-assembly to obtain novel solid-state materials with desired physiochemical properties is recognized as crystal engineering. Crystal engineering over the past sixty years have evolved from trying to understand the crystal packing to be able predict the physiochemical properties.

One of the best examples of crystal engineering adaptation is co-crystallization. Co-crystallization involves combining two or more different molecular compounds, held together by noncovalent interactions for developing novel materials that otherwise cannot be accessed via traditional covalent synthesis (Figure 1.3). Cocrystals have found uses in many fields including agrochemicals¹⁷, energetics¹⁸, nutraceuticals¹⁹, flexible crystals⁸ and pharmaceutical industry²⁰.

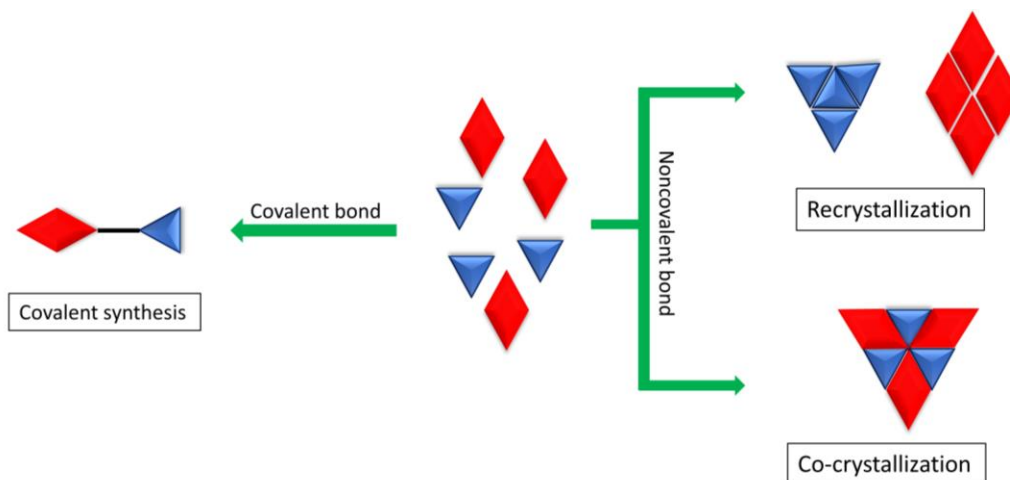


Figure 1.3 Schematic showing irreversible covalent synthesis and reversible supramolecular synthesis.

To obtain a finer control of these synthon assemblies driven by the reversible noncovalent interaction's fundamental aspects of intermolecular forces needs to be better understood. Over the

past century the most explored noncovalent interaction has been the hydrogen bond²¹ however, other intermolecular interactions such as dipole-dipole interactions, ion-ion interactions, ion-dipole interactions, π - π stacking and van der Waals forces have also been studied and understood along with hydrogen bonds. Recently novel intermolecular forces such as halogen²² and chalcogen bonding²³⁻²⁵ have become more attractive due to the nature of directionality and controllability of these σ -hole interactions.

1.3 σ -hole interactions

Hydrogen bonding (HB) is a special type of dipole-dipole interaction that can be defined as an attractive interaction between the positive electrostatic potential on a hydrogen atom and the negative electrostatic potential on an acceptor atom (Lewis base) Figure 1.4.

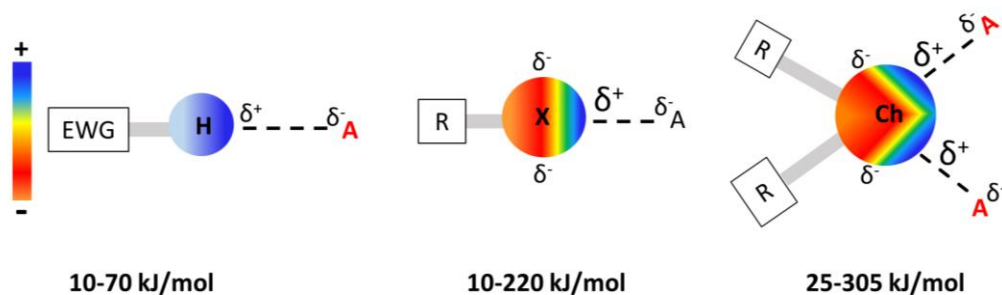


Figure 1.4 Schematic showing hydrogen, halogen and chalcogen bonding and their relative strength.

σ -hole interactions share some similarities to hydrogen bonds however unlike the hydrogen atom, halogen and chalcogen atom consist of an electron deficient region (δ^+) appearing directly opposite to the group its bonded to which is what's known as σ -hole. Based on the electrostatic stand point the attractive interaction formed between the σ -hole and the electron rich (δ^-) region of an acceptor (Lewis base/nucleophile) is defined as a halogen bond (XB)²⁶ or a chalcogen bond

(ChB)²⁷ Figure 1.3. The exact nature of these two nonbonding interactions are still under debate however these have been examined with both experimental UV-Vis that suggests the charge transfer component²² while others suggest the discussed coulombic electrostatic nature²⁸.

Several different types of XB and ChB interactions have been identified over the years and only the main ones are discussed herein. First is the conventional XB and ChB between the σ -hole and an acceptor either on the same molecule or a different molecule/fragment. Second the Type I contact that forms due to close packing and driven by dispersive forces. Third is Type II that form between σ -hole and the negative region of the halogen or chalcogen atom acting as the acceptor. The geometrical features of these XB and ChB are shown in Figure 1.5.

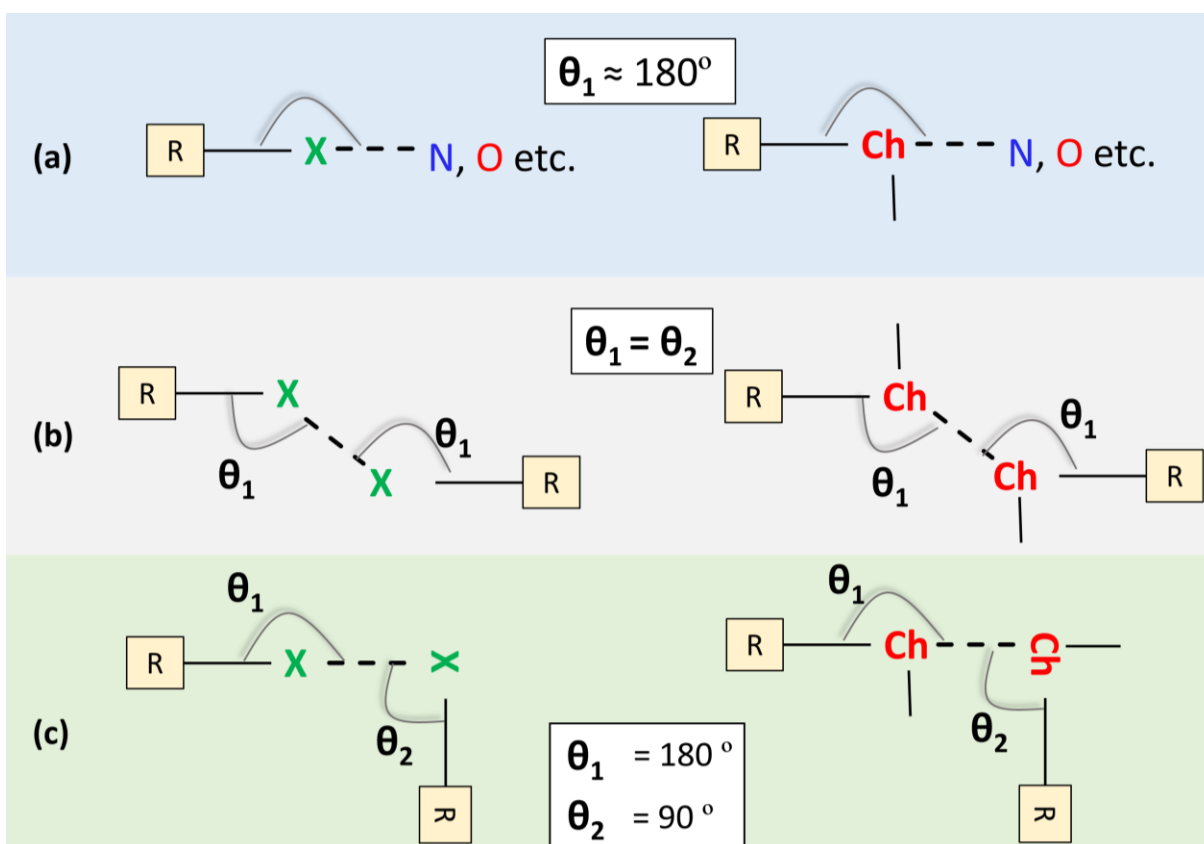


Figure 1.5 Different halogen and chalcogen bond geometries (a) conventional (b) Type I contact (c) Type II.

Unlike the hydrogen bond, these σ -hole interactions consist of a much wider range of intermolecular bond strengths, Figure 1.4, making them highly tunable and attractive towards generating supramolecular assemblies and cocrystals. In this dissertation we will focus on hydrogen, halogen and chalcogen bonding interactions.

1.4 Significance of HBs, XBs, and ChBs in supramolecular chemistry

Novel active pharmaceutical ingredients (APIs) are incredibly diverse and can contain multiple functional groups with hydrogen-, halogen-, and chalcogen-bond donors. Two examples of such a complex recently FDA approved drugs, *Ponesimod* that's used to treat sclerosis and *Voquezna* a K^+/H^+ -ATPase potassium channel blocker is shown in Figure 1.6. The structure of *Ponesimod* contains hydrogen-, halogen- and chalcogen-bond donors and multiple acceptor sites. Though these interactions are somewhat similar in an electrostatic stand point the fundamental differences and the variability and the tunability of the strength of intermolecular interactions means they could potentially compete for supremacy in the drug-receptor recognition and even more so in the solid-state. Though studies with regards to competing hydrogen, halogen bonding and halogen, chalcogen bonding have been done the novelty of these σ -hole interactions means that it still lacks enough fundamental data to properly understand the nature of these interactions in complex systems. Most importantly, to the best of our knowledge a competing study between hydrogen, halogen and chalcogen bonding in a single molecular skeleton has not been done previously.

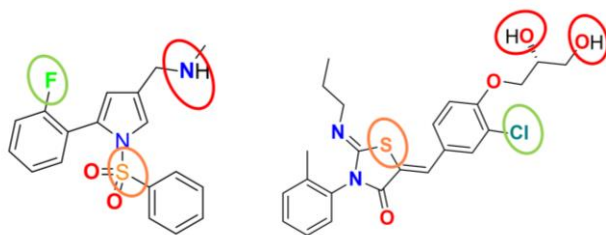


Figure 1.6 Structure of *Vaquezna* and *Ponesimod* (left to right).

Recent advancements in our understanding of chalcogen bonding have shown that organochalcogen species can be potential chemotherapeutic agents²⁹ and ChBs can be used to facilitate supramolecular self-assembly and host-guest interactions^{30,31} (Figure 1.7). Development of reliable avenues of materials design with controlled ChB donor ability and supramolecular self-assembly still remains a challenge.

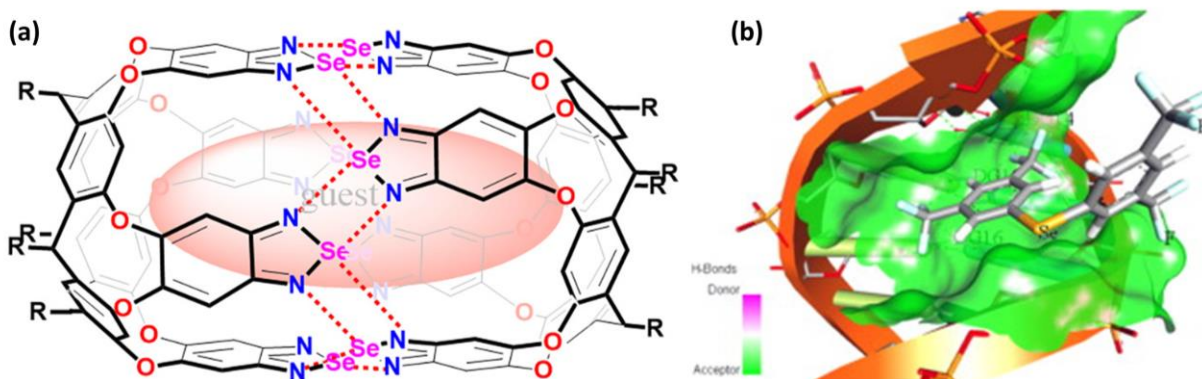


Figure 1.7 Chalcogen bond driven supramolecular cavitand capsules³⁰ and molecular docked model of novel 3,5-bis(trifluoromethyl)phenyl with DNA²⁹.

1.5 Goals of this dissertation

The fundamental aspects of noncovalent interactions and their rational use in supramolecular architecture design and control will be addressed in this dissertation and the main goals of the dissertation can be divided into four major sections. First, the fundamental

understanding of the relatively less explored chalcogen bonding will be improved. Second, the improved understanding of such noncovalent interactions are utilized to explore and predict the supramolecular synthon assembly and cocrystal design. Third, the structure property relationship between mechanically responsive crystal systems and the intermolecular interactions will be established. Fourth, chalcogen-bond is employed to drive supramolecular host-guest chemistry.

This dissertation will focus on the following specific goals,

Chapter 2. Explores the ability to control and fine-tune σ -hole potential of a series of alkyselenoacetylenes chalcogen-bond donors.

Chapter 3. Investigates the “triple activation” strategy to fine-tune both σ -hole potentials and the potential effect of atom-to-atom chalcogen-bond donor substitution on chemotherapeutic properties.

Chapter 4. Explores the balance between hydrogen bonds, halogen bonds, and chalcogen bonds in the crystal structures of a series of 1,3,4-chalcogenadiazole derivatives.

Chapter 5. Describes a systematic co-crystallization experiment of 1,3,4-chalcogenadiazole derivatives and their ability to form salts and cocrystals. Predictability of the proton transfer is assessed based on FT-IR, ΔpK_a , computational methods and single crystal structures.

Chapter 6. Explores the competition between halogen and chalcogen bonding in a series of 2-halo-5-(4-halophenyl)-1,3,4-chalcogenadiazole.

Chapter 7. Explores the potential for designing flexible crystals and for correlating the mechanical response to the differences in intermolecular forces present.

Chapter 8. Describes the synthesis of cavitands functionalized with chalcogen-bond donors and investigates binding abilities in solution with suitable guests.

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Chapter 2 – Controlling and predicting chalcogen bonding in alkylselenoacetylenes

2.1 Introduction

Crystal engineering involves the design and synthesis of solid-state materials with desired physiochemical and biological properties through the proper control of noncovalent interactions. A bottom-up assembly of such materials and formulations require a delicate control of noncovalent interactions involved in such architectures.¹ Hydrogen bonds (HBs) have been the most versatile tool used in laying out the foundation in crystal engineering over the past century and that arsenal have been expanded with the emergence of novel and directional halogen-bond (XB) interactions.^{2–5} Further expansion into more complex and highly tunable chalcogen bonds (ChB) have allowed for a much larger toolkit in the field of controllable supramolecular assemblies with desired physiochemical properties.^{6,7}

Pnictogen, halogen and chalcogen bonds are also known as σ -hole interactions in which the accumulation of positive electrostatic potential appearing due to reduced electron density directly opposite the covalent bonds these atoms are attached to is defined as the σ -hole (Figure 2.1).^{6,8–10} The magnitude of the σ -hole is proportional to the strength of the intermolecular interaction that its associated with. Having control of the magnitude of the σ -hole can allow the control over the assembly of the solid-state and hence affect physiochemical properties and the binding affinities towards acceptors.

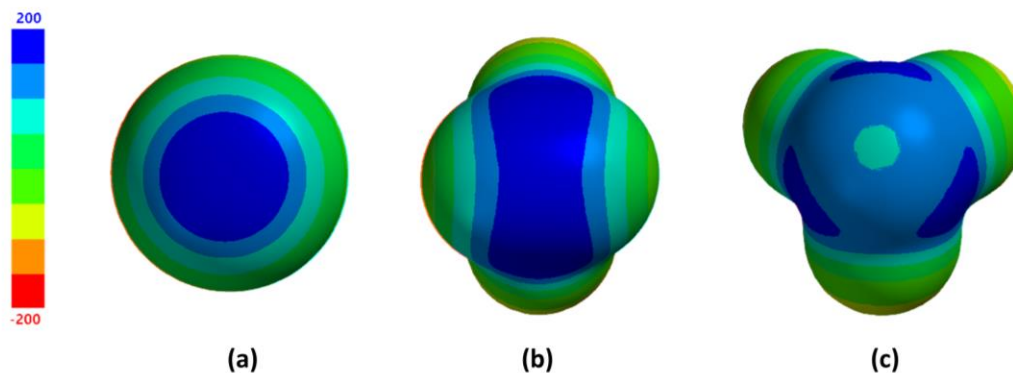


Figure 2.1 (a) Halogen (one σ -hole) (b) chalcogen (two σ -holes) (c) pnictogen σ -hole (three σ -holes).

The energy components of a σ -hole interaction can be divided into electrostatic, dispersion, polarization, and repulsion.¹¹ One of the major contributors to the interaction is the electrostatic part and hence the σ -hole interaction can be partly defined as the Coulombic attraction between the σ -hole (most positive electrostatic potential) and the acceptor (most negative electrostatic potential).⁶ In general, molecular electrostatic potential maps (MEPs) can be used to evaluate the magnitude of the σ -hole potentials, and also to design molecules with predetermined σ -hole magnitudes and hence control the directionality of the σ -hole interaction.¹²

Chalcogen bonding in crystal engineering have been underutilized compared to hydrogen and halogen bonds owing to the lack of in-depth fundamental analysis of the characteristics of σ -holes on the chalcogen and its behavior. Recently, though chalcogen bonds have also been recognized to be capable to performing functional properties such as anion recognition and catalysis.^{13–15} In our attempt to contribute to the fundamental understanding of underlying aspects and behaviors of chalcogen bonding we decided to use literature reported ‘activation’ of the σ -hole through electron withdrawing groups (EWGs) and *sp*-hybridization to reduce the electron density from the polarizable chalcogen atoms to control the magnitude of the σ -hole on the

chalcogen atoms. There have been two reports in which linear oligoalkynes with chalcogenamethyl^{16,17} groups and *bis*(alkynyl)chalcogenamethyl⁷ derivatives were used to study chalcogen bonding and its influence on co-crystallization, however neither study attempted to fine-tune the σ -hole potentials.

In our work, a library of activated molecules with controlled σ -hole strength were synthesized utilizing electron withdrawing groups such as F, CN, NO₂ and sp-hybridized C $\equiv$ C bonds. For the substitution on the chalcogen atom we decided to employ the same literature reported chalcogenamethyl group which could also be changed to EWGs to control both σ -holes present on the chalcogen atom Figure 2.2.

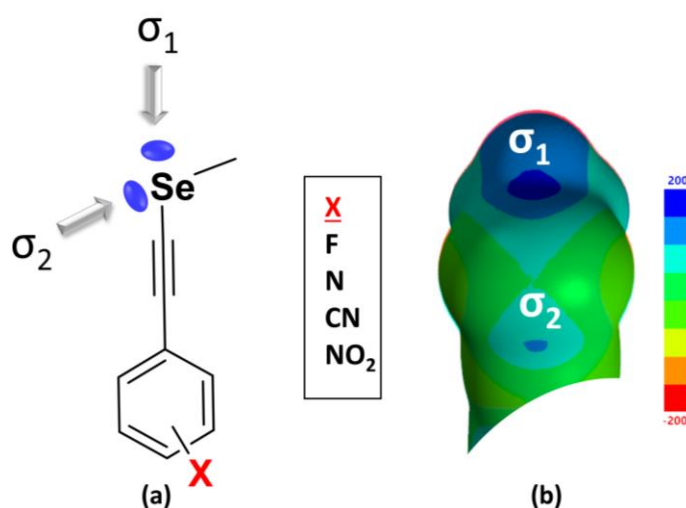


Figure 2.2 Strategy used in synthesizing activated ChB donors.

For our initial attempt at controlling the σ -hole potential, we focused our attention firstly on the σ -hole (σ_1) directly opposite to the triple bond which is also in conjugation with the aromatic ring. The library of compounds synthesized in this study is shown in Figure 2.3.

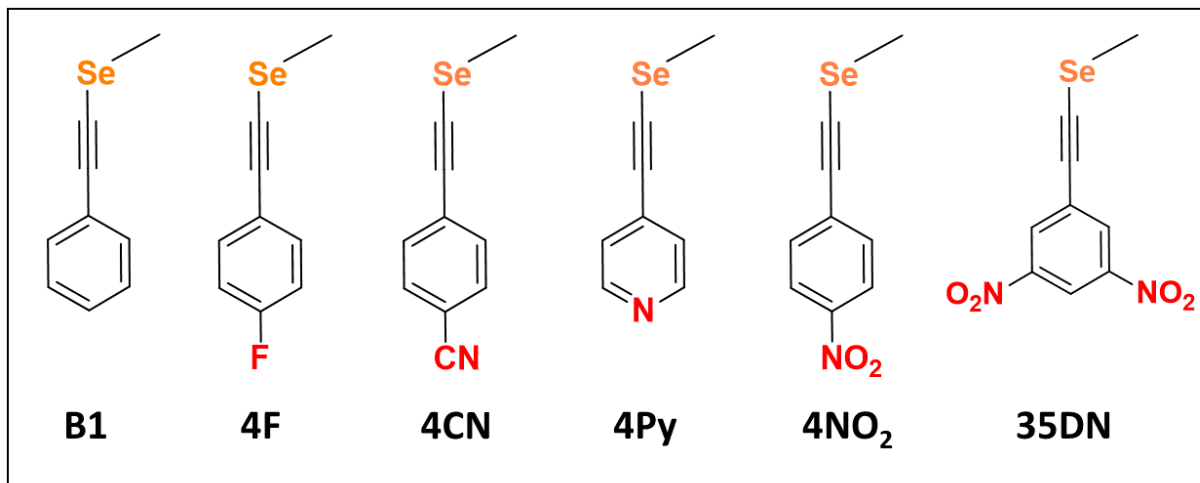


Figure 2.3 Library of target molecules synthesized and explored in this study.

By synthesizing these molecules, we wanted to address the following questions,

Question 1 - Can molecular electrostatic potentials predict the directionality of σ -hole interactions?

Question 2 - Can interaction-energy calculations assess which interactions are stronger and preferred?

Question 3 – Do crystal structures show the postulated structural outcomes?

Question 4 – Can we fine-tune the magnitudes of both σ -holes on the chalcogen atom?

2.2 Experimental

2.2.1 General

Commercial reagents were purchased from commercially available sources and used without further purification. Anhydrous THF and all other solvents were purchased from Fisher scientific and used without further purification. Melting points were measured using a TA instruments DSC Q20 differential scanning calorimeter. Nuclear magnetic resonance (NMR) data

were measured on a Bruker Ascend 400 MHz spectrometer. The residual solvent peak was used as the internal reference for ^1H and ^{13}C NMR. For ^{77}Se NMR the selenium peak was referenced against the residual solvent peak in its corresponding ^1H NMR spectrum. Single crystal X-ray diffraction data were collected using a Rigaku XtaLAB Synergy-S diffractometer and the structures were solved using Olex2¹⁸ with SHELXT¹⁹. All computational calculations were performed using Spartan14 software package.

2.2.2 Computational calculations

2.2.2.1 Molecular electrostatic potential calculations

Molecular electrostatic potentials were calculated using Spartan14 Wavefunction. The compounds were sketched and saved using ChemDraw 12 and loaded into Spartan14²⁰ software followed by geometry optimization for the most stable conformation using density functional theory B3LYP hybrid functional and 6-311++G** basis set for selenium compounds. A positive point charge in the vacuum was used as a probe against the surface to determine the positive and negative regions on the molecular surface. The electrostatic potentials presented herein are given in kJ/mol and a negative number is representative of an electron rich acceptor and a positive number of an electron poor donor.

2.2.2.2 Interaction energy calculations

Interaction energies (IE) were calculated for all the targets using an ammonia molecule as the acceptor. The target and the ammonia were drawn in ChemDraw12 and loaded into Spartan14. The position of the NH_3 was adjusted firstly to overlap with the σ -hole directly opposite to the triple bond and secondly directly opposite to the methyl group attached to the chalcogen atom, Fig.

2.4. For these complexes the geometry was first optimized using B3LYP hybrid functional and 6-311++G** basis set in vacuum. Upon geometry optimization, single point energy calculations were carried out using the B3LYP hybrid functional and 6-311++G** basis set in vacuum and the interaction energies were counterpoise corrected using basis set superposition error. Additional inputs such as GEOMETRYCYCLES=1000, OPTCYCLE=1000 and MEM_STATIC=300 were necessary to improve the calculations.

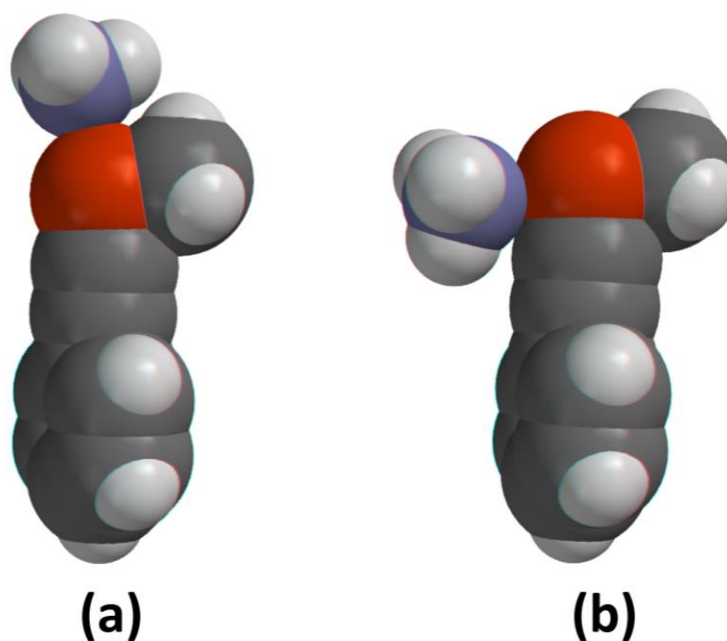
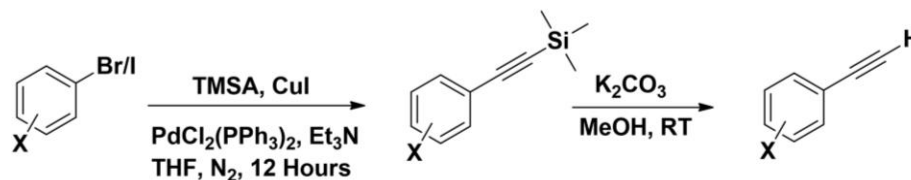


Figure 2.4 Unsubstituted B1 + ammonia complex with **(a)** σ_1 and **(b)** σ_2 .

2.2.3 Synthesis

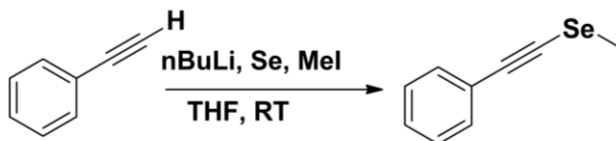
2.2.3.1 General Synthesis of ethynyl intermediates



Appropriately substituted haloaromatic species were dissolved in a triethylamine and THF 1:1 mixture and degassed with dry dinitrogen for 10-20 min. To this mixture, CuI (5% mol), *bis*(triphenylphosphine)palladium(II) dichloride (10%mol) and trimethylsilyl acetylene (2 eq) were added and stirred overnight at room temperature. Completion was confirmed by TLC. After completion the mixture was rotary evaporated, and the crude was purified by column chromatography.

The resulting TMS compound was dissolved in a dichloromethane (DCM) and methanol 1:1 mixture and K₂CO₃ (2eq) was added to this and stirred at room temperature under air for 6 hours. Upon completion the solvent was evaporated, and the product was purified by a flash column.^{21–23}

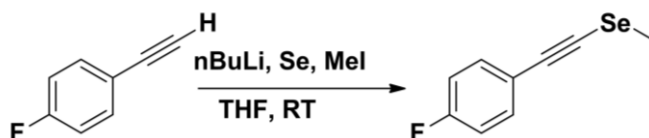
2.2.3.2 Synthesis of methyl(phenylethynyl)selane (B1)



Ethynylbenzene (1 mmol) was placed in an oven dried 100 ml round bottom flask and sealed with a septum. This was evacuated and filled with dry N₂ three times and after the third cycle, anhydrous THF(10 ml) was added followed by refilling with dry N₂. Then the mixture was cooled to -78 °C using dry ice and acetone bath for 20 minutes after which $n\text{BuLi}$ (1.2 mmol) was added dropwise and stirred for 30 min then Se powder (1mmol) was added, and the dry ice bath was removed to allow the reaction mixture to reach room temperature. The mixture was stirred at room temperature for 4 hours and then MeI (1.2 mmol) was added and continued to stir overnight. The progress of the reaction was monitored by TLC and then silica was added to the reaction mixture and the solvent was removed by rotary evaporator. The pure product was isolated by

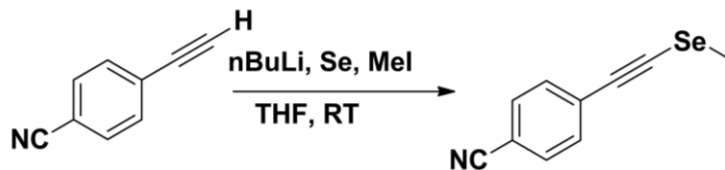
column chromatography. The product was a light yellow liquid. Yield 90%. ^1H NMR (400 MHz, chloroform-*d*) δ 7.41 (d, J = 3.8 Hz, 2H), 7.32 – 7.26 (m, 3H), 2.37 (s, 2H). ^{77}Se NMR (76 MHz, chloroform-*d*) δ 76.09 (q, J = 12.6 Hz). ^{13}C NMR (101 MHz, chloroform-*d*) δ 131.65, 128.38, 128.24, 123.62, 98.40, 71.38, 9.92.

2.2.3.3 Synthesis of ((4-fluorophenyl)ethynyl)(methyl)selane (4F)



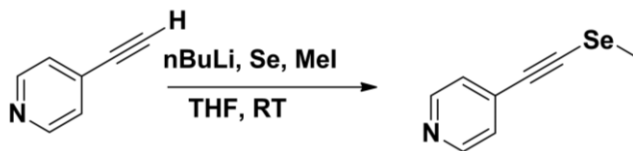
4-Bromoethynylbenzene (1 mmol) was placed in an oven dried 100 ml round bottom flask and sealed with a septum. This was evacuated and filled with dry N_2 three times and after the third cycle, anhydrous THF(10 ml) was added followed by refilling with dry N_2 gas. Then the mixture was cooled to -78°C using dry ice and acetone bath for 20 minutes after which $n\text{BuLi}$ (1.2 mmol) was added dropwise and stirred for 30 min then Se powder (1mmol) was added, and the dry ice bath was removed to allow the reaction mixture to reach room temperature. The mixture was stirred at room temperature for 4 hours and then MeI (1.2 mmol) was added and continued to stir overnight. The progress of the reaction was monitored by TLC and then silica was added to the reaction mixture and the solvent was removed by rotary evaporator. The pure product was isolated by column chromatography. The product was a brown liquid. Yield 88%. ^1H NMR (400 MHz, chloroform-*d*) δ 7.42-7.36 (m, J = 3.8 Hz, 2H), 7.02 – 6.95 (m, 2H), 2.41 (s, 3H). ^{77}Se NMR (76 MHz, chloroform-*d*) δ 76.45 (q, J = 12.6 Hz). ^{13}C NMR (101 MHz, chloroform-*d*) δ 162.3, 133.4, 119.8, 115.598.2, 70.2, 9.80.

2.2.3.4 Synthesis of 4-((methylselanyl)ethynyl)benzonitrile (4CN)



4-Cyanoethynylbenzene (1 mmol) was placed in an oven dried 100 ml round bottom flask and sealed with a septum. This was evacuated and filled with dry N_2 three times and after the third cycle, anhydrous THF(10 ml) was added followed by refilling with dry N_2 gas. Then the mixture was cooled to -78°C using dry ice and acetone bath for 20 minutes after which nBuLi (1.2 mmol) was added dropwise and stirred for 30 min then Se powder (1mmol) was added, and the dry ice bath was removed to allow the reaction mixture to reach room temperature. The mixture was stirred at room temperature for 4 hours and then MeI (1.2 mmol) was added and continued to stir overnight. The progress of the reaction was monitored by TLC and then silica was added to the reaction mixture and the solvent was removed by rotary evaporator. The pure product was isolated by column chromatography. Yield 72%. Yellow white solid. Mp $67\text{--}72^\circ\text{C}$. ^1H NMR (400 MHz, chloroform- d) δ 7.55 (d, $J = 7.6$ Hz, 2H), 7.43 (d, $J = 7.7$ Hz, 2H), 2.38 (s, 3H). ^{77}Se NMR (76 MHz, chloroform- d) 85.50 (q, $J = 16.4$ Hz). ^{13}C NMR (101 MHz, chloroform- d) δ 132.06, 131.61, 128.37, 118.60, 111.10, 97.27, 78.08, 10.03.

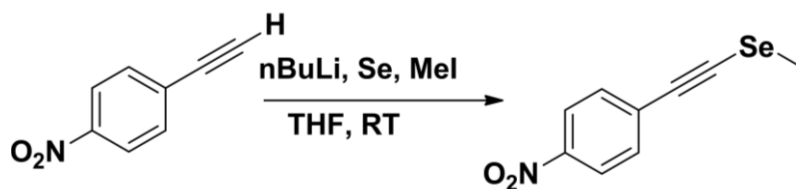
2.2.3.5 Synthesis of 4-((methylselanyl)ethynyl)pyridine (4Py)



4-Ethynylpyridine (1 mmol) was placed in an oven dried 100 ml round bottom flask and sealed with a septum. This was evacuated and filled with dry N_2 three times and after the third cycle, anhydrous THF(10 ml) was added followed by refilling with dry N_2 gas. Then the mixture

was cooled to -78 °C using dry ice and acetone bath for 20 minutes after which nBuLi (1.2 mmol) was added dropwise and stirred for 30 min then Se powder (1mmol) was added, and the dry ice bath was removed to allow the reaction mixture to reach room temperature. The mixture was stirred at room temperature for 4 hours and then MeI (1.2 mmol) was added and continued to stir overnight. The progress of the reaction was monitored by TLC and then silica was added to the reaction mixture and the solvent was removed by rotary evaporator. The pure product was isolated by column chromatography. The product was greenish black solid. Yield 79%. Mp 50-52 °C. ¹H NMR (400 MHz, chloroform-d) δ 8.51 (d, J = 5.5 Hz, 2H), 7.20 (d, J = 5.5 Hz, 2H), 2.39 (s, 3H). ⁷⁷Se NMR (76 MHz, chloroform-d) δ 85.40 (q, J = 12.7 Hz). ¹³C NMR (101 MHz, chloroform-d) δ 149.79, 131.58, 125.00, 96.43, 78.65, 10.02.

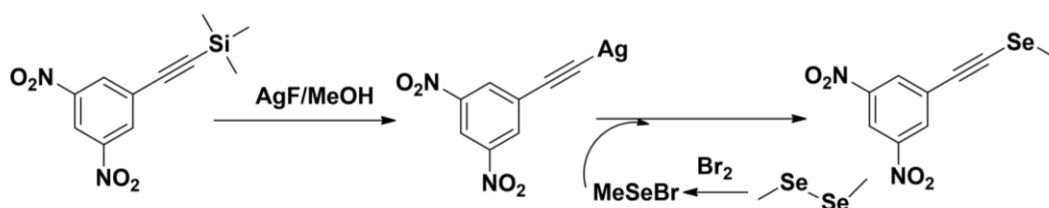
2.2.3.6 Synthesis of methyl((4-nitrophenyl)ethynyl)selane (4NO2)



4-Nitroethynylbenzene (1 mmol) was placed in an oven dried 100 ml round bottom flask and sealed with a septum. This was evacuated and filled with dry N₂ three times and after the third cycle anhydrous THF(10 ml) was added followed by refilling with dry N₂ gas. Then the mixture was cooled to -78 °C using dry ice and acetone bath for 20 minutes after which nBuLi (1.2 mmol) was added dropwise and stirred for 30 min then Se powder (1mmol) was added, and the dry ice bath was removed to allow the reaction mixture to reach room temperature. The mixture was stirred at room temperature for 4 hours and then MeI (1.2 mmol) was added and continued to stir overnight. The progress of the reaction was monitored by TLC and then silica was added to the

reaction mixture and the solvent was removed by rotary evaporator. The pure product was isolated by column chromatography. The product was a greenish white solid. Mp 90-94 °C. ^1H NMR (400 MHz, chloroform- d) δ 8.16 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 2.42 (s, 3H). ^{77}Se NMR (76 MHz, chloroform- d) δ 88.20 – 86.60 (m). ^{13}C NMR (101 MHz, chloroform- d) δ 146.63, 131.64, 130.32, 123.65, 97.23, 79.38, 10.01.

2.2.3.7 Synthesis of ((3,5-dinitrophenyl)ethynyl)(methyl)selane (35DN)



TMS compound (1 mmol) was dissolved in acetonitrile (25 ml) and a suspension of AgF (1.2 eq.) in methanol (15 ml) was added, giving an immediate precipitate of the silver acetylide. Reaction was continued for another 30 min and solvent was evaporated using rotary evaporator under reduced pressure. The obtained yellow solid was dried under vacuum and suspended in dry THF (20 ml).

In a separate beaker Me₂Se₂ (0.5 eq) was dissolved in dry THF (10 ml) and Br₂ (0.5 eq) in a syringe was added to it at 0 °C, resulting in the formation of MeSeBr (1 eq). This solution was brought to room temperature and added to the silver acetylide suspension. The reaction mixture was stirred for 2h. The reaction mixture was passed through a Celite plug and the filtrate was concentrated using the rotary evaporator. The crude product was purified by column chromatography and recrystallized to obtain the pure product. The product was yellowish orange. Yield 40%. Mp 122-127 °C. ^1H NMR (400 MHz, chloroform- d) δ 8.90 (s, 1H), 8.49 (s, 2H), 2.45

(s, 3H). ^{77}Se NMR (76 MHz, chloroform-d) δ 90.43 (q, $J = 12.5$ Hz). ^{13}C NMR (101 MHz, chloroform-d) δ 148.62, 132.05, 130.78, 127.30, 117.51, 94.85, 10.11.

2.2.4 Crystal growth

The synthesized targets were recrystallized from different solvents using slow evaporation to obtain single crystals suitable for single crystal X-ray diffraction (SC-XRD), Table 2.1.

Table 2.1 Solvents used for crystal growth and crystal descriptions

Compound	Code	Solvent	Color and Morphology	Melting point
methyl(phenylethynyl)silane	B1	N/A	Colorless liquid	N/A
((4-bromophenyl)ethynyl)(methyl)silane	4F	N/A	Brown liquid	N/A
4-((methylsilyl)ethynyl)benzonitrile	4CN	Hexane/Ethylacetate	Colorless, Needle	67-72 °C
4-((methylsilyl)ethynyl)pyridine	4Py	Hexane/Ethylacetate	Colorless, Irregular	50-52 °C
methyl((4-nitrophenyl)ethynyl)silane	4NO2	Methanol	Orange, Irregular	90-94 °C
((3,5-dinitrophenyl)ethynyl)(methyl)silane	35DN	Methanol	Orange, Plate	122-127

2.3 Results

2.3.1 Molecular electrostatic potential maps

The electrostatic potentials of the two σ -holes on the selenium atom were calculated at B3LYP/6-311**G++ level of theory at iso=0.002. The molecules explored in this study are summarized in Figure 2.5.

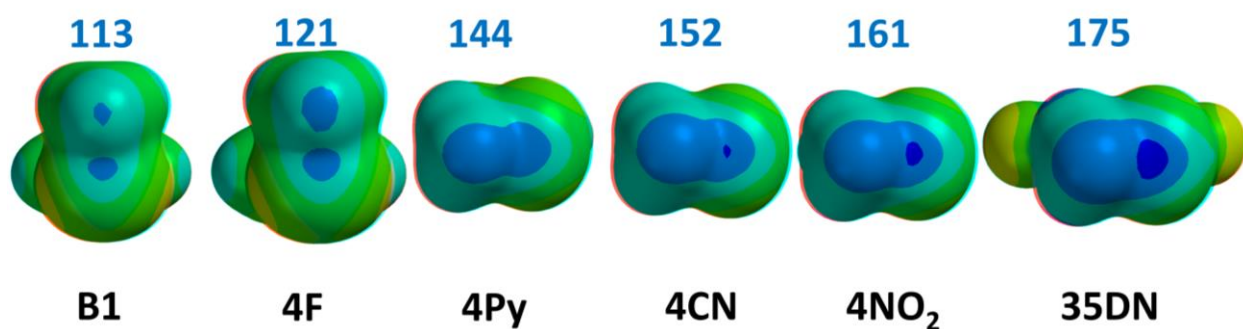


Figure 2.5 Calculated σ -hole potentials (kJ/mol) on the selenium atom for all the molecules in this study.

2.3.2 Interaction energies (IE)

The calculated interaction energies between the target molecules as the chalcogen-bond donor and the NH_3 as the acceptor at B3LYP/6-311**G++ level of theory with counterpoise correction is given in Table 2.2.

Table 2.2 The calculated interaction energies and the σ -hole potentials for ChB

Compound	σ_1 kJ/mol	IE ₁ kJ/mol	σ_2 kJ/mol	IE ₂ kJ/mol
B1	113	-9.49	40	-2.80
4F	121	-10.14	47	-2.78
4Py	144	-11.59	74	-3.38
4CN	152	-11.96	84	-3.91
4NO ₂	161	-12.49	90	-3.97
35DN	175	-14.08	105	-6.37

2.3.3 Single crystal structures

The crystal structure of **4Py** only showed a ChB between the $\text{Se}\cdots\text{N}$, 3.017 (8) Å and $\text{C}\cdots\text{N}$ of 179.0 (4)° angle. Instead of the pyridine ring, adding a benzene and using $\text{C}\equiv\text{N}$ EWG at para position in **4CN** target had led to the formation of ChB between $\text{Se}\cdots\text{N}$, 3.426(3) Å and $\text{Se}\cdots\text{N}-\text{C}$ of 163.27(9)° angle. However, the nitrogen of the **4CN** acts as a nonconventional hydrogen-bond acceptor for the hydrogens on the methyl group which has resulted in a bifurcated interaction (Figure 2.6). In both structures only the σ_1 on the chalcogen atom forms a $\text{Se}\cdots\text{N}$ ChB and no interaction was observed for the σ_2 .

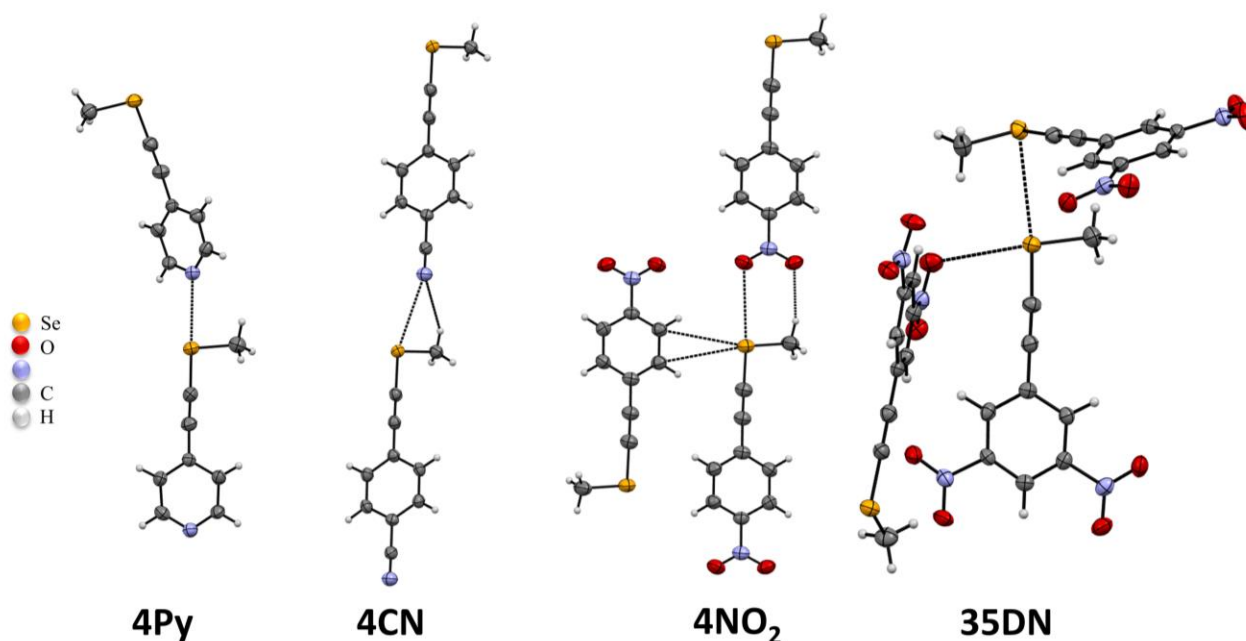


Figure 2.6 Crystal structures obtained, and the primary ChBs observed.

In the crystal structures of **4NO₂** the σ_1 formed a $\text{Se}\cdots\text{O}=\text{N}$ ChB, at 3.523(3) Å and 174.62(10)° $\text{C}-\text{Se}\cdots\text{N}$ bond angle. The σ_2 formed a $\text{Se}\cdots\pi$ ChB with the electron cloud on $\text{C}\equiv\text{C}$ with bond distance and an angle of 4.246(3) Å and 95.41(19)° respectively. Similar to **4CN**, **4NO₂**

had an O $\cdots$ H-C nonconventional hydrogen bond. Though both **4Py** and **4CN** lacked any ChBs with respect to σ_2 , **4NO₂** showed a ChB with π -electron cloud and the benzene ring, Se $\cdots$ C=C at 4.246(3) Å and 95.41(19)°. Contrast to the previous 3 structures, the fourth crystal structure of **35DN** displayed a Type II ChB between the σ_1 on the selenium atom and the lone pair on a second selenium atom leading to Se $\cdots$ Se with a bond distance of 3.357(6) Å and a bond angle of 173.49(15)°. The σ_2 however, formed a Se $\cdots$ O=N ChB at 3.310(4) Å and 176.9(2)°. All the relevant bond distances and angles are given in Table 2.3.

Table 2.3 Bond parameters of all four crystal structures

Target	R-D $\cdots$ A	D $\cdots$ A (Å)	R-D $\cdots$ A (deg)
4Py	C-Se $\cdots$ N	3.017(8)	179.0(4)
	C-H $\cdots$ N	3.394(13)	117.3(13)
4CN	C-Se $\cdots$ N	3.426(3)	163.27(9)
	C-H $\cdots$ N	3.387(4)	141.0(4)
4NO₂	C-Se $\cdots$ O	3.523(3)	174.62(10)
	C-H $\cdots$ O	3.398(4)	162.3(2)
	C-Se $\cdots$ C	4.246(3)	95.41(19)
35DN	C-Se $\cdots$ Se	3.357(6)	173.49(15)
	C-Se $\cdots$ O	3.310(4)	176.9(2)

2.4 Discussion

2.4.1 Theoretical calculations

2.4.1.1 Molecular electrostatic potentials

The molecular electrostatic potentials calculated for both σ_1 and σ_2 showed that the σ -hole, σ_1 , directly opposite to the C $\equiv$ C bond showed a much larger σ -hole potential compared to the σ -hole directly opposite to the methyl group, σ_2 . This was due to inductive and conjugation effects

by the substituent leading to electron withdrawal from the polarizable selenium atom (Figure 2.7).²⁴ The results showed that the lowest σ -hole potential for σ_1 was observed for the unsubstituted **B1** at 113 kJ/mol and the largest σ -hole for **35DN** at 175 kJ/mol. The σ_1 potential increased from **B1** < **4F** < **4Py** < **4CN** < **4NO2** < **35DN** while a similar effect was observed for σ_2 as well even though not as significant as it was with σ_1 . For σ_2 , similar to σ_1 the lowest σ -hole potential was observed for **B1** at 40 kJ/mol and the highest for **35DN** at 105.3 kJ/mol which is almost comparable to σ_1 of the **B1**. Furthermore, a good correlation was established with the $\sigma_{\text{para/meta}}$ Hammet parameters in the synthesized compounds which provide more evidence towards the para and meta substituent effect and the σ -hole (Figure 2.8). The use of stronger electron withdrawing groups²⁵ and the sp-hybridization^{5,26} has succeeded in activating both σ -holes on the chalcogen atom Table 2.2.

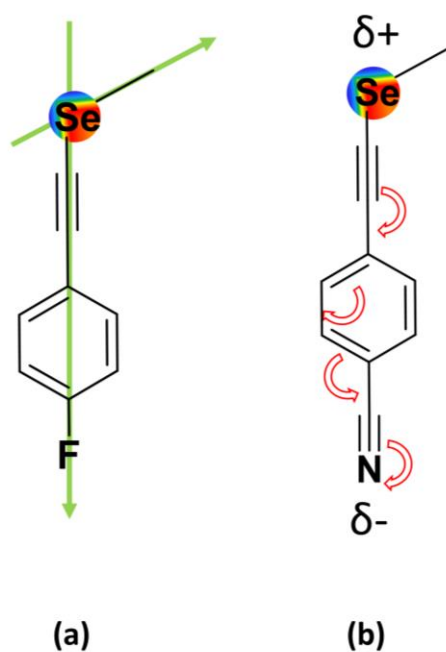


Figure 2.7 Influence of **(a)** inductive effects and **(b)** resonance effects.

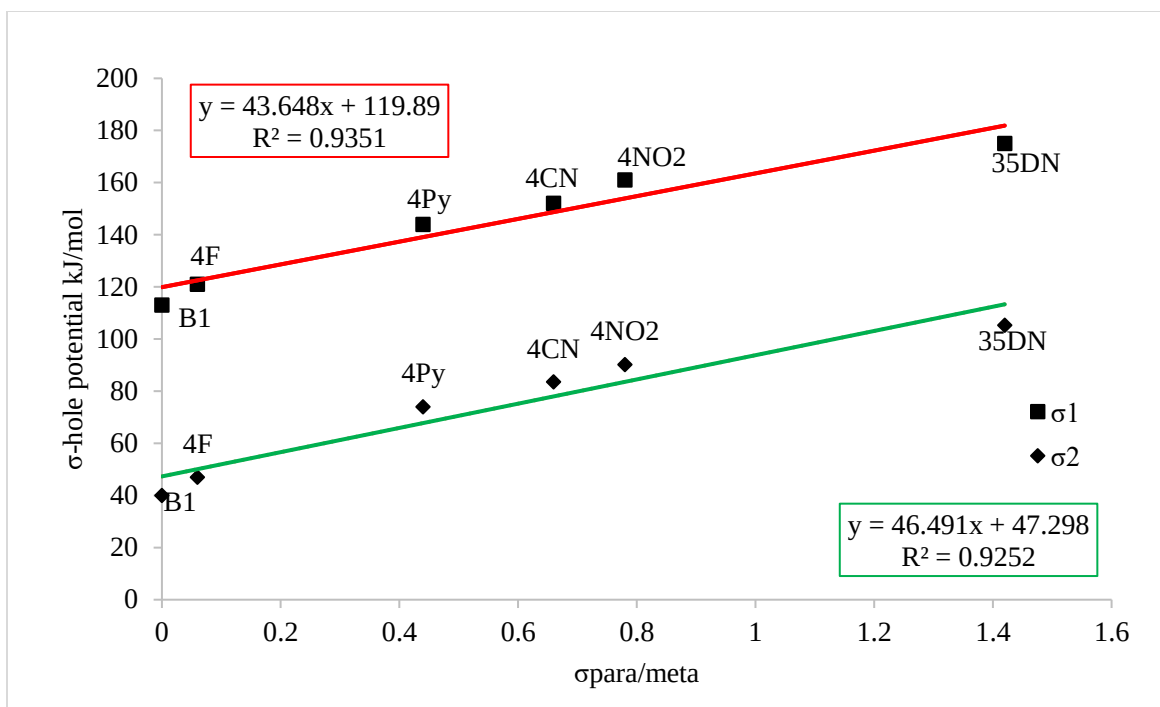


Figure 2.8 Correlation between the σ -hole potential and the $\sigma_{\text{para/meta}}$.

2.4.1.2 Interaction energies

In our attempt to establish a possible correlation between the interaction energies and the σ -hole potentials on the directionality of the ChB interactions a plot of interaction energies between the chalcogen bond donor targets and the ammonia as the acceptor was plotted for both the σ_1 and σ_2 (Figure 2.9).

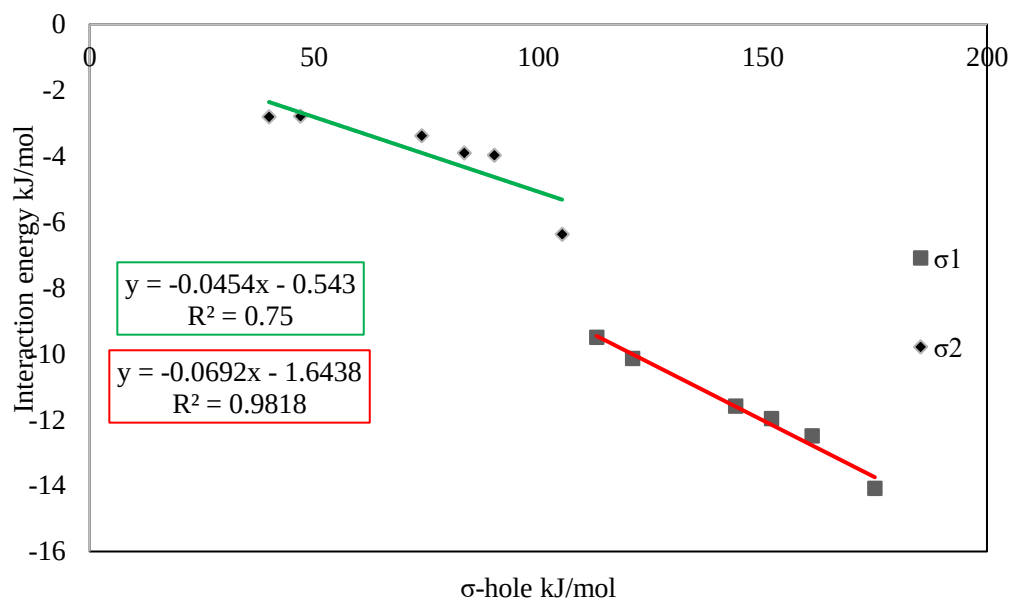


Figure 2.9 Correlation between the interaction energies and σ -hole potentials.

For σ_1 , there was an excellent correlation ($R^2 = 0.98$) between the σ -hole and the interaction energies which shows that when the magnitude of the σ -hole is bigger it will in general lead to higher interaction energies. In this interaction, due to the presence of the methyl group when the ammonia molecules get closer to the chalcogen atom there is a certain degree of overlap of the σ -hole with the hydrogen atoms on the methyl group which would contribute to the interaction energy. A similar overlap was observed in the crystal structure of the **4CN**, and this overlap can be observed for all the optimized geometries. Correlation between the σ_2 , σ -hole size and the interaction energies were modest ($R^2 = 0.75$), and this could be attributed the rotational flexibility of the methyl group as well as the rotation of the phenyl ring which was noted when analyzing the changes in the optimized dihedral angles between the benzene ring and the methyl group.

2.4.2 Predicting directionality of σ -hole interactions and the acceptor preference

The contributing factors of σ -hole interactions can be attributed to electrostatic (Coulombic), charge transfer and dispersion forces. Among these contributors the Coulombic forces are a major force^{6,11}, hence, ChB can be defined as a coulombic interaction between a positive electrostatic potential of the σ -hole on the chalcogen atom and the negative electrostatic potential on the donor. Based on this definition we can surmise that the largest positive electrostatic potential on the target should preferentially interact with the largest negative electrostatic potential on the target to form a ChB interaction. Out of the two σ -holes the σ_1 displayed the largest positive potential. The primary sites of negative potentials were generally observed for the substitute groups added onto the benzene ring and in addition to that there were other regions of negative potentials, which were the π electron cloud on arene and the $C\equiv C$ bond as well as the lone pairs on the chalcogen atom which can act as a chalcogen bond acceptor (Figure 2.10).

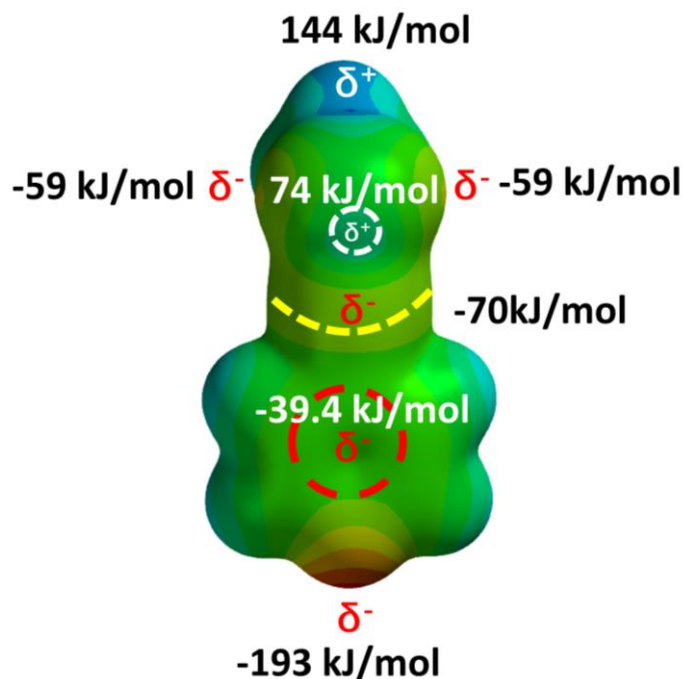


Figure 2.10 DFT predicted regions of positive and negative potentials.

Based on the electrostatic potentials it was possible to postulate the potential outcomes for ChB preference, which was shown to be correct in all cases, Fig. 2.11.

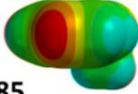
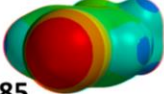
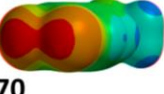
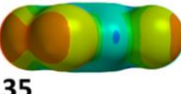
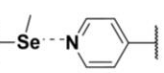
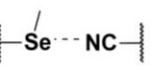
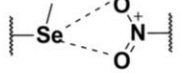
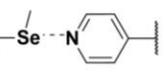
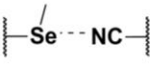
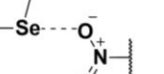
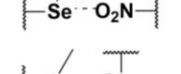
Compound	4Py	4CN	4NO2	35DN
$V_{s, \min}$ kJ/mol	 -185	 -185	 -170	 -135
Postulated				
Experimental				

Figure 2.11 Postulated structural outcomes based on the MEPs and the experimental outcomes.

2.5 Conclusions

This study has shown that the use of electron-withdrawing groups in conjunction with sp-hybridized C≡C can be used to improve and fine-tune the σ -hole potentials on the chalcogen atoms. In the library of molecules studied, the highest σ -hole potential was for a selenium atom on **35DN** (175 kJ/mol), which is comparable to current literature reported highest value of 186.6 kJ/mol of the tellurium atom in 1,4-bis(methyltelluroethynyl)tetrafluorobenzene⁷.

Unlike halogen atoms where there is only one σ -hole, due to presence of two σ -holes, the use of EWGs have affected both while the σ_1 was affected much more significantly than the σ_2 due to conjugation. Adding electron withdrawing substituents such as a CN group instead of the methyl group would result in the increase of the σ_2 but it will inevitably increase the σ_1 as well.

The σ -hole potential of the σ_1 and the interaction energies had a strong correlation which shows that larger σ -hole potential would lead to stronger ChB interactions. Though the correlation for σ_2 was low, a general trend similar to σ_1 can be observed.

Molecular electrostatic potential maps showed that the predictability of ChB based on coulombic attraction can be a very useful tool for crystal engineering: The larger positive potential is likely to interact with the larger negative electrostatic potential during the self-assembly, both in solution and during the subsequent nucleation and crystallization.

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Chapter 3 – Activation of two σ -holes in chalcogens for designing strong chemotherapeutic agents

3.1 Introduction

In Chapter 2, we successfully identified a method for “activating” molecules containing chalcogen atoms to drive the chalcogen bonding (ChB) through exceptional σ -hole potentials. The significant improvement to the magnitude of the σ -hole potential was achieved through the use of electron withdrawing groups and sp-hybridization that results in combined, inductive and resonance effects. This reduces the electron density on the polarizable chalcogen atom along a C-Ch axis and increases the positive potential thereby activating the σ -hole.^{1,2} In this study we wanted to explore a new class of small molecular chalcogen species using a “triple” activation³ strategy (Figure 3.1) that was previous employed for halogen species and atom-to-atom substitution, to further improve the chalcogen-bond donor ability of the species.

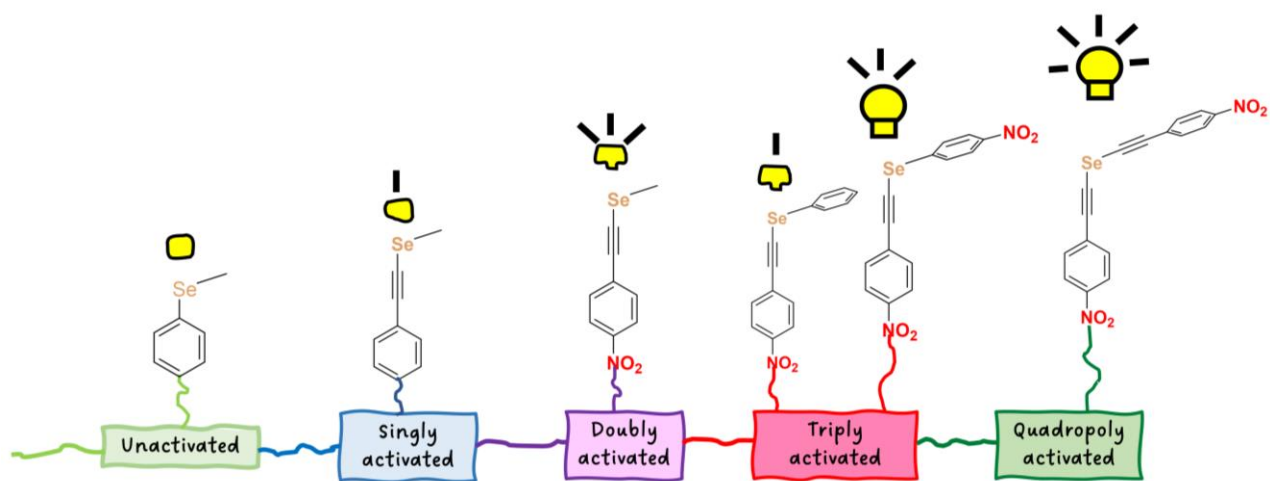


Figure 3.1 Strategy for "activating" chalcogen-bond donor ability.

Selenium is an essential nutrient required by the body for synthesis of various enzymes and proteins in trace amounts whereas higher amounts can be toxic. Recently, small molecule

organoselenium compounds have emerged as potential chemotherapeutic agents owing to lower toxicity levels in comparison to traditional anticancer agents such as cisplatin.⁴⁻⁷ One of the most important clinically used organoselenium compound during last three decades is Ebselen⁸ which has shown strong antioxidant properties. However, species such as bis(3,5-bis(trifluoromethyl)phenyl)selane, which can penetrate cancer cells and cleave CT-DNA, are providing important design strategies towards creating novel chemotherapeutic species.⁵ Compared to selenium, organotellurium compounds are scarcely studied in the context of both chemical and biological properties. Although tellurium is generally considered to be more toxic than its selenium metal counterpart and is more prone to undergoing oxidation towards higher valency numbers, its chemical and biological properties are of considerable significance leading to even more avenues in discovering novel compounds for the treatment of diseases such as cancer.

In our attempt to design and control the σ -hole potential through triple activation and to assess whether these small molecular organochalcogen species are biologically active, we developed our target library consisting of five selenium targets and six tellurium targets, Fig. 3.2.

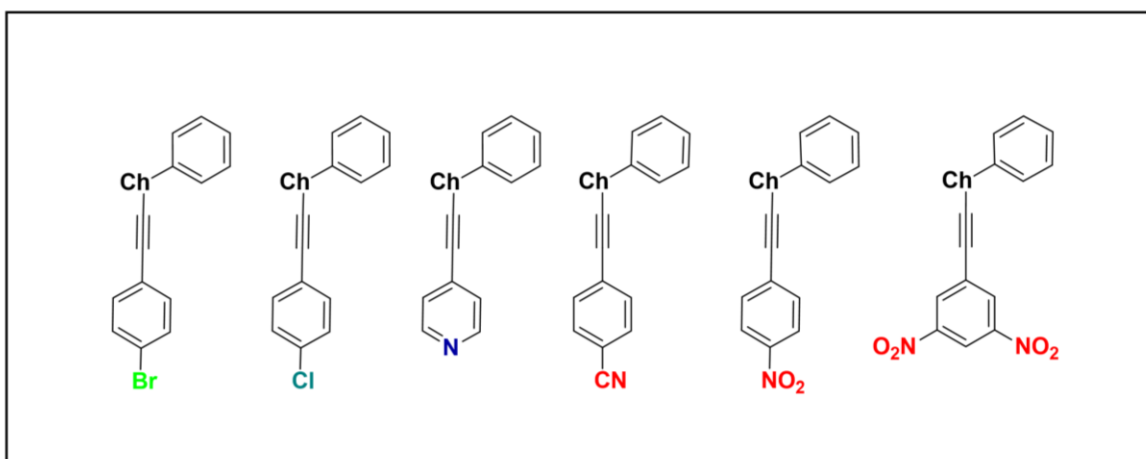


Figure 3.2 Library of target molecules synthesized and explored in this study (Ch – Se/Te).

By synthesizing these compounds, we wanted to answer the following questions,

Question 1. How does the σ -hole potential in these compounds compare to the previous series obtained in chapter 2?

Question 2. What are the structural outcomes based on the σ -hole ?

Question 3. How can we assess possible and plausible intermolecular interactions based on structure and potential?

Question 4. How does the atom-to-atom substitution and σ -hole potential translate into enhanced chemotherapeutic properties?

3.2 Experimental

3.2.1 General

Reagents and solvents were purchased from commercially available sources and used without further purification. Melting points were measured using a TA instruments DSC Q20 differential scanning calorimeter. Nuclear magnetic resonance (NMR) data were measured on a Bruker Ascend 400 MHz spectrometer. The residual solvent peak was used as the internal reference for ^1H and ^{13}C NMR. For ^{77}Se and ^{125}Te NMR the selenium and tellurium peaks were referenced against the residual solvent peak in its corresponding ^1H NMR spectrum. Single crystal X-ray diffraction data were collected using a Rigaku XtaLAB Synergy-S diffractometer and the structures were solved using Olex2⁹ with SHELXT¹⁰. All computational calculations were performed using Spartan14¹¹ software package.

3.2.2 Molecular electrostatic potential maps

Molecular electrostatic potentials were calculated using Spartan14¹¹ Wavefunction. The compounds were sketched and saved using ChemDraw 12 and loaded into Spartan14 software followed by geometry optimization for the most stable conformation using density functional theory B3LYP hybrid functional and 6-311++G** basis set for all the reported selenium targets and 6-31G* basis set for all the tellurium targets. A positive point charge in the vacuum was used as a probe against the surface to determine the positive and negative regions on the molecular surface. The electrostatic potentials presented herein are given in kJ/mol and a negative number is representative of an electron rich acceptor and a positive number of an electron poor donor.

3.2.3 Cell viability test

All cell viability tests were performed by Wei Wu and Dr. Ping Li at Kansas State University as a collaborative project in the Department of Chemistry. Test compounds were dissolved in DMSO at 25mM concentration. HeLa cells were maintained in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% FBS (Fetal Bovine Serum, FB-02, Omega Scientific), and 1% antimycotic (Corning). Cells were incubated in CO₂ incubator at 5% CO₂ and 37 °C.

The procedure follows a previous report in which a total of 5,000 HeLa cells were seeded per well in 96-well plates and cultured for 24 h. The medium was then removed and replaced with fresh medium containing DMSO (as a control) or testing compounds at various concentrations. Wells containing the same contents but without cells were used as blank. After the plates were incubated for another 24 h, 10 μ L solution consisting of 5 mM WST-8 and 0.2 mM 1-methoxyphenazinium salt in 150 mM NaCl was added to each well and incubated for 2 h in the

CO₂ incubator. Absorbance at 460 nm was determined using a SpectraMaxR Plus 384 microplate reader (Molecular Devices). Experiments were done in triplicate. Prism 9 (GraphPad) was used to determine IC₅₀.¹²

3.2.4 Synthesis

All intermediates and the final targets were synthesized using modified conditions of previously reported procedures (Figure 3.3).^{13,14}

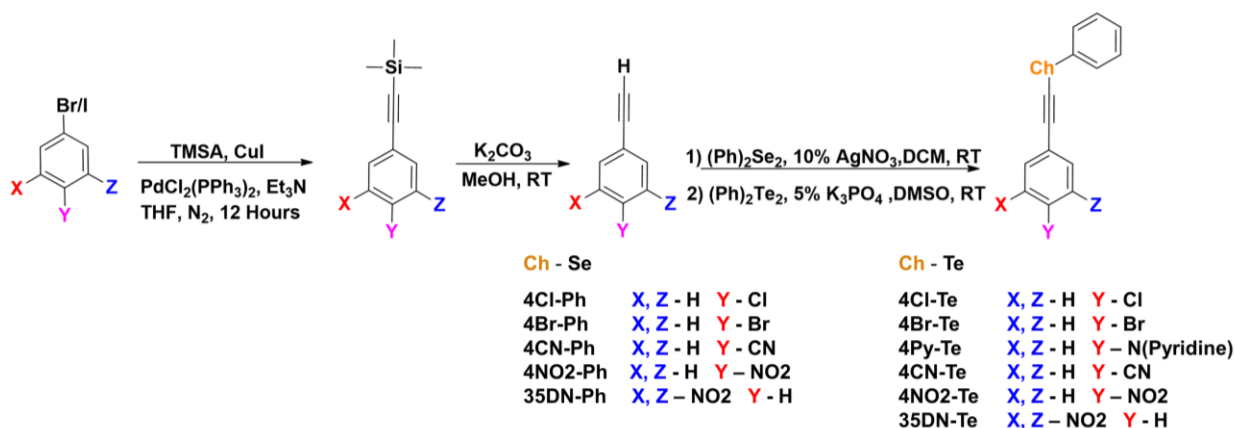


Figure 3.3 Summary of the three-step synthetic procedure used to synthesize the target compounds.

3.2.4.1 General synthesis of ethynyl intermediates

Appropriately substituted haloaromatic species were dissolved in a triethylamine and THF 1:1 mixture and degassed with dry dinitrogen for 10-20 min. To this mixture, CuI (5% mol), bis(triphenylphosphine)palladium(II) dichloride (10%mol) and trimethylsilyl acetylene (2 eq) were added and stirred overnight at room temperature. Completion was confirmed by TLC. After completion the mixture was rotary evaporated, and the crude was purified by column chromatography.

The resulting TMS compound was dissolved in a dichloromethane (DCM) and methanol 1:1 mixture and K₂CO₃ (2eq) was added and stirred at room temperature under air for 6 hours.

Upon completion the solvent was evaporated, and the product was purified by a flash column.¹⁵⁻

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3.2.4.2 Synthesis of ((4-bromophenyl)ethynyl)(phenyl)selane (4Br-Ph)

1-Bromo-4-ethynylbenzene (1 mmol) was dissolved in dichloromethane (5 ml) in a 100 ml round bottom flask. This was stirred and AgNO₃ (10% mol/mol, 0.1 mmol) was added followed by the addition of diphenyl diselenides (0.5 mmol). A septum was placed on the round bottom and the mixture was stirred at room temperature under air overnight. The solvent was evaporated, and the crude was purified by column chromatography. Yield 93%. Mp : 82-86 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 7.66 (s, 2H), 7.61 (s, 2H), 7.49 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.33 (t, J = 7.1 Hz, 1H). ⁷⁷Se NMR (76 MHz, DMSO-d₆) δ 272.35. ¹³C NMR (101 MHz, DMSO-d₆) δ 133.28, 131.80, 129.89, 128.86, 128.04, 127.39, 122.39, 121.42, 101.62, 71.68.

3.2.4.3 Synthesis of ((4-chlorophenyl)ethynyl)(phenyl)selane (4Cl-Ph)

1-Chloro-4-ethynylbenzene (1 mmol) was dissolved in dichloromethane (5 ml) in a 100 ml round bottom flask. This was stirred and AgNO₃ (10% mol/mol, 0.1 mmol) was added followed by the addition of diphenyl diselenides (0.5 mmol). A septum was placed on the round bottom and the mixture was stirred at room temperature under air overnight. The solvent was evaporated, and the crude was purified by column chromatography. Yield 85%. Mp: 75-80 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 7.68 – 7.62 (m, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.37 (dt, J = 32.0, 7.3 Hz, 3H). ⁷⁷Se NMR (76 MHz, DMSO-d₆) δ 272.11. ¹³C NMR (101 MHz, DMSO-d₆) δ 133.71, 133.14, 129.89, 128.91, 128.85, 128.07, 127.38, 121.08, 101.53, 71.50.

3.2.4.4 Synthesis of 4-((phenylselanyl)ethynyl)benzonitrile (4CN-Ph)

4-ethynylbenzonitrile (1 mmol) was dissolved in dichloromethane (5 ml) in a 100 ml round bottom flask. This was stirred and AgNO₃ (10% mol/mol, 0.1 mmol) was added followed by the addition of diphenyl diselenides (0.5 mmol). A septum was placed on the round bottom and the mixture was stirred at room temperature under air overnight. The solvent was evaporated, and the crude was purified by column chromatography. Yield 70%. Mp : 73-78 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 7.91 – 7.85 (m, 2H), 7.74 – 7.64 (m, 4H), 7.47 – 7.39 (m, 2H), 7.39 – 7.31 (m, 1H). ⁷⁷Se NMR (76 MHz, DMSO-d₆) δ 276.58. ¹³C NMR (101 MHz, DMSO-d₆) δ 132.60, 131.80, 129.96, 129.09, 127.77, 127.57, 126.96, 118.41, 110.89, 101.50, 76.05.

3.2.4.5 Synthesis of ((4-nitrophenyl)ethynyl)(phenyl)selane (4NO₂-Ph)

1-Ethynyl-4-nitrobenzene (1 mmol) was dissolved in dichloromethane (5 ml) in a 100 ml round bottom flask. This was stirred and AgNO₃ (10% mol/mol, 0.1 mmol) was added followed by the addition of diphenyl diselenides (0.5 mmol). A septum was placed on the round bottom and the mixture was stirred at room temperature under air overnight. The solvent was evaporated, and the crude was purified by column chromatography. This was further recrystallized to obtain the pure product. Yield 57%. Mp : 68-81 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 8.24 (d, J = 8.9 Hz, 2H), 7.78 (d, J = 8.9 Hz, 2H), 7.69 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.4 Hz, 2H), 7.36 (t, J = 7.3 Hz, 1H). ⁷⁷Se NMR (76 MHz, DMSO-d₆) δ 278.64. ¹³C NMR (101 MHz, DMSO-d₆) δ 146.70, 132.12, 129.98, 129.19, 128.89, 127.71, 127.64, 123.92, 101.34, 77.54.

3.2.4.6 Synthesis of ((3,5-dinitrophenyl)ethynyl)(phenyl)selane (35DN-Ph)

1-Ethynyl-3,5-dinitrobenzene (1 mmol) was dissolved in dichloromethane (5 ml) in a 100 ml round bottom flask. This was stirred and AgNO₃ (10% mol/mol, 0.1 mmol) was added followed by the addition of diphenyl diselenides (0.5 mmol). A septum was placed on the round bottom and the mixture was stirred at room temperature under air overnight. The solvent was evaporated, and the crude was purified by column chromatography. This was further recrystallized to obtain the pure product. Yield 41%. Mp : 127-132 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 8.77 (t, J = 2.1 Hz, 1H), 8.72 (d, J = 2.1 Hz, 2H), 7.73 (dd, J = 8.3, 1.1 Hz, 2H), 7.48 – 7.41 (m, 2H), 7.40 – 7.34 (m, 1H). ⁷⁷Se NMR (76 MHz, DMSO-d₆) δ 279.15. ¹³C NMR (101 MHz, DMSO-d₆) δ 148.27, 131.08, 129.97, 129.43, 127.71, 127.39, 125.09, 118.19, 98.91, 77.53.

3.2.4.7 Synthesis of ((4-chlorophenyl)ethynyl)(phenyl)tellane (4Cl-Te)

1-Chloro-4-ethynylbenzene (1 mmol), diphenyl ditelluride (0.5 eq) and K₃PO₄ (5% mol) was dissolved in DMSO (3 ml) in a 100 ml round bottom flask. The mixture was stirred at room temperature in an open container under air overnight. The reaction mixture was diluted with ethyl acetate (50-100 ml) and the organic layer was washed with water 3-4 times. The organic layer was dried over anhydrous MgSO₄, filtered and rotary evaporated to obtain the crude product. The crude was purified by column chromatography to obtain the pure product. Yield 94%. Mp : 100-104 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 7.81 (dd, J = 6.5, 3.0 Hz, 2H), 7.46 (s, 4H), 7.33 – 7.27 (m, 3H). ¹²⁵Te NMR (126 MHz, DMSO-d₆) δ 497.89. ¹³C NMR (101 MHz, DMSO-d₆) δ 135.27, 133.29, 133.11, 129.59, 128.79, 121.90, 110.63, 56.83, 38.90.

3.2.4.8 Synthesis of ((4-bromophenyl)ethynyl)(phenyl)tellane (4Br-Te)

1-Bromo-4-ethynylbenzene (1 mmol), diphenyl ditelluride (0.5 eq) and K_3PO_4 (5% mol) was dissolved in DMSO (3 ml) in a 100 ml round bottom flask. The mixture was stirred at room temperature in a open container under air overnight. The reaction mixture was diluted with ethyl acetate (50-100 ml) and the organic layer was washed with water 3-4 times. The organic layer was dried over anhydrous $MgSO_4$, filtered and rotary evaporated to obtain the crude product. The crude was purified by column chromatography to obtain the pure product. Yield 79%. Mp : 108-111 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 7.81 (dd, J = 6.9, 2.6 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.33 – 7.27 (m, 3H). ^{125}Te NMR (126 MHz, DMSO- d_6) δ 498.46. ^{13}C NMR (101 MHz, DMSO- d_6) δ 135.28, 133.27, 131.68, 129.59, 127.57, 122.24, 121.96, 115.07, 110.70, 57.08.

3.2.4.9 Synthesis of 4-((phenyltellanyl)ethynyl)pyridine (4Py-Te)

4-Ethynylpyridine (1 mmol), diphenyl ditelluride (0.5 eq) and K_3PO_4 (5% mol) were dissolved in DMSO (3 ml) in a 100 ml round bottom flask. The mixture was stirred at room temperature in an open container under air overnight. The reaction mixture was diluted with ethyl acetate (50-100 ml) and the organic layer was washed with water 3-4 times. The organic layer was dried over anhydrous $MgSO_4$, filtered and rotary evaporated to obtain the crude product. The crude was purified by column chromatography to obtain the pure product. Yield 79%. Mp : 128-133 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 8.57 (d, J = 5.9 Hz, 2H), 7.84 (dd, J = 6.2, 3.2 Hz, 2H), 7.40 – 7.29 (m, 5H). ^{125}Te NMR (126 MHz, DMSO- d_6) δ 507.24. ^{13}C NMR (101 MHz, DMSO- d_6) δ 150.34, 136.13, 131.07, 130.12, 128.22, 125.44, 115.53, 109.83, 63.94.

3.2.4.10 Synthesis of 4-((phenyltellanyl)ethynyl)benzonitrile (4CN-Te)

4-Ethynylbenzonitrile (1 mmol), diphenyl ditelluride (0.5 eq) and K_3PO_4 (5% mol) was dissolved in DMSO (3 ml) in a 100 ml round bottom flask. The mixture was stirred at room temperature in an open container under air overnight. The reaction mixture was diluted with ethyl acetate (50-100 ml) and the organic layer was washed with water 3-4 times. The organic layer was dried over anhydrous $MgSO_4$, filtered and rotary evaporated to obtain the crude product. The crude was purified by column chromatography to obtain the pure product. Yield 87%. Mp : 111-115 °C. ^1H NMR (400 MHz, $DMSO-d_6$) δ 7.87 – 7.81 (m, 4H), 7.59 (d, J = 8.5 Hz, 2H), 7.33 – 7.29 (m, 3H). ^{125}Te NMR (126 MHz, $DMSO-d_6$) δ 506.15. ^{13}C NMR (101 MHz, $DMSO-d_6$) δ 135.53, 132.52, 131.85, 129.63, 127.69, 118.43, 115.14, 110.51, 62.57.

3.2.4.11 Synthesis of ((4-nitrophenyl)ethynyl)(phenyl)tellane (4NO₂-Te)

4-Nitroethynylbenzene (1 mmol), diphenyl ditelluride (0.5 eq) and K_3PO_4 (5% mol) was dissolved in DMSO (3 ml) in a 100 ml round bottom flask. The mixture was stirred at room temperature in a open container under air overnight. The reaction mixture was diluted with ethyl acetate (50-100 ml) and the organic layer was washed with water 3-4 times. The organic layer was dried over anhydrous $MgSO_4$, filtered and rotary evaporated to obtain the crude product. The crude was purified by column chromatography to obtain the pure product. Yield 75%. Mp : 119-123 °C. ^1H NMR (400 MHz, $DMSO-d_6$) δ 8.22 (d, J = 8.9 Hz, 2H), 7.88 – 7.82 (m, 2H), 7.66 (d, J = 8.9 Hz, 2H), 7.35 – 7.29 (m, 3H). ^{125}Te NMR (126 MHz, $DMSO-d_6$) δ 509.69. ^{13}C NMR (101 MHz, $DMSO-d_6$) δ 146.45, 135.65, 132.14, 129.64, 129.61, 127.75, 123.86, 115.21, 110.42, 64.51.

3.2.4.12 Synthesis of ((3,5-dinitrophenyl)ethynyl)(phenyl)tellane (35DN-Te)

1-Ethynyl-3,5-dinitrobenzene (1 mmol), diphenyl ditelluride (0.5 eq) and K₃PO₄ (5% mol) was dissolved in DMSO (3 ml) in a 100 ml round bottom flask. The mixture was stirred at room temperature in an open container under air overnight. The reaction mixture was diluted with ethyl acetate (50-100 ml) and the organic layer was washed with water 3-4 times. The organic layer was dried over anhydrous MgSO₄, filtered and rotary evaporated to obtain the crude product. The crude was purified by column chromatography to obtain the pure product. Yield 58%. 113-117 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 8.73 (t, J = 2.1 Hz, 1H), 8.55 (d, J = 2.1 Hz, 2H), 7.88 (dd, J = 6.4, 3.1 Hz, 2H), 7.36 – 7.30 (m, 3H). ¹²⁵Te NMR (126 MHz, DMSO-d₆) δ 515.05. ¹³C NMR (101 MHz, DMSO-d₆) δ 148.21, 135.97, 131.01, 129.66, 127.84, 125.70, 117.83, 114.97, 107.67, 64.77.

3.2.5 Crystal Growth

Synthesized targets were crystallized from different solvents using slow evaporation to obtain single crystals suitable for single crystal X-Ray diffraction (SC-XRD), Table 3.1.

Table 3.1 Crystal growth conditions and crystal descriptions

Compound	Code	Solvent	Color and morphology	Melting point °C
((4-chlorophenyl)ethynyl)(phenyl)selane	4Cl-Ph	Acetonitrile	Light yellow, prism	75-80
((4-bromophenyl)ethynyl)(phenyl)selane	4Br-Ph	Hexane	Colorless, irregular	82-86
4-((phenylselanyl)ethynyl)benzonitrile	4CN-Ph	Hexane/ethyl acetate	Colorless, plate	73-78
((4-nitrophenyl)ethynyl)(phenyl)selane	4NO ₂ -Ph	Acetonitrile	Yellow, plate	68-81
((3,5-dinitrophenyl)ethynyl)(phenyl)selane	35DN-Ph	Acetonitrile	Colorless, irregular	127-132
((4-chlorophenyl)ethynyl)(phenyl)tellane	4Cl-Te	Hexane	Colorless, block	100-104
((4-bromophenyl)ethynyl)(phenyl)tellane	4Br-Te	Hexane	Colorless, needle	108-111
4-((phenyltellanyl)ethynyl)pyridine	4Py-Te	Hexane/ethyl acetate	Colorless, plate	128-133
4-((phenyltellanyl)ethynyl)benzonitrile	4CN-Te	Hexane/ethyl acetate	Light yellow, needle	111-115
((4-nitrophenyl)ethynyl)(phenyl)tellane	4NO ₂ -Te	Hexane/ethyl acetate	Yellow, plate	119-123
((3,5-dinitrophenyl)ethynyl)(phenyl)tellane	35DN-Te	Methanol/dichloromethane	Orange, irregular	113-117

3.3 Results

3.3.1 Molecular electrostatic potential maps

The electrostatic potentials of the two σ -holes on the selenium atoms were calculated at B3LYP/6-311**G++ and for tellurium at B3LYP/6-31G* at iso=0.002. The results are summarized in Figure 3.4.

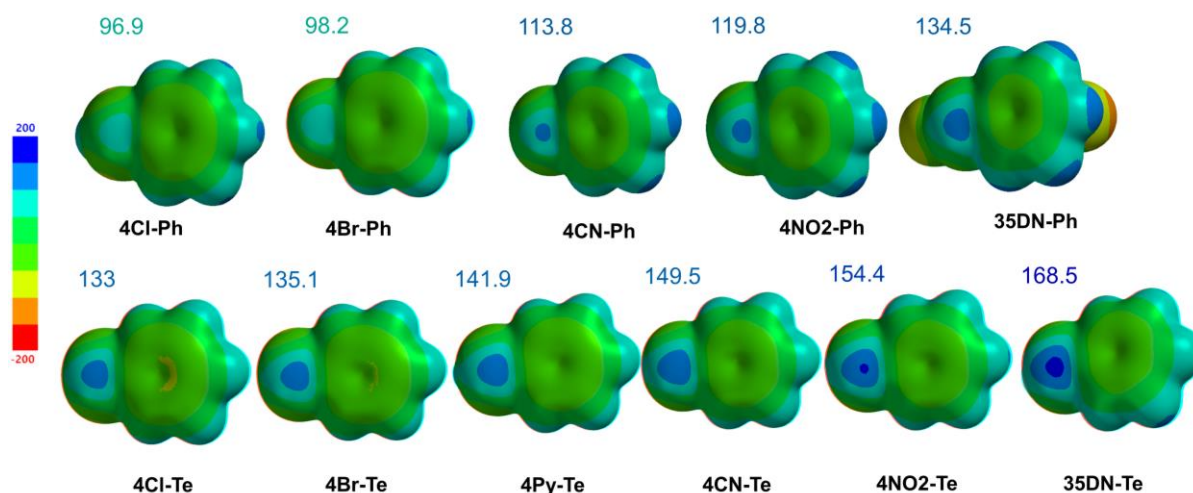


Figure 3.4 Calculated σ -hole potentials (kJ/mol) on the selenium and tellurium atoms of the two series studied.

3.3.2 Cell viability test

In-vitro analysis of the activity of the select compounds against HeLa cancer cell lines were tested by Wei Wu and Dr. Ping Li at Kansas State University to determine the potency of the synthesized materials. A summary of the assays performed with relevance to the target compounds is given in the Table 3.2 and Figure 3.5.

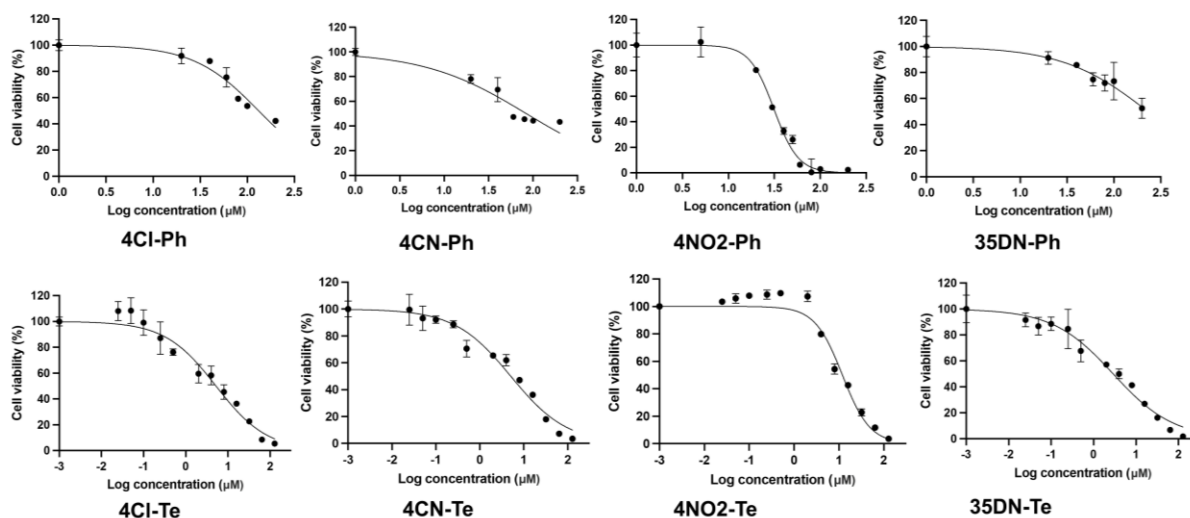


Figure 3.5 Cell viability of the tested compounds against the concentration (Wu and Li).

Table 3.2 Observed IC₅₀ values of the synthesized ligands against HeLa cell lines (Wu and Li)

Electron Withdrawing Group	IC ₅₀ (μM)	
	Selenium	Tellurium
4Cl	132	5.21
4CN	84.1	5.08
4NO ₂	31.3	12
35DN	231	2.9

3.3.3 Crystal structures

The crystal structures of **4Cl-Ph**¹⁸, **4Cl-Te** and **4Br-Te** were all isostructural and crystallized in the same non-centrosymmetric P2₁ space group. Though **4Br-Ph** had a similar interaction map to the previous three compounds, it crystallized in a centrosymmetric P2_{1/n} space group. All four structures showed ChB between Ch···π and Ch···X, through both σ₁ and σ₂ respectively. In addition to this primary ChB, hydrogen bonding was observed between C-H···π in all four structures. The **4CN-Ph** only showed ChB between Se···π for both σ-holes. The nitro

substituted species had vastly different crystal packing. The **4NO₂-Ph** showed a ChB dimer between $\text{Se}\cdots\pi$ while **35DN-Ph** had three symmetrically independent molecules in the asymmetric unit ($Z'=3$). Two of these independent molecules had $\text{Se}\cdots\text{N}$ and $\text{Se}\cdots\pi$ ChBs while the other only showed $\text{Se}\cdots\text{O}$ ChB. All relevant bond distances and angles are given in the Figure 3.6 and Table 3.3.

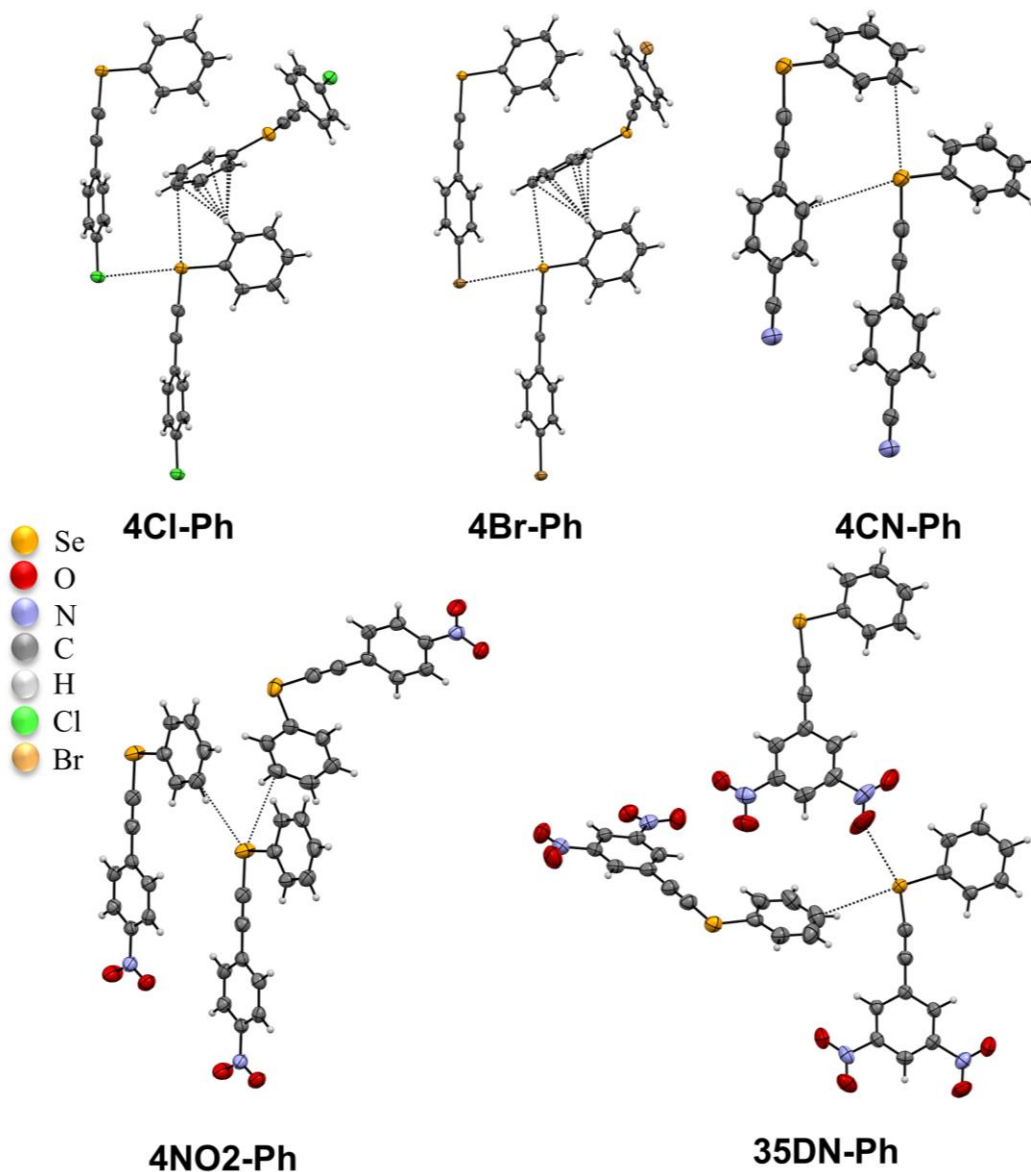


Figure 3.6 Primary interactions observed for the single crystal structures of selenophenyl compounds.

Table 3.3 Bond parameters of the crystal structures of selenophenyl compounds

Target	R-DH/X/Ch...A	D/X/Ch...A (Å)	R-DH/X/Ch...A (deg)
4Cl-Ph	Se9...Cl16	3.650(9)	169.96(10)
	Se9...C13	3.837(4)	164.59(13)
	C15-H15...C14	3.771(5)	154.10(10)
4Br-Ph	Se9...Br16	3.796(8)	168.80(4)
	Se9...C13	3.821(15)	164.59(6)
	C11-H11...C12	3.755(2)	153.83(9)
4CN-Ph	Se1...C11	3.800(6)	158.52(19)
	Se1...C3	3.705(6)	175.10(19)
4NO2-Ph	Se12...C2	3.908(4)	161.70(15)
	Se12...C15	3.695(5)	144.03(16)
	Se12...C17	3.810(5)	142.02(16)
35DN-Ph	Se9...C34	3.681(5)	173.66(12)
	Se9...O62	3.129(4)	156.73(14)
	Se30...C17	3.060(3)	154.65(12)
	Se30...O59	3.187(3)	169.98(12)
	Se51...C55	3.850(4)	150.46(11)
	Se30...O59	3.544(3)	167.08(11)

The remaining tellurium species crystallized in different space groups and showed unique ChB features through both σ -holes. The **4Py-Te** crystallized in $P_{\bar{1}}$ space group and formed a unique Type I ChB along $\text{Te}\cdots\text{Te}$ with σ_2 and a $\text{Te}\cdots\text{N}$ ChB with σ_1 . Though **4CN-Te** and **4NO2-Te** crystallized in a centrosymmetric $P2_1/n$ and non-centrosymmetric $P2_1$ space group respectively, they both had similar intermolecular interactions with a ferrocene type ChB between $\text{Te}\cdots\pi$ with σ_1 and $\text{Te}\cdots\text{C}\equiv\text{C}(\pi)$ with σ_2 . Similar to **4Py-Te**, **35DN-Te** also crystallized in the same space group and form ChBs along $\text{Te}\cdots\text{O}$ for both σ -holes. All relevant bond distances and angles are given in the Figure 3.7 and Table 3.4.

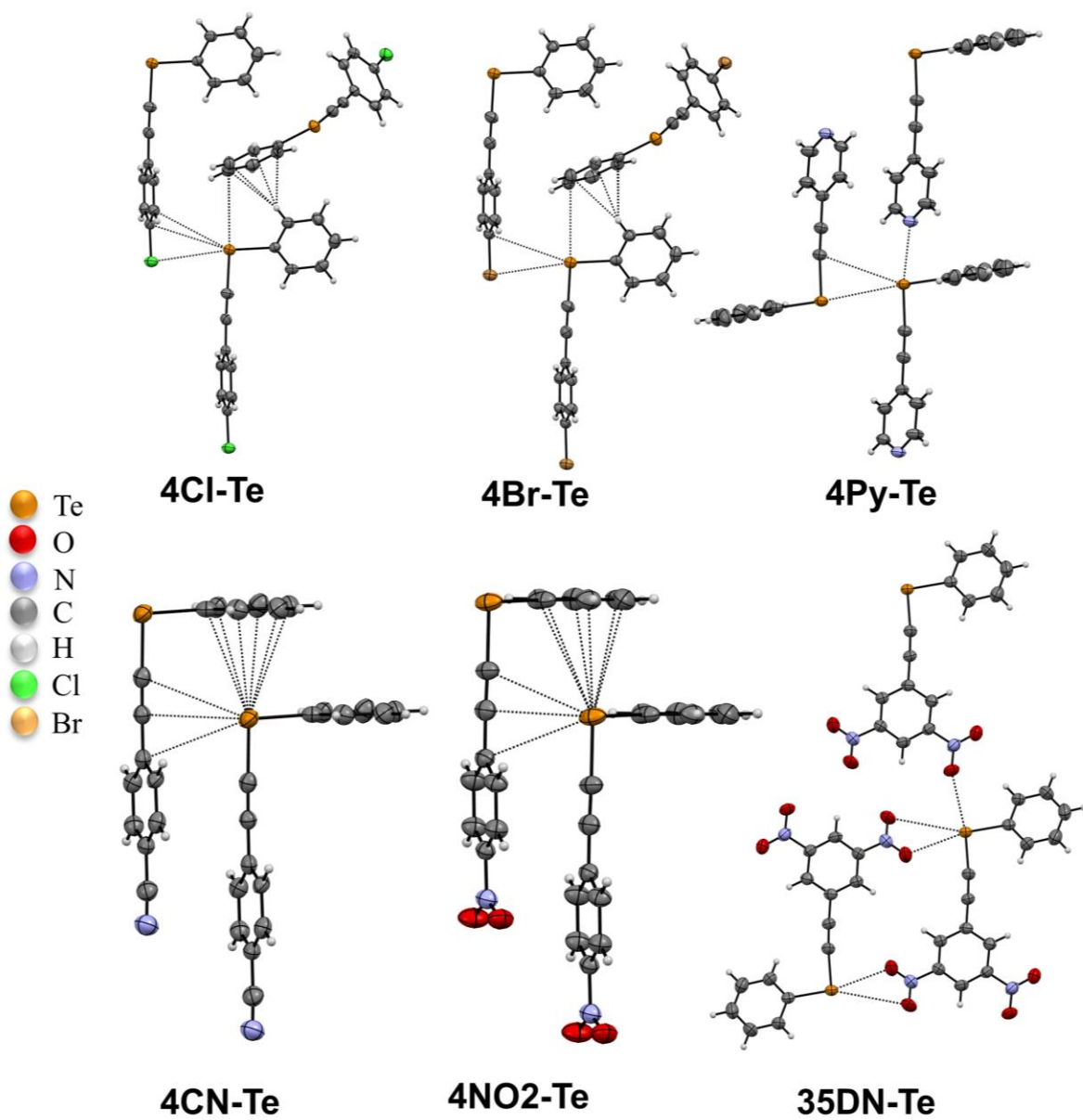


Figure 3.7 Primary interactions observed for the single crystal structures of tellurophenyl compounds.

Table 3.4 Bond parameters of the crystal structures of tellurophenyl compounds

Target	R-DH/X/Ch...A	D/X/Ch...A (Å)	R-DH/X/Ch...A (deg)
4Cl-Te	Te9...Cl16	3.681(14)	167.69(14)
	Te9...C13	3.756(7)	162.8(2)
	C11-H11...C11	3.773(7)	156.9(3)
4Br-Te	Te9...Br16	3.763(5)	167.48(12)
	Te9...C13	3.791(6)	162.72(16)
	C11-H11...C12	3.774(5)	158.9(2)
4Py-Te	Te1...N7	2.808(3)	170.99(12)
	Te1...Te1	3.761(5)	150.55(11)
4CN-Te	Te1...C3	3.539(6)	173.8(2)
	Te1...C14	3.802(8)	160.0(2)
4NO₂-Te	Te9...C7	3.740(5)	171.86(14)
	Te9...C14	3.641(8)	165.44(18)
35DN-Te	Te1...O21	3.065(4)	171.33(17)
	Te1...O17	3.114(5)	165.57(17)

3.4 Discussion

3.4.1 Molecular electrostatic potential maps

In comparison to the “doubly” activated chalcogenamethyl species discussed in Chapter 2, these two series of compounds employed a chalcogenaphenyl functionality in which the phenyl ring can be considered more electron withdrawing in comparison to the methyl group to achieve a “triple” activation. This electron withdrawing nature should ideally result in an increase of positive σ -hole potential however, analysis of the MEPs showed less positive potential on the phenyl substituted σ -hole compared to the methyl substituted species. This behavior can be attributed to the overlapping of the negative π -electron cloud of the phenyl ring along with the σ_1 leading to an overall reduction of positive potential (Figure 3.8).

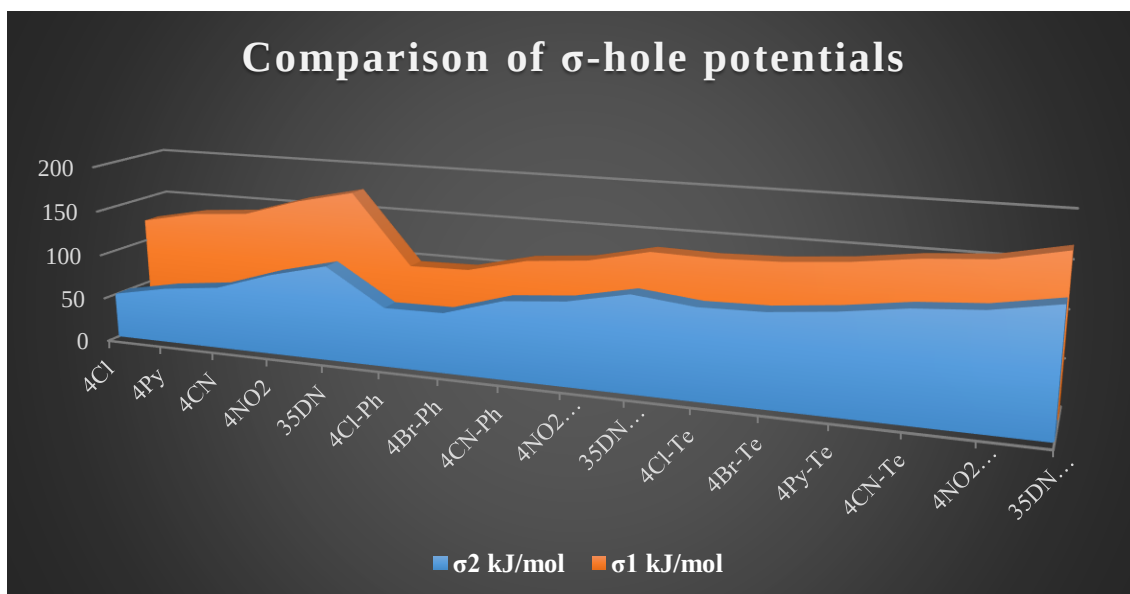


Figure 3.8 Summarized comparison of the σ -hole potentials of selenamethyl, selenophenyl (abbreviation - Ph) and tellurophenyl (abbreviation - Te) species.

MEPs calculations revealed that though the σ -hole potentials were lower than anticipated, triple activation nevertheless enhances the σ -hole potentials similarly to what was noted in Chapter 2. The lowest σ -hole potential was observed for chloro species while the highest was for the nitro substituted compounds. The σ_1 potential of the compounds increased from **4Cl-Ph** < **4Br-Ph** < **4CN-Ph** < **4NO2-Ph** < **35DN-Ph** and **4Cl-Te** < **4Br-Te** < **4Py-Te** < **4CN-Te** < **4NO2-Te** < **35DN-Te** for selenium and tellurium compounds respectively. A similar effect was observed for the σ_2 and a comparison of the σ_1 and σ_2 is shown in Figure 3.9. The strong correlation between the σ -hole potentials of both σ_1 and σ_2 further consolidates the fact that when using double or triple activation, both σ -holes are being affected by inductive and resonance effects leading to enhancements on both. The use of atom-to-atom substitution in which selenium atom is being replaced by tellurium significantly improves the σ -hole potential of these tellurium derivatives in which the highest positive potential of σ_1 , 168.5 kJ/mol, of **35DN-Te** is comparable to the highest

potential 175 kJ/mol of **35DN**, Chapter 2. The σ_2 value of **35DN-Te**, 132.7 kJ/mol is close to that of the **35DN-Ph** σ_1 , 134.5 kJ/mol .

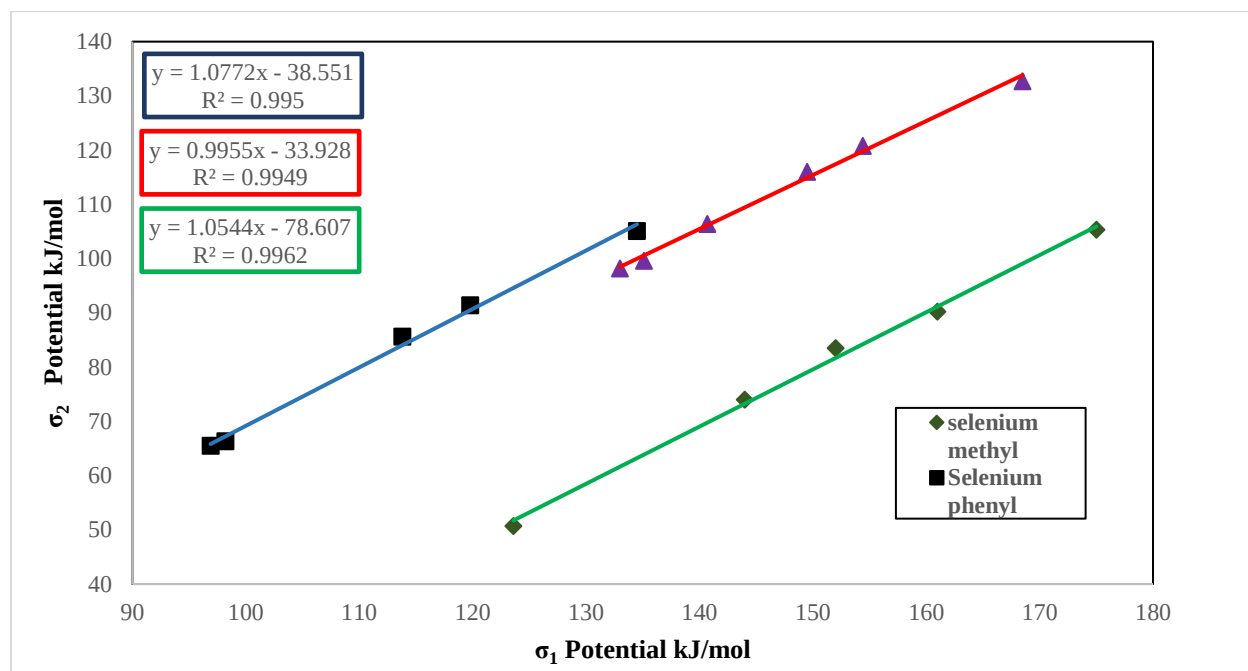


Figure 3.9 Correlation between the σ_1 and σ_2 electrostatic potentials.

3.4.2 What is the preference of ChB synthon?

In Chapter 2 we established the predictability of the ChB interactions based on the electrostatic attractions between the most positive potential (σ -hole) and the most negative potentials on the molecule. A similar predictability can be achieved with these selenophenyl and tellurophenyl analogues as they consist of the same electron withdrawing functional groups. To extend our understanding of the structural preference of the ChB beyond the context of electrostatic potentials towards a more structural analysis, we benchmarked the ChB geometrical features of selenophenyl and tellurophenyl compounds against similar interactions mined from the Cambridge Structural Database (CSD) using ConQuest 2022.3.0. Only crystal structures with $R < 0.1$, non-disordered, nonionic, organic and single crystal structures were considered.

One of the two main ChB interaction observed with the halogen substituted target compounds for both selenium and tellurium compounds were between the chalcogen-bond donor and the halogen acceptor site. The CSD search resulted in 113 crystal structures having 132 instances of C-Ch $\cdots$ X synthons. In comparison to the reported synthon features the “triple activated” species consist of more linear ChBs with moderate bond distances. A summary of these synthons is shown in Figure 3.10.

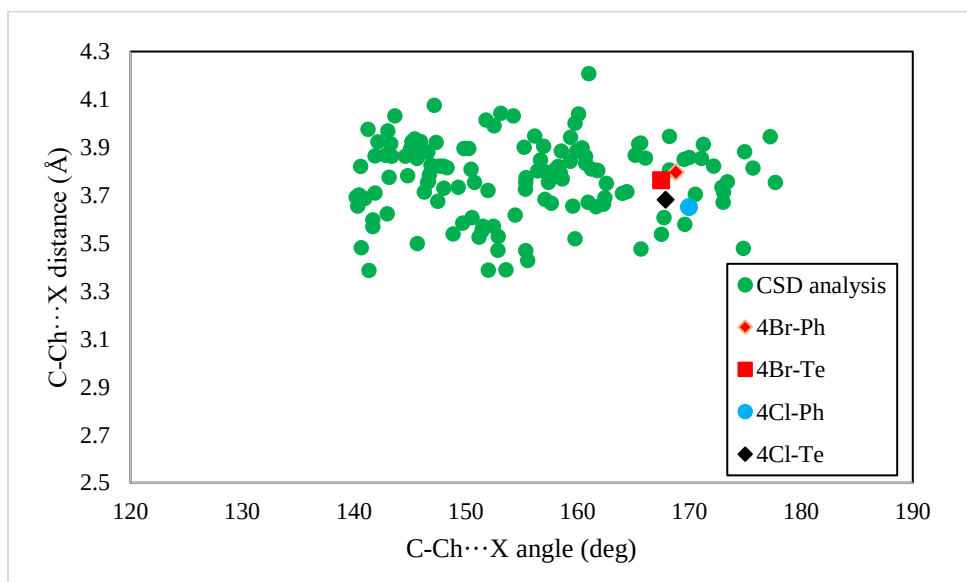


Figure 3.10 Distribution of C-Ch $\cdots$ X bond distances and angles for crystal structures in the CSD database and all obtained selenium and tellurium phenyl compounds.

The majority of the crystal structures obtained in this study contained C-Ch $\cdots$ C=C/C $\equiv$ C ChB interaction which suggests that the π -electron cloud acts as a more reliable ChB acceptor compared to methyl group in selenomethyl analogues in chapter 2. This feature not only showed the dominance of ChB as a structure directing interactions but also shows the structural influence of π - π stacking towards better packing features, due to the presence two arene rings in these compounds with respect to selenomethyl species which lacked the second arene ring. There were 1582 crystal structures in the CSD database with 3817 similar synthons. In this large pool of

interactions “triply activated” tellurium species showed ChB angles closer to 180° and shorter bond distances compared to its selenium counterparts that translates to stronger interactions Figure 3.11.

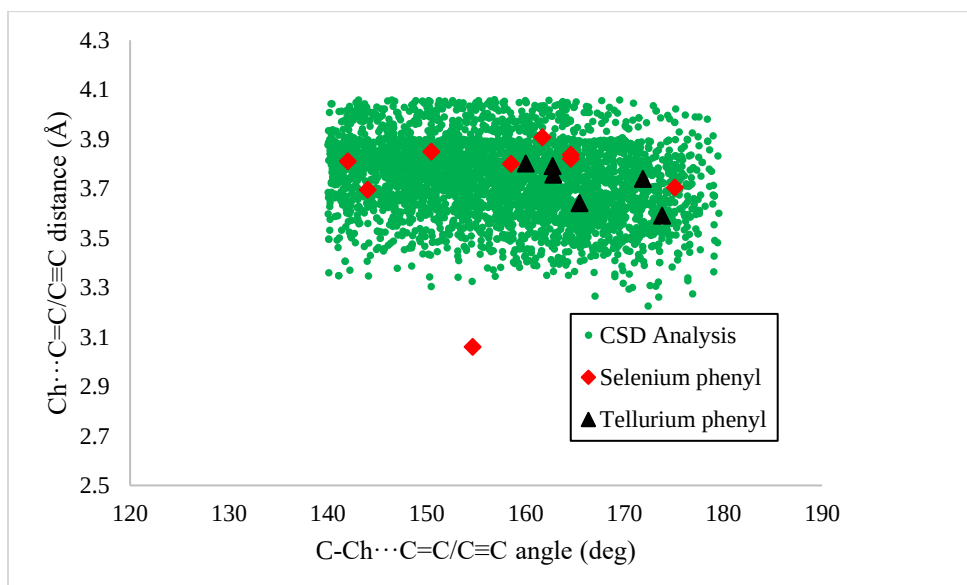


Figure 3.11 Distribution of C-Ch...C=C/C≡C bond distances and angles for crystal structures in the CSD and all obtained selenium and tellurium phenyl compounds.

The only compounds containing oxygen as a chalcogen-bond acceptor were the nitro substituted species. However, in this study only the **35DN-Ph** and **35DN-Te** showed Ch...O ChBs and the CSD analysis returned 164 crystal structures with 213 instances of this ChB synthon. The lack of Ch...O interaction in para-nitro substituted species shows the competing nature of the acceptor sites present in these compounds (Figure 3.12).

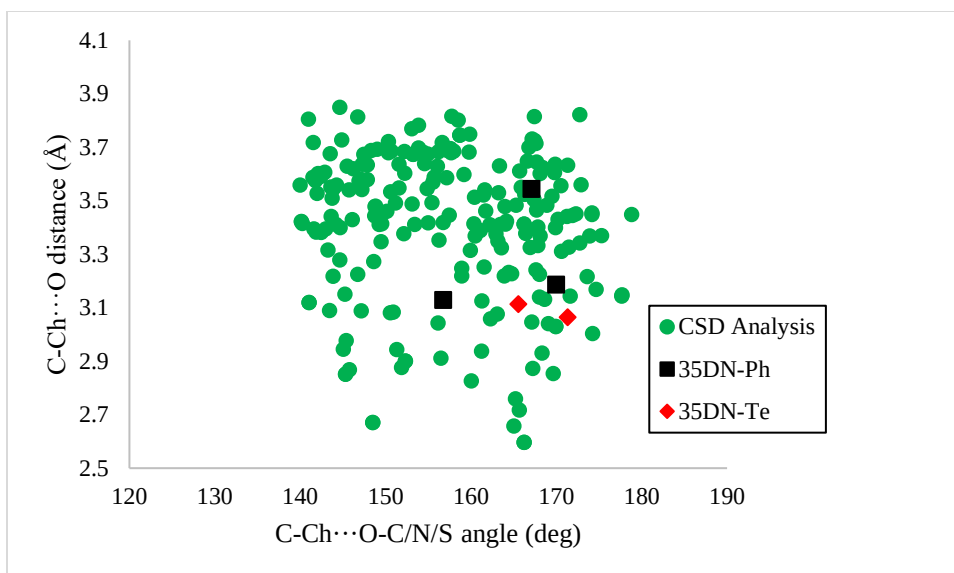


Figure 3.12 Distribution of C-Ch $\cdots$ O-C bond distances and angles for crystal structures in the CSD database and all obtained selenium and tellurium phenyl compounds.

The only compound that showed Type I Ch $\cdots$ Ch interactions was **4Py-Te**. The CSD analysis showed a pool of 754 (233 with just Te) crystal structures with 1451 moieties having a similar ChB synthon. Given the fact that the primary σ_1 is already occupied with Ch $\cdots$ N ChB, the less negatively charged lone pairs on chalcogens act as a chalcogen-bond acceptors for the secondary σ_2 to form a relatively rare Type I ChB (Figure 3.13).

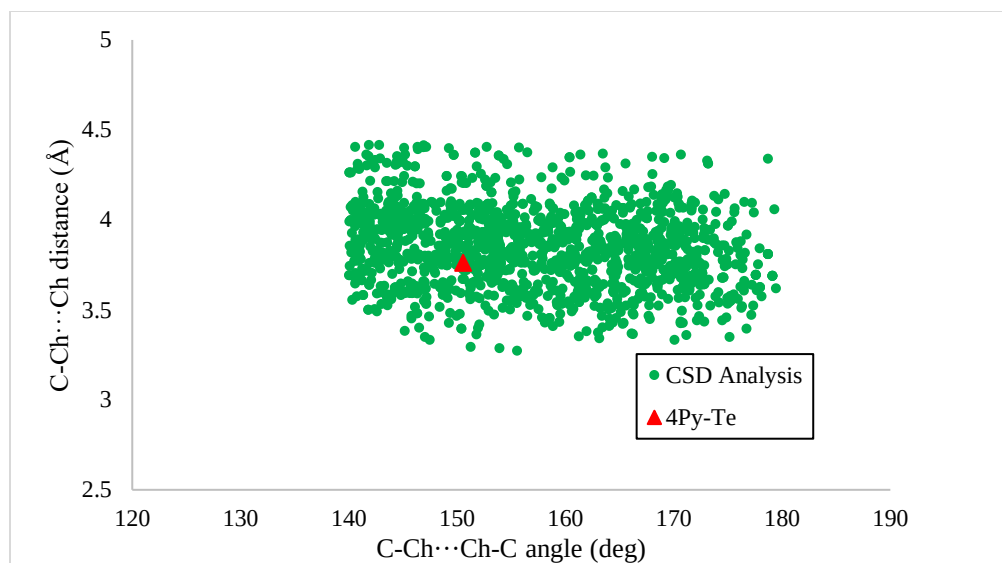


Figure 3.13 Distribution of C-Ch...Ch-C bond distances and angles for crystal structures in the CSD database and all obtained selenium and tellurium phenyl compounds.

3.4.3 Chemotherapeutic properties

Assessment of the biological activity of these developed libraries of compounds were conducted with the cell viability assays against HeLa cell lines. The select selenium species used in the study showed much higher IC_{50} values ranging from highest 231 μM for **35DN-Ph** to lowest 31.3 μM for **4NO2-Ph** with no clear structure property correlation with respect to the ChB donor ability. Overall, for the selenium species the IC_{50} decreased in the order of **35DN-Ph** > **4Cl-Ph** > **4CN-Ph** > **4NO2-Ph**.

It has previously been shown that for diarylchalcogenides the substitution of selenium with tellurium can result in an increase of its antioxidant activity⁴ however, such increment was not previously observed with respect to chemotherapeutic properties of organochalcogen derivatives. In this study, the tellurium derivatives showed a pronounced increase of the anticancer properties against HeLa cell lines compared to selenium derivatives. For these tellurium derivatives the IC_{50} values decreased in the order of **4NO2-Te** > **4Cl-Te** > **4CN-Te** > **35DN-Te**. Although all four Te

compounds showed improvements, the **35DN-Te** showed the highest improvement in IC_{50} , which dropped from 231 to 2.9 μM . Compared to the existing studies of organoselenium chemotherapeutic compounds^{5,19} Figure 3.14, selenium compounds in the current study showed comparable if not better activities while tellurium derivatives improved those properties furthermore.

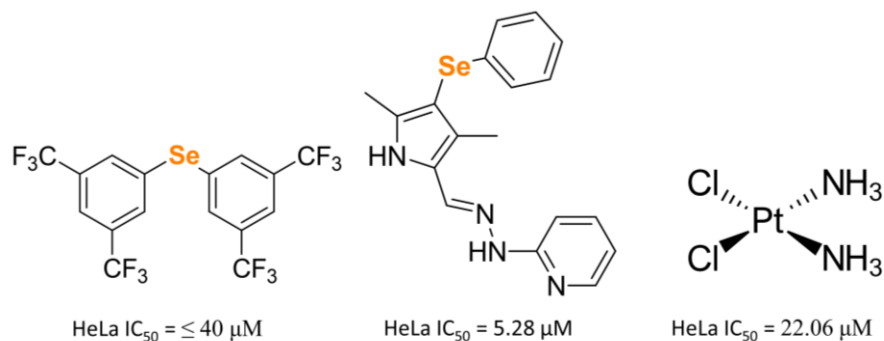


Figure 3.14 Cytotoxicity of bis(3,5-bis(trifluoromethyl)phenyl)selenane (left), 2-(2-((3,5-Dimethyl-4-(phenylselanyl)-1H-pyrrol-2-yl)methylene)hydrazineyl)pyridine (middle) and cisplatin (right).

3.5 Conclusions

In summary, this study has shown that in addition to the electron withdrawing groups and sp-hybridization, atom-to-atom substitution of selenium with tellurium significantly improves the polarizability which in turn increases the σ -hole potentials. Unlike the methyl substituted compounds in chapter 2, phenyl substituted selenium and tellurium derivatives had a lower σ_1 potential than anticipated. In return, adding the phenyl ring in place of methyl provides control over the σ_2 along with σ_1 resulting in a ‘triple activation’ showing the expected incremental improvement of the σ -hole potential with **35DN-Te** having the largest σ -hole potential.

The preference of competing acceptor site for the formation of ChB in the crystal structures showed a preference towards the π -electron clouds in most cases along with several unique structural features like Type I and ferrocene type ChBs. Comparison of these synthon preferences

with similar literature reported geometrical features showed that stronger chalcogen-bond donors such as tellurium led to more directional ChBs over selenium derivatives.

An investigation into the effects of atom-to-atom substitution in a biological context showed that these compounds are active against HeLa cancer cell lines. Among the two series tellurium compounds showed the highest activity with **35DN-Te** showing the smallest the IC_{50} of 2.9 μM compared to its selenium counterpart **35DN-Ph** with the highest IC_{50} of 231 μM .

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Chapter 4 – The balance between hydrogen, halogen, and chalcogen bonds in the crystal structures of a series of 1,3,4-chalcogenadiazoles

4.1 Introduction

One of the main goals of crystal engineering is to employ intermolecular interactions in the assembly of crystalline materials with desired physiochemical properties.^{1,2} To realize this objective, and to effectively manipulate these synthetic vectors, we need to further improve our understanding of the nature of these interactions.

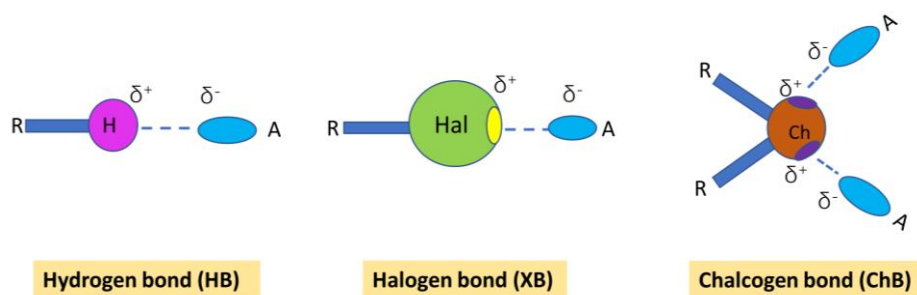


Figure 4.1 A simple view of the electrostatic component of hydrogen, halogen, and chalcogen bonds.

The most influential and well understood intermolecular force is, undoubtedly, the hydrogen bond^{3,4} (Figure 4.1), and, consequently, the active use of this supramolecular tool has been extensively mapped out.⁵⁻⁷ Hydrogen bonding as a structure directing force has found many practical applications in pharmaceutical co-crystallizations^{8,9}, new agricultural formulations¹⁰, as well as in the design of new energetic materials¹¹. However, over the past few decades, the recognition and understanding of potentially competing intermolecular interactions, such as

halogen and chalcogen bonding, have opened alternative ways for bottom-up design of new crystalline materials.^{12,13}

Chapters 2 and 3 successfully finetuned the σ -hole potentials and controlled the directionality through activation of the ChB using both electrons withdrawing groups and sp-hybridization. The designed molecules in chapter 3 showed the influence of substitution of Se with Te in which the chemotherapeutic properties improved significantly. However, active pharmaceutical ingredients are not limited to a single functional group and generally contain multiple functional groups comprising of hydrogen, halogen and chalcogen atoms. The presence of these can lead to increasing complexity as to how molecules interact not only in drug formulations, such as co-crystals, but also at an active site of specific receptors. Such complexities can be utilized in crystal engineering for creating competition between hydrogen, halogen and chalcogen bonding.^{14,15}

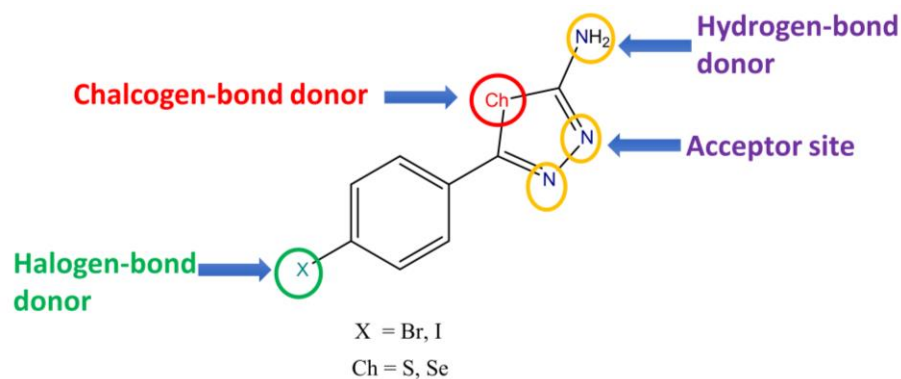


Figure 4.2 1,3,4-Chalcogenadiazole derivative with multiple donor and acceptor sites.

Each approved drug costs billions of dollars in research and development, and many potentially useful candidates fail due to low solubility or poor stability, and such problems may be addressed with a more complete understanding of how the balance between intermolecular forces leads to a specific structure with unique bulk properties. Furthermore, 1,3,4-chalcogenadiazole

(Figure 4.2) moieties are known to show anti-inflammatory and anti-cancer properties^{16–18}, and broadly speaking, chalcogen and halogen atoms and their structural influence can also positively impact not just biological properties but also synthetic transformations and catalysis. Given the fact that chalcogenadiazole moieties contain a variety of domains that can act as chalcogen-bond and halogen-bond donor/acceptor sites, they present a unique source for the formation of a multitude of intermolecular interactions. The balance and competition between these noncovalent interactions will significantly impact solid-state structure and subsequently the properties of the resulting bulk solid. In addition, the presence of chalcogen and halogen bonds can, in principle, compete with or disrupt an intended supramolecular synthetic strategy. These increased complexities can give rise to unexpected or unpredictable structural influences, hence a systematic study of the possible structure directing interactions of these moieties are required. Herein, we present a systematic structural study on how the increased complexity of multiple competing intermolecular forces in a single molecule is manifested in the solid-state. We focus on the 1,3,4-chalcogenadiazole moiety (Figure 4.2) with different substituents in the second and fifth position as this allows us to alter the chalcogen-bond donor from S to Se and the halogen-bond donor from Br to I that can be activated through the addition of electron withdrawing and subsequent sp-hybridized carbon atoms, allowing us to explore the balance between these interactions. In this study, twelve molecules were synthesized with diverse structural influence (Figure 4.3).

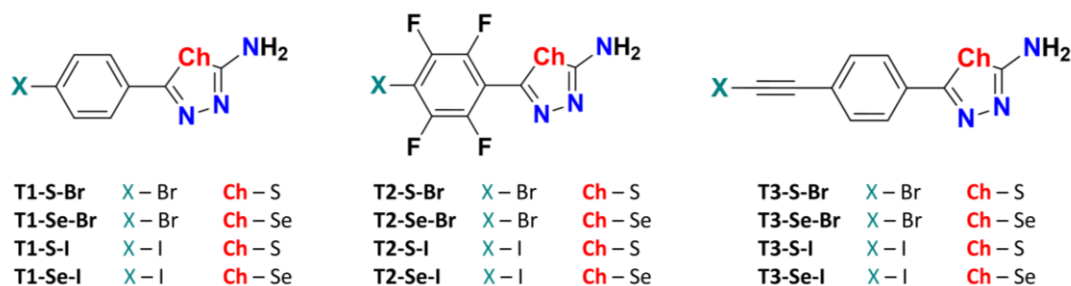


Figure 4.3 Target library.

Using this library of molecules, we wanted to map out the structural landscape of 1,3,4-chalcogenadiazoles and address the following specific questions:

Question 1. To what extent do atom-to-atom replacements change electrostatic potentials?

Question 2. Which structure directing synthons are formed and how do they control assembly? Figure 4.4

Question 3. Can the balance between hydrogen bonds, halogen bonds, and chalcogen bonds be deliberately modulated?

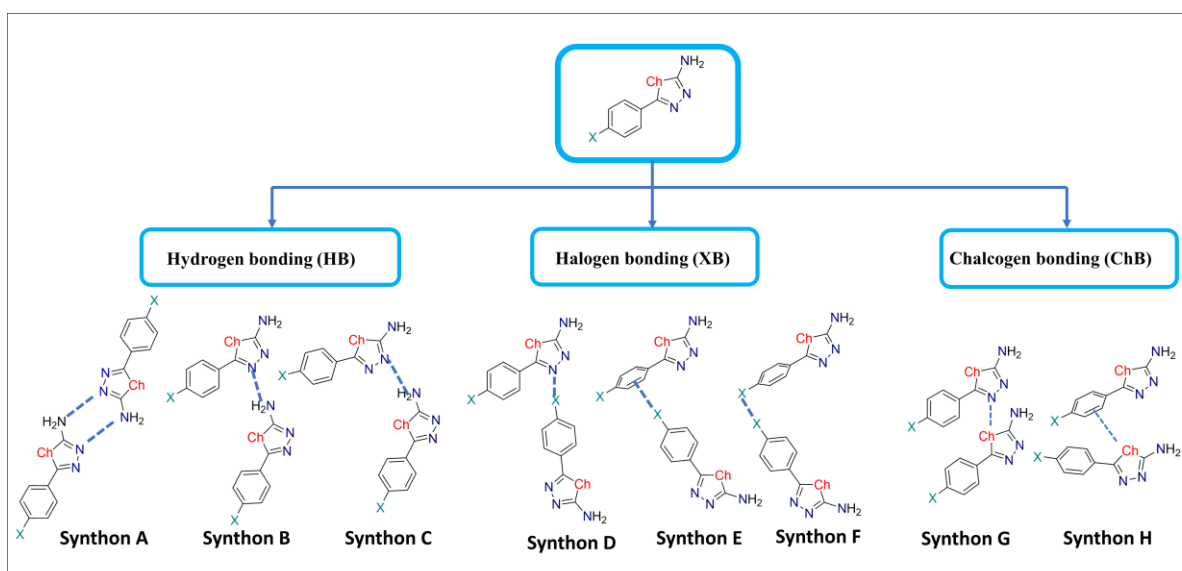


Figure 4.4 Postulated interactions in the solid-state landscape of 1,3,4-chalcogenadiazoles.

4.2 Experimental

4.2.4 General

Reagents and solvents were purchased from commercially available sources and used without further purification. Melting points were measured using a TA instruments DSC Q20 differential scanning calorimeter. Nuclear magnetic resonance (NMR) data were measured on a Bruker Ascend 400 MHz spectrometer. The residual solvent peak was used as the internal

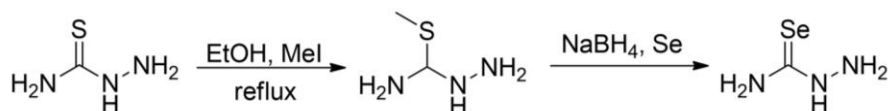
reference for ^1H and ^{13}C NMR. For ^{77}Se NMR the selenium peak was referenced against the residual solvent peak in its corresponding ^1H NMR spectrum. Single crystal X-ray diffraction data were collected using a Rigaku XtaLAB Synergy-S diffractometer and the structures were solved using Olex2¹⁹ with SHELXT²⁰. All computational calculations were performed using Spartan14²¹ software package.

4.2.5 Molecular electrostatic potential maps

Molecular electrostatic potentials were calculated using Spartan14 Wavefunction. The compounds were sketched and saved using ChemDraw 12 and loaded into Spartan14 software followed by geometry optimization for the most stable conformation using density functional theory B3LYP hybrid functional and 6-311++G** basis set. A positive point charge in the vacuum was used as a probe against the surface to determine the positive and negative regions on the molecular surface. The electrostatic potentials presented herein are given in kJ/mol and a negative number is representative of an electron rich acceptor and a positive number of an electron poor donor.

4.2.6 Synthesis

4.2.6.1 Synthesis of selenosemicarbazide

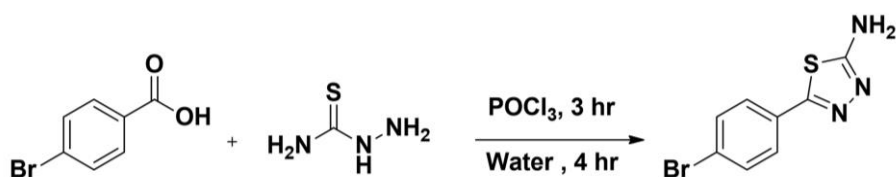


Thiosemicarbazide (3.64 g, 0.04 mol) was dissolved in dry ethanol and to this, iodomethane (5.67 g, 0.04 mol) was added and the mixture was refluxed at 80 °C for 3 h. Upon cooling the

mixture in an ice bath, the product, hydrazinyl(methylthio)methanamine, precipitated and this was air dried overnight and used for the following step.

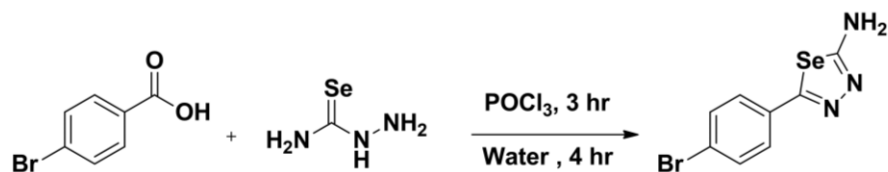
To a mixture of Se and NaBH₄ cooled to 0 °C with ice, dry ethanol was added under N₂ atmosphere. Once all the Se dissolved, hydrazinyl(methylthio)methanamine dissolved in dry ethanol was added slowly. This was stirred overnight, and the resulting precipitate was filtered in the fume hood, and the product was purified through column chromatography producing a grey/violet solid.²² Yield 60%. Decomp: 174–176 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 9.07 (s, 1H), 7.97 (s, 1H), 7.64 (s, 1H), 4.52 (s, 2H). ⁷⁷Se NMR (400 MHz, DMSO-d₆) δ 146.16.

4.2.6.2 Synthesis of 5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine (T1-S-Br)



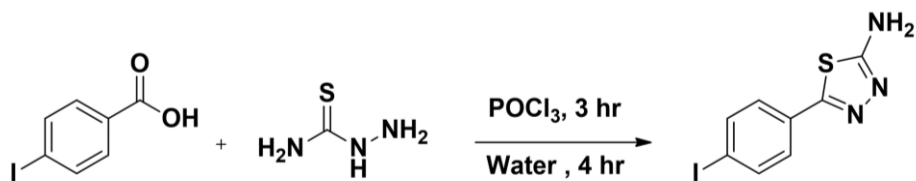
First, 4-bromobenzoic acid (2.01 g, 0.01 mol), thiosemicarbazide (0.91g, 0.01 mol), and POCl₃ (5.0 ml) were mixed in a round-bottomed flask. This was refluxed at 75 °C for 3 h. After cooling to room temperature, water (50.0 ml) was added slowly to the mixture and the reaction mixture was further refluxed for 4 h. The progress of the reaction was monitored using TLC and after the completion, the mixture was cooled to room temperature and was basified to pH 8 using 30% NH₄OH. The resulting precipitate was filtered, and the product was purified using column chromatography. The product was a light-yellow solid. Yield of 85%. Mp: 212–214 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 7.68 (q, J = 8.7 Hz, 4H), 7.50 (s, 2H).

4.2.6.3 Synthesis of 5-(4-bromophenyl)-1,3,4-selenadiazol-2-amine (T1-Se-Br)



First, 4-bromobenzoic acid (2.01g, 0.01 mol), selenosemicarbazide (1.38g, 0.01 mol), and POCl_3 (5.0 ml) were mixed in a round-bottomed flask. This was refluxed at 75 °C for 3 h. After cooling to room temperature, water (50.0 ml) was added slowly to the mixture and the reaction mixture was further refluxed for 4 h. The progress of the reaction was monitored using TLC and after the completion, the mixture was cooled to room temperature and was basified to pH 8 using 30% NH_4OH . The resulting precipitate was filtered, and the product was purified using column chromatography. The product was a light pink color solid. Yield of 65%. MP: 222–224 °C. ^1H NMR(400 MHz, $\text{DMSO}-d_6$) δ 7.64 (m, J = 8.5 Hz, 4H). ^{77}Se NMR (400 MHz, $\text{DMSO}-d_6$) δ 562.04.

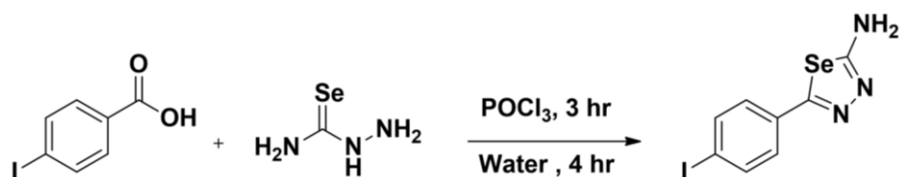
4.2.6.4 Synthesis of 5-(4-iodophenyl)-1,3,4-thiadiazol-2-amine (T1-S-I)



First, 4-iodobenzoic acid (2.48g, 0.01 mol), thiosemicarbazide (0.91g, 0.01 mol), and POCl_3 (5.0 ml) were mixed in a round-bottomed flask. This was refluxed at 75 °C for 3 h. After cooling to room temperature, water (50.0 ml) was added slowly to the mixture and the reaction mixture was further refluxed for 4 h. The progress of the re-action was monitored using TLC and after the completion, the mixture was cooled to room temperature and was basified to pH 8 using 30% NH_4OH . The resulting precipitate was filtered, and the product was purified using column chromatography. The product was a white solid. Yield of 70%. Mp: Form I 239–241 °C, From II

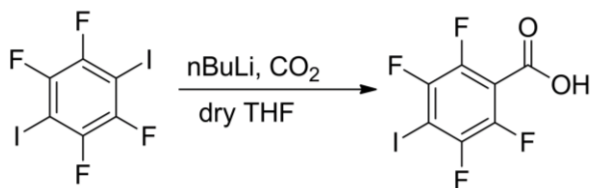
240–242 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 7.83 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz 2H), 7.49 (s, 2H).

4.2.6.5 Synthesis of 5-(4-iodophenyl)-1,3,4-selenadiazol-2-amine (T1-Se-I)



First, 4-iodobenzoic acid (2.48g, 0.01 mol), selenosemicarbazide (1.38g, 0.01 mol), and POCl_3 (5.0 ml) were mixed in a round-bottomed flask. This was refluxed at 75 °C for 3 h. After cooling to room temperature, water (50.0 ml) was added slowly to the mixture and the reaction mixture was further refluxed for 4 h. The progress of the reaction was monitored using TLC and after the completion, the mixture was cooled to room temperature and was basified to pH 8 using 30% NH_4OH . The resulting precipitate was filtered, and the product was purified using column chromatography. The product was a greyish solid. Yield of 55%. Mp: 219–221 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 7.80 (d, J = 8.4 Hz, 2H), 7.61 (s, 2H), 7.51 (d, J = 8.4 Hz, 2H). ^{77}Se NMR (400 MHz, DMSO- d_6) δ 560.97.

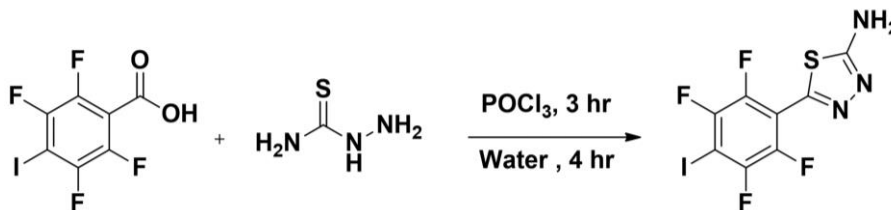
4.2.6.6 Synthesis of 2,3,5,6-tetrafluoro-4-iodobenzoic acid



To an oven dried round bottom flask 1,4-diiodotetrafluorobenzene (0.320 g, 1 mmol) was added along with a stir bar. This was evacuated and filled with dry N_2 three times and after the

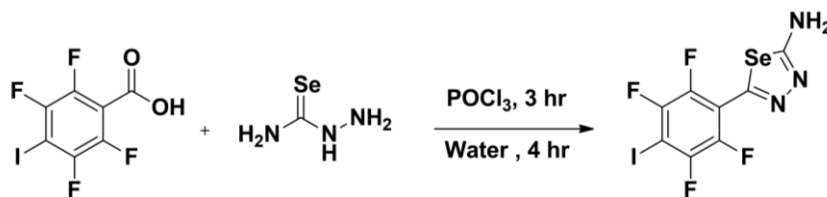
third cycle, anhydrous THF(10 ml) was added followed by refilling with dry N₂. Then the mixture was cooled to -78 °C using dry ice and acetone bath for 20 minutes after which nBuLi (2.6 M solution in hexane, 0.46 ml,1.2 mmol) was added dropwise and stirred for 30 min. The reaction mixture was then purged with CO₂ for another 15 min and slowly allowed to reach 0 °C and quenched with 2M HCl. The solvent was removed, and the crude was dissolved in DCM and the organic phase was washed with sat. sodium thiosulphate and brine and the organic layer was collected dried using anhydrous MgSO₄ and concentrated to yield the crude product. This was triturated with cold hexane and filtered to obtain the pure product. Yield 56%. Decomp: 140 °C. All the other characterization data matches with previously reported data.²³

4.2.6.7 Synthesis of 5-(2,3,5,6-tetrafluoro-4-iodophenyl)-1,3,4-thiadiazol-2-amine (T2-S-I)



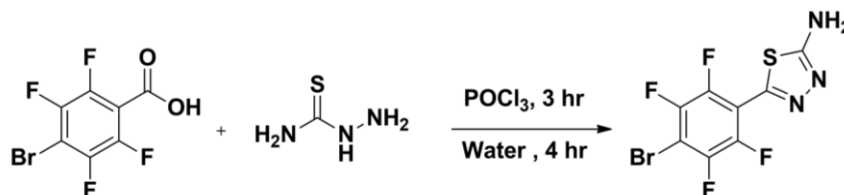
First, 4-iodotetrafluorobenzoic acid (0.319 g, 0.001 mol), thiosemicarbazide (0.91 g, 0.001 mol), and POCl₃ (5.0 ml) were mixed in a round-bottomed flask. This was refluxed at 75 °C for 3 h. After cooling to room temperature, water (50.0 ml) was added slowly to the mixture and the reaction mixture was further refluxed for 4 h. The progress of the reaction was monitored using TLC and after the completion, the mixture was cooled to room temperature and was basified to pH 8 using 30% NH₄OH. The resulting precipitate was filtered, and the product was purified using column chromatography. The product was a white solid. Yield of 65%. Mp: 225-229 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 7.74 (s, 2H).

4.2.6.8 Synthesis of 5-(2,3,5,6-tetrafluoro-4-iodophenyl)-1,3,4-selenadiazol-2-amine (T2-Se-I)



First, 4-iodotetrafluorobenzoic acid (0.319 g, 0.001 mol), selenosemicarbazide (0.138 g, 0.001 mol), and POCl_3 (5.0 ml) were mixed in a round-bottomed flask. This was refluxed at 75 °C for 3 h. After cooling to room temperature, water (50.0 ml) was added slowly to the mixture and the reaction mixture was further refluxed for 4 h. The progress of the reaction was monitored using TLC and after the completion, the mixture was cooled to room temperature and was basified to pH 8 using 30% NH_4OH . The resulting precipitate was filtered, and the product was purified using column chromatography. The product was an orange solid. Yield of 45%. Mp: 195-202 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.61 (s, 2H).

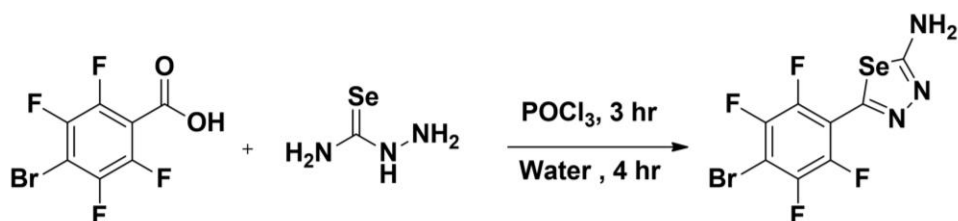
4.2.6.9 Synthesis of 5-(2,3,5,6-tetrafluoro-4-bromophenyl)-1,3,4-thiadiazol-2-amine (T2-S-Br)



First, 4-bromotetrafluorobenzoic acid (0.271 g, 0.001 mol), thiosemicarbazide (0.91 g, 0.001 mol), and POCl_3 (5.0 ml) were mixed in a round-bottomed flask. This was refluxed at 75 °C for 3 h. After cooling to room temperature, water (50.0 ml) was added slowly to the mixture and the reaction mixture was further refluxed for 4 h. The progress of the reaction was monitored using

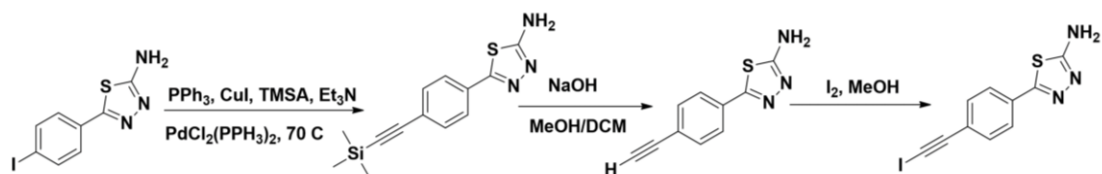
TLC and after the completion, the mixture was cooled to room temperature and was basified to pH 8 using 30% NH_4OH . The resulting precipitate was filtered, and the product was purified using column chromatography. The product was a white solid. Yield of 70 %. Mp: 218-222 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.74 (s, 2H).

4.2.6.10 Synthesis of 5-(2,3,5,6-tetrafluoro-4-bromophenyl)-1,3,4-selenadiazol-2-amine (T2-Se-Br)



First, 4-bromotetrafluorobenzoic acid (0.271 g, 0.001 mol), selenosemicarbazide (0.138 g, 0.001 mol), and POCl_3 (5.0 ml) were mixed in a round-bottomed flask. This was refluxed at 75 °C for 3 h. After cooling to room temperature, water (50.0 ml) was added slowly to the mixture and the reaction mixture was further refluxed for 4 h. The progress of the reaction was monitored using TLC and after the completion, the mixture was cooled to room temperature and was basified to pH 8 using 30% NH_4OH . The resulting precipitate was filtered, and the product was purified using column chromatography. The product was a white solid. Yield of 72%. Mp: 214-219 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.65 (s, 2H).

4.2.6.11 Synthesis of 5-(4-(iodoethynyl)phenyl)-1,3,4-thiadiazol-2-amine (T3-S-I)



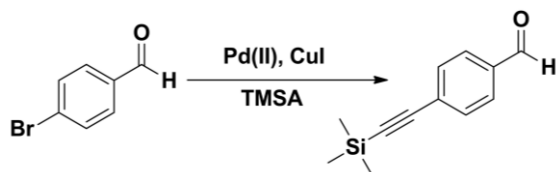
Into a RB 5-(4-iodophenyl)-1,3,4-thiadiazol-2-amine (3.03 g, 0.01 mol) was added and this was dissolved in a mixture of THF (100 ml) and Et₃N (100 ml). The mixture was stirred at room temperature and purged with N₂ for 10 minutes followed by the addition of triphenylphosphine (5% mol, 0.131 g, 0.5 mmol), CuI (5% mol, 0.095 g, 0.5 mmol), PdCl₂(PPh₃)₂ (5% mol, 0.351 g, 0.5 mmol) and trimethylsilylacetylene (2.82 ml, 0.02 mol). This was refluxed at 80 °C for overnight the progress of the reaction was monitored by TLC. Upon completion the solvent was removed by rotary evaporation and the product was purified by column chromatography. Yield 90%. ¹H NMR (400 MHz, DMSO-d₆) δ 7.74 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 4H), 0.24 (s, 9H).

The 5-(4-((trimethylsilyl)ethynyl)phenyl)-1,3,4-thiadiazol-2-amine (2.73 g, 0.01 mol) was dissolved in methanol and DCM 3:1 mixture and K₂CO₃ (2 eq, 2.76 g, 0.02 mol) was added to this and stirred at room temperature for 6 hr. Upon completion the mixture was poured into water and the product was extracted with ethyl acetate and the organic layer was washed dried over anhydrous MgSO₄ and the solvent was evaporated to obtain the pure product. Yield 73%. ¹H NMR (400 MHz, DMSO-d₆) δ 7.76 (d, J = 7.3 Hz, 2H), 7.56 (d, J = 7.3 Hz, 2H), 7.51 (s, 2H), 4.36 (s, 1H).

The 5-(4-ethynylphenyl)-1,3,4-thiadiazol-2-amine (0.402 g, 2 mmol) was dissolved in methanol and cooled to 0 °C and NaOH (2eq, 0.16 g, 4 mmol) was added directly into the mixture. Iodine (2eq, 1.015 g, 4 mmol) dissolved in methanol was added dropwise until there was no further color change (in some case whole 2 equivalence might be required) and the reaction was stirred under room temperature for overnight. Water was added to the mixture and washed with sat. sodium thiosulfate and dried over anhydrous MgSO₄. The solvent was evaporated to give the crude

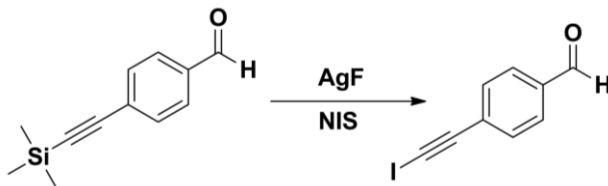
product and purified by column chromatography. Yield 47%. Decomposition > 150 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 7.83 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.48 (s, 2H).

4.2.6.12 Synthesis of 4-((trimethylsilyl)ethynyl)benzaldehyde



Into an RB 4-bromobenzaldehyde (0.185 g, 0.01 mol) was added and this was dissolved in a mixture of THF (100 ml) and Et_3N (100 ml). The mixture was stirred at room temperature and purged with N_2 for 10 minutes followed by the addition of CuI (5% mol, 0.095 g, 0.5 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (5% mol, 0.351 g, 0.5 mmol) and trimethylsilylacetylene (2.82 mol, 0.02 mol). This was refluxed at 60 °C for overnight and the progress of the reaction was monitored by TLC. Upon completion the solvent was removed by rotary evaporation and the crude product was purified by column chromatography. Yield 95%. Mp : 77-80 °C. ^1H NMR (400 MHz, Chloroform- d) δ 9.99 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H), 0.26 (s, 9H).

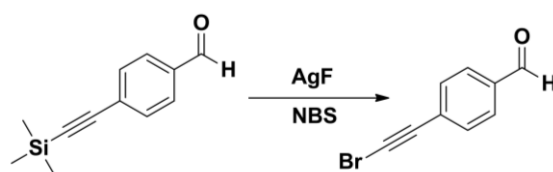
4.2.6.13 Synthesis of 4-(iodoethynyl)benzaldehyde



4-((Trimethylsilyl)ethynyl)benzaldehyde (1.01 g, 5 mmol) is dissolved in acetonitrile (70.0 ml) in an RB covered in foil, to which AgF (0.953 g, 7.5 mmol) and NIS (1.688 g, 7.5 mmol) was added. The mixture is stirred at RT under N_2 for overnight. The resulting mixture was filtered, and

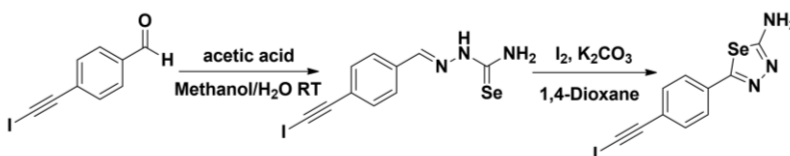
the solvent was evaporated under reduced pressure to obtain the crude which was dissolved in ethyl acetate and washed with water three times and finally with brine. The organic layer was dried over anhydrous MgSO_4 and concentrated under rotary evaporator to obtain the pure product. Yield 98%. Mp : 141-143 °C. ^1H NMR (400 MHz, Chloroform- d) δ 9.99 (s, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H).

4.2.6.14 Synthesis of 4-(bromoethynyl)benzaldehyde



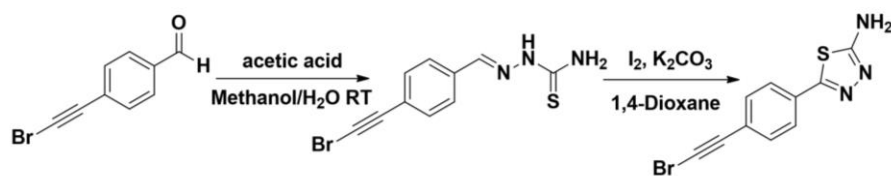
4-((Trimethylsilyl)ethynyl)benzaldehyde (1.01 g, 5 mmol) is dissolved in acetonitrile (70.0 ml) in an RB covered in foil, to which AgF (0.953 g, 7.5 mmol) and NBS (1.688 g, 7.5 mmol) was added. The mixture is stirred at RT under N_2 for overnight. The resulting mixture was filtered, and the solvent was evaporated under reduced pressure to obtain the crude which was dissolved in ethyl acetate and washed with water three times and finally with brine. The organic layer was dried over anhydrous MgSO_4 and concentrated under rotary evaporator to obtain the pure product. Yield 96%. Mp : 99-102 °C. ^1H NMR (400 MHz, Chloroform- d) δ 10.00 (s, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H).

4.2.6.15 Synthesis of 5-(4-(iodoethynyl)phenyl)-1,3,4-selenadiazol-2-amine (T3-Se-I)



To a stirred solution of selenosemicarbazide (0.138 g, 1 mmol) and acetic acid (1-4 mmol) in H₂O (2 ml) was added a solution of the 4-(iodoethynyl)benzaldehyde (0.256 g, 1 mmol) in MeOH (2-4 ml). After being stirred at room temperature for 30-60 min, the solvent was evaporated under reduced pressure, and the resulting residue was redissolved in 1,4-dioxane (5-10 ml), followed by addition of K₂CO₃ (3.2 eq, 0.442 g, 3.2 mmol) and iodine (1.5 eq, 0.381 g, 1.5 mmol) in sequence. The reaction mixture was refluxed at 75 °C under N₂ overnight and the completion of the reaction was monitored by TLC. After completion the reaction mixture was allowed to cool to room temperature, and this was treated with sat. Na₂S₂O₃ and extracted with ethyl acetate (50 ml x 2). The combined organic layer was dried over anhydrous MgSO₄ and concentrated using rotary evaporator. The crude was purified through column chromatography. Yield 54%. Decomposition > 150 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 7.70 (d, J = 8.5 Hz, 2H), 7.63 (s, 2H), 7.48 (d, J = 8.5 Hz, 2H). ⁷⁷Se NMR (76 MHz, DMSO-d₆) δ 560.80. ¹³C NMR (101 MHz, DMSO-d₆) δ 173.20, 161.13, 134.42, 133.07, 127.52, 124.07, 92.75, 20.80.

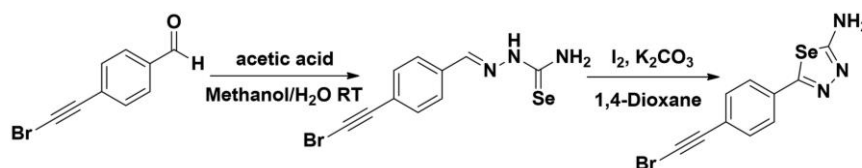
4.2.6.16 Synthesis of 5-(4-(bromoethynyl)phenyl)-1,3,4-thiadiazol-2-amine (T3-S-Br)



To a stirred solution of thiosemicarbazide (0.91 g, 1 mmol) and acetic acid (1-4 mmol) in H₂O (2 ml) was added a solution of the 4-(bromoethynyl)benzaldehyde (0.209 g, 1 mmol) in MeOH (2-4 ml). After being stirred at room temperature for 30-60 min, the solvent was evaporated under reduced pressure, and the resulting residue was dried and redissolved in 1,4-dioxane (5-10 ml), followed by addition of K₂CO₃ (3.2 eq, 0.442 g, 3.2 mmol) and iodine (1.5 eq, 0.381 g, 1.5

mmol) in sequence. The reaction mixture was refluxed at 75 °C under N₂ overnight and the completion of the reaction was monitored by TLC. After completion the reaction mixture was allowed to cool to room temperature, and this was treated with sat. Na₂S₂O₃ and extracted with ethyl acetate (50 ml x 2). The combined organic layer was dried over anhydrous MgSO₄ and concentrated using rotary evaporator. The crude was purified through column chromatography. Yield 61%. Decomposition > 150 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 7.76 (d, J = 7.3 Hz, 2H), 7.57 (d, J = 7.3 Hz, 2H), 7.52 (s, 2H).

4.2.6.17 Synthesis of 5-(4-(bromoethynyl)phenyl)-1,3,4-thiadiazol-2-amine (T3-Se-Br)



To a stirred solution of selenosemicarbazide (0.138 g, 1 mmol) and acetic acid (1-4 mmol) in H₂O (2 ml) was added a solution of the 4-(bromoethynyl)benzaldehyde (0.209 g, 1 mmol) in MeOH (2-4 ml). After being stirred at room temperature for 30-60 min, the solvent was evaporated under reduced pressure, and the resulting residue was dried and redissolved in 1,4-dioxane (5-10 ml), followed by addition of K₂CO₃ (3.2 eq, 0.441 g, 3.2 mmol) and iodine (1.5 eq, 0.381 g, 1.5 mmol) in sequence. The reaction mixture was refluxed at 75 °C under N₂ overnight and the completion of the reaction was monitored by TLC. After completion the reaction mixture was allowed to cool to room temperature, and this was treated with sat. Na₂S₂O₃ and extracted with ethyl acetate (50 ml x 2). The combined organic layer was dried over anhydrous MgSO₄ and concentrated using rotary evaporator. The crude was purified through column chromatography. Decomposition > 150 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 7.72 (d, J = 8.5 Hz, 2H), 7.65 (s, 2H), 7.53 (d, J = 8.5 Hz, 2H). ⁷⁷Se NMR (76 MHz, DMSO-d₆) δ 560.90.

4.2.7 Crystal Growth

The targets were recrystallized from different solvents using slow evaporation to obtain singles crystals suitable for single crystal X-ray diffraction (SC-XRD), Table 4.1.

Table 4.1 Solvents used for crystal growth and crystal descriptions

Compound	Code	Solvent	Color and morphology	Melting point °C
5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine	T1-S-Br	Methanol	clear yellow, needle	212-214
5-(4-bromophenyl)-1,3,4-selenadiazol-2-amine	T1-Se-Br	Methanol	Clear, Needle	222-224
5-(4-iodophenyl)-1,3,4-thiadiazol-2-amine	T1-S-I Form I	Acetonitrile	Clear, plates	236-241
	T1-S-I Form II	Methanol	Clear, Needle	240-242
5-(4-iodophenyl)-1,3,4-selenadiazol-2-amine	T1-Se-I	Methanol	Colorless, rectangular	219-221
5-(2,3,5,6-tetrafluoro-4-iodophenyl)-1,3,4-thiadiazol-2-amine	T2-S-I	Methanol	Colorless, needle	225-229
5-(2,3,5,6-tetrafluoro-4-iodophenyl)-1,3,4-selenadiazol-2-amine	T2-Se-I	Ethanol	Colorless, needle	195-202
5-(2,3,5,6-tetrafluoro-4-bromophenyl)-1,3,4-thiadiazol-2-amine	T2-S-Br	Ethanol	Colorless, irregular	218-222
5-(2,3,5,6-tetrafluoro-4-bromophenyl)-1,3,4-selenadiazol-2-amine	T2-Se-Br	Ethanol	Colorless, irregular	214-219
5-(4-(iodoethynyl)phenyl)-1,3,4-thiadiazol-2-amine	T3-S-I hydrate	Methanol	yellowe, retangular	Decomp.
5-(4-(iodoethynyl)phenyl)-1,3,4-selenadiazol-2-amine	T3-Se-I solvate	THF	Colorless, irregular	Decomp.
5-(4-(bromoethynyl)phenyl)-1,3,4-thiadiazol-2-amine	T3-S-Br	THF/methanol	Clear yellow, plate	Decomp.
	T3-S-Br solvate	THF	Clear yellow, plate	Decomp.

4.3 Results

4.3.1 Molecular electrostatic potential maps

The calculated MEP values are shown in Figure 4.5.

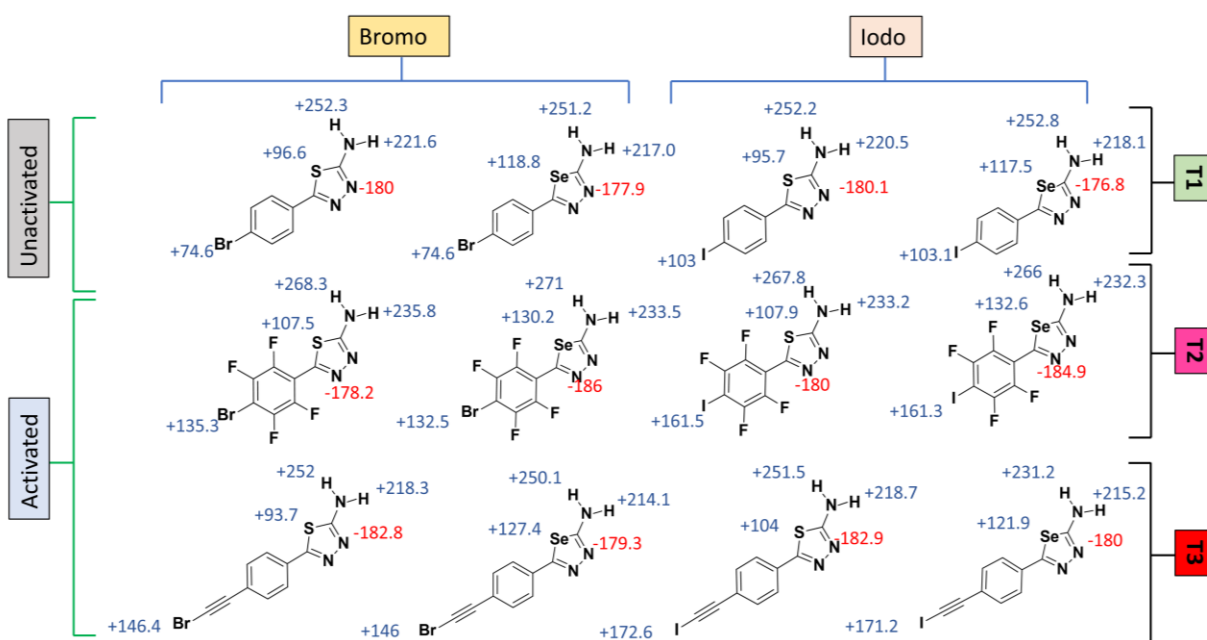


Figure 4.5 MEP values of the highest negative and positive potentials.

4.3.2 Crystal structures

In all the chalcogenadiazole crystal structures discussed herein, hydrogen bonds exist as a prominent intermolecular interaction. To easily identify the hydrogen bonding synthons, graph set notation can be used as a classification. Graph set can be specified by $G_d^a(r)$ in which a descriptor (G), donor (d), acceptor (a) and the degree (r) describes the pattern.²⁴ In any system four basic descriptors can be identified, intramolecular or self-bonding ring (S), a dimeric ring (R), an infinite chain (C) or a discrete pattern (D). In the **T1** series of compounds, four crystal structures showed $R_2^2(8)$ HB dimer formation between the 2-amino-1,3,4-chalcogenadiazole heterocycle through $N-H\cdots N$ interactions with only Form I of **T1-S-I** being the exception to the series. In the crystal structure of the previously reported **T1-S-Br**²⁵, $Z'=1$, the bromine atom did not participate in any notable XBs; however, the sulfur atom engaged in a ChB with the π -electron cloud, $S\cdots C(\pi)$. In contrast to **T1-S-Br**, the crystal structure of **T1-Se-Br** contains two unique molecules ($Z'=2$) in

the asymmetric unit with each of them showing different interactions with respect to the surrounding molecules. The halogen atom in one of them formed a near-linear halogen bond (Figure), $\text{Br}\cdots\text{C}(\pi)$, while the other formed an irregular $\text{Br}\cdots\text{Br}$ contact in an almost perpendicular fashion, 99° . The selenium atoms formed a bifurcated chalcogen bond, $\text{Se}\cdots\text{C}(\pi)$ and $\text{Se}\cdots\text{N}$ (Figure 4.6).

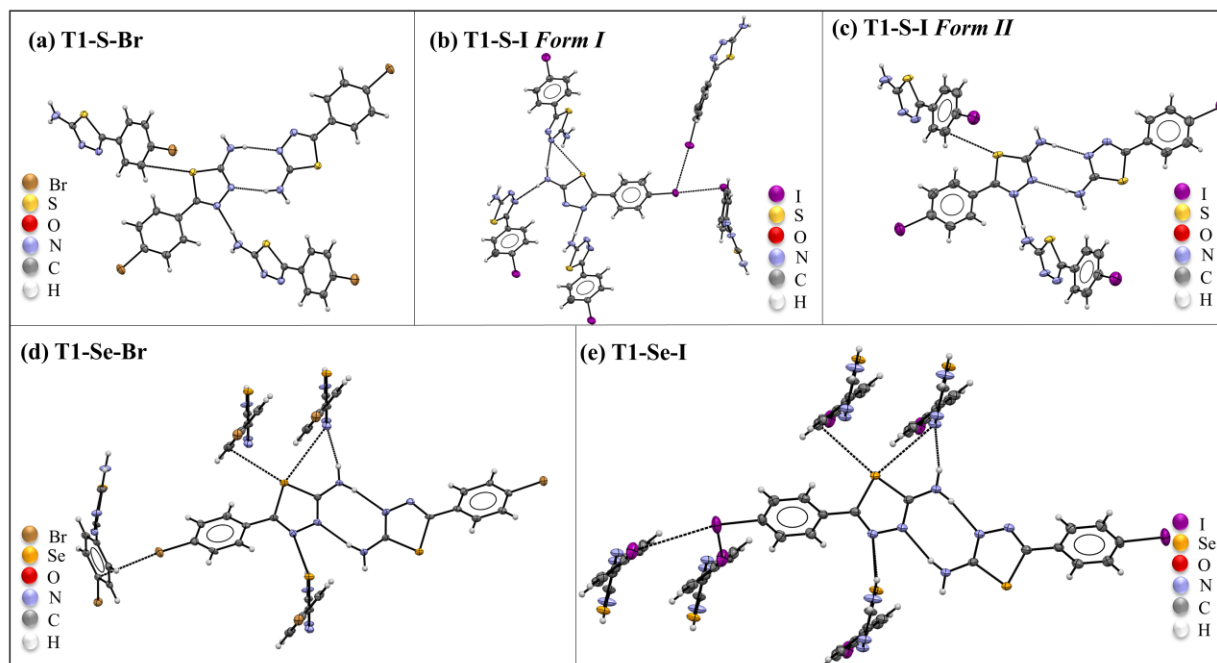


Figure 4.6 Primary intermolecular interactions observed for the crystal structures of the **T1** series.

T1-S-I crystallized in two different polymorphs. Form I was obtained from acetonitrile, and Form II from methanol. The polymorphs had different numbers of symmetry-independent molecules (Z') and completely different intermolecular connectivity. Form I resulted in $Z' = 4$, where all of them displayed closely related intermolecular connectivity but with different bond geometries. Two molecules in the asymmetric unit formed Type II halogen bonds that formed with the electrophilic area on one halogen atom with an electron rich area on the other halogen. In this

halogen bonding, the halogen atom simultaneously acted as both the donor and acceptor and the other two unique molecules did not show any halogen bonds. The sulfur atoms engaged in chalcogen bonds between $S \cdots N$ in which the nitrogen atom acted as a chalcogen-bond acceptor as well as a hydrogen-bond acceptor, indicating that the hydrogen bond was most likely the prominent interaction. In addition, two hydrogen bonds per molecule were formed between $NH \cdots N$ (Figure 6), $C_1^1(4)$, leading to a 1-D chain-like assembly (Figure 4.7).

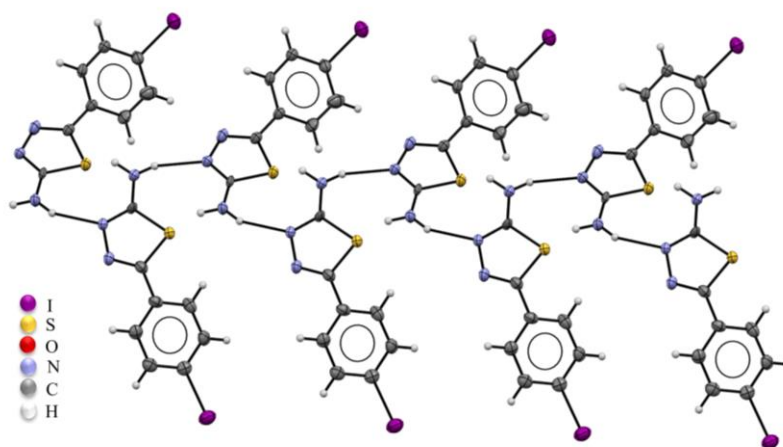


Figure 4.7 T1-S-I (Form I) Hydrogen-bonded 1D-chain.

Similar to **T1-S-Br**, the crystal structure of **T1-S-I** (Form II) and **T1-Se-I** (Figure 4.6) contained a hydrogen bonded dimer. Form II lacked any XBs but contained a chalcogen bond comprised of $S \cdots C(\pi)$. In the crystal structure of **T1-Se-I**, consistent with the interaction observed for Se in **T1-Se-Br**, the selenium atom of **T1-Se-I** also showed bifurcated ChB, $Se \cdots C(\pi)$, and $Se \cdots N$. In addition, the structure contains one Type II XB, $I \cdots I$. All the relevant hydrogen, halogen and chalcogen bond geometries in the five crystal structures are given in Table 4.2.

Table 4.2 Hydrogen, halogen, and chalcogen bond parameters of the five crystal structures of **T1**

Target	R-DH/X/Ch...A	D/X/Ch...A (Å)	R-DH/X/Ch...A (deg)
T1-S-Br	N3-H1...N1	2.957	163.42
	N3-H2...N1	2.996	167.1
	S1...C5	3.497	161.2
T1-Se-Br	N33-H33b...N11	2.943(8)	165.3(2)
	N13-H13b...N31	2.942(8)	166.1(2)
	N33-H33a...N32	2.981(7)	157.05(19)
	N13-H13a...N12	2.976(7)	157.82(19)
	Se29...N32	3.646(5)	154.39(19)
	Se29...C25	3.416(6)	162.6(2)
	Se9...N12	3.603(6)	155.39(19)
	Se9-C3	3.406(6)	163.3(2)
	Br27...C4	3.517(6)	170.0(2)
T1-S-I Form I	N1B-H1BA...N3D	3.013(13)	176.8(7)
	N1A-H1AA...N3C	3.016(13)	179.2(7)
	N1C-H1CA...N3A	3.028(13)	179.2(7)
	N1D-H1DA...N3B	3.008(13)	178.9(8)
	N1C-H1CB...N2B	3.031(12)	157.4(6)
	N1A-H1AB...N2D	2.992(12)	155.5(6)
	N1D-H1DB...N2A	3.033(13)	158.7(13)
	N1B-H1BB...N2C	3.027(12)	159.5(6)
	S1C...N2B	3.507(9)	163.6(4)
	S1D...N1A	3.517(10)	164.6(4)
	S1A...N2D	3.525(10)	162.4(4)
	S1B...N2C	3.559(10)	163.1(4)
	I1C...I1A	3.892(1)	174.7(3)
	I1A...I1B	3.813(1)	176.3(3)
T1-S-I Form II	N6-H6B...N4	2.979(8)	178(8)
	N6-H6A...N5	3.019(7)	172(6)
	S2...C9	3.568(7)	162.1(2)
T1-Se-I	N13-H13A...N11	2.940(5)	165.6(3)
	N13-H13B...N12	2.957(4)	157.7(3)
	Se9...N12	3.613(3)	154.88(13)
	Se9...C3	3.487(4)	165.75(14)
	I7...I7	4.0468(4)	162.8(1)
	I7...I7	4.0468(4)	93.14(11)

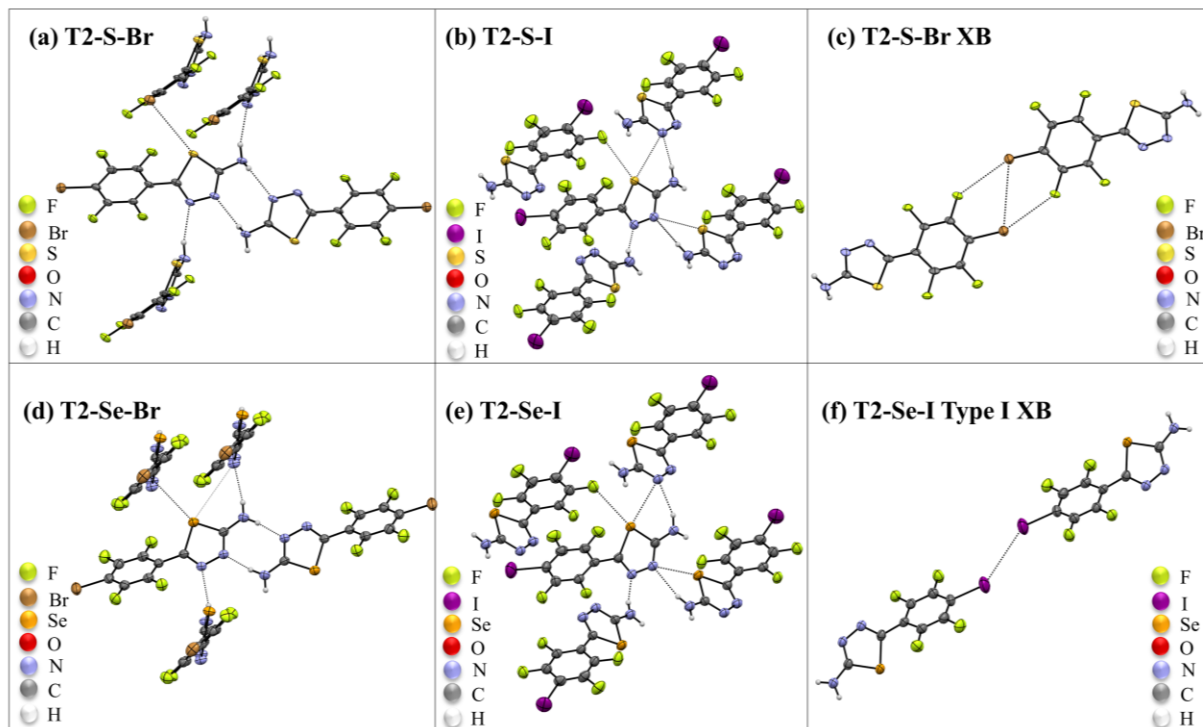


Figure 4.8 Primary intermolecular interactions in the crystal structures of the **T2** series.

In the **T2** series of compounds only two out of four crystal structures showed the $R_2^2(8)$ HB dimer and the others showed $C_1^1(5)$, HB formation. Both iodo species resulted in Type I XB between $I \cdots I$ and for bromo analogues, a XB dimer between $Br \cdots F$ was apparent. As a result of this XB dimer a Type I contact with a higher bond angle becomes visible between $Br \cdots Br$ (Figure 4.8 (c)). Interestingly, with the exception of **T2-S-Br** all the other crystal structures showed bifurcated chalcogen bond formation between $S/Se \cdots N$ and $S \cdots F$ while **T2-S-Br** formed a single chalcogen bond formation between $S \cdots C(\pi)$. All the relevant hydrogen, halogen and chalcogen bond geometries in the four structures are given in Table 4.3.

Table 4.3 Hydrogen, halogen, and chalcogen bond parameters of the five crystal structures of **T2**

Target	R-DH/X/Ch...A	D/X/Ch...A (Å)	R-DH/X/Ch...A (deg)
T2-S-Br	N12-H12B...N9	2.975(6)	148.4(3)
	N12-H12A...N9	2.980(5)	162.8(3)
	S11...C5	3.698(4)	160.12(16)
	Br13...F15	3.315(2)	157.62(13)
	Br13...Br13	3.739(9)	107.97(12)
T2-Se-Br	N17-H17A...N14	2.964(4)	163.50(16)
	N17-H17B...N13	3.019(3)	160.27(18)
	Se16...C4	3.618(3)	144.93(10)
	Se16...N13	3.876(2)	153..07(9)
	Br9...F10	3.653(2)	159.72(11)
	Br9...Br9	3.660(4)	113.8(1)
T2-S-I	N6-H6B...N4	3.037(8)	166(10)
	N6-H6A...N5	3.142(8)	166(6)
	S2...N4	3.266(5)	172.4(2)
	S2...F16	3.358(5)	157.80(19)
	C10-I15...I15	3.887(12)	144.23(18)
T2-Se-I	N008-H00A...N007	3.092(7)	154(8)
	N008-H00B...N009	3.103(7)	167(7)
	Se02...N007	3.154(4)	167.99(18)
	Se02...F005	3.199(4)	162.33(13)
	C00H-I01...I01	4.001(12)	144.90(16)

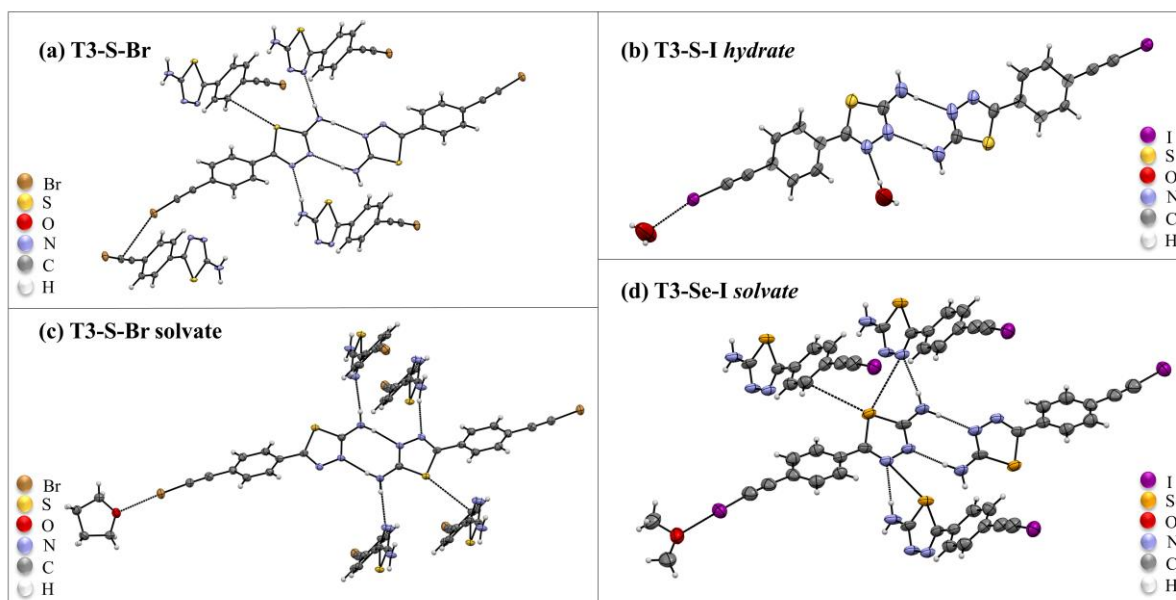


Figure 4.9 Primary intermolecular interactions in the crystal structures of the **T3** series.

Similar to **T1** and **T2**, the **T3** series also primarily showed the $R_2^2(8)$ dimer formations in all the crystal structures obtained. However, unlike the other two series, out of the 4 crystal structures obtained three of them were either solvates or hydrates. The only single component crystal structure obtained was for **T3-S-Br** which showed a ChB between $S \cdots C(\pi)$ and a XB between $Br \cdots C \equiv C(\pi)$, Figure 4.9. Two symmetrically independent target molecules and one THF molecule were present in the asymmetric unit of **T3-S-Br** solvate. Main difference in the solvate form of **T3-S-Br** arise in the XB in which XB occurred between $Br \cdots O$ (THF solvent). **T3-S-I** hydrate, and **T3-Se-I** solvate showed a similar XB between the $I \cdots O$ (solvent) in which the solvent molecules were disordered. The crystal structure of **T3-Se-I** showed a bifurcated ChB formation between the $Se \cdots C(\pi)$ and $Se \cdots N$, and we were not successful in our attempt to acquire the **T3-Se-Br** crystal structure. All the relevant hydrogen, halogen and chalcogen bond geometries in the four crystal structures are given in Table 4.4.

Table 4.4 Hydrogen, halogen, and chalcogen bond parameters of the five crystal structures of **T3**

Target	R-DH/X/Ch...A	D/X/Ch...A (Å)	R-DH/X/Ch...A (deg)
T3-S-Br	N12-H12B...N9	2.944(3)	162.2(3)
	N12-H12A...N8	2.956(3)	164.7(3)
	S11...C3	3.504(2)	162.22(8)
	Br15...C14	3.529(3)	157.82(2)
T3-S-Br solvate	N00B-H00C...N009	2.962(5)	162.9(3)
	N00B-H00D...N008	2.985(5)	167.1(3)
	S004...C00T	3.528(4)	162.70(15)
	Br005...O005	2.859(4)	178.60(16)
T3-S-I hydrate	N6-H6B...N4	2.98(3)	161(17)
	O16-H16B...N5	2.1(2)	146(30)
	I15...O16	3.10(2)	169.7(6)
T3-Se-I Solvate	N12-H12B...N9	2.923(11)	169.8(6)
	N12-H12A...N8	3.002(9)	163.5(7)
	Se11...N8	3.648(7)	158.5(3)
	Se9...C5	3.692(11)	170.4(3)
	I15...O16	2.855(8)	178.6(4)

4.4 Discussion

The calculated MEPs showed that when the smaller atoms (Br, S) were replaced by a more polarizable alternative (I, Se), the electrostatic potentials undergo significant transformations (Figure 4.5). Changing bromine to iodine resulted in a 40% increase in the positive σ -hole potential, while a selenium replacement of sulfur produced a 23% enhancement. The introduction of electron withdrawing groups in **T2** and **T3** series only resulted in a small increase over the σ -hole potential on the chalcogen atoms. However, this had a significant influence over the σ -hole potential of the halogen, making them potentially stronger XB donors. This explains as to why only one bromo analogue showed halogen bonding in the unactivated **T1** series which had the lowest σ -hole potential among the bromo species. Among the activated species, all the bromo and iodo analogues showed Type I and conventional XBs. Unactivated iodo species showed XB

formation in 2/3 structures while for the activated species this was increased to a 100% probability making these highly directional (Figure 4.10). In the solvates and hydrate structures of the **T3** series the halogen preferably forms XBs with the oxygen atom of the solvent molecules which further confirms the preference of the σ -hole positive potential towards the highest negative potential present within the system when the $R_2^2(8)$ dimer formation was predominant. The lack of XBs in previously reported fluorine²⁶ and chlorine²⁷ analogs further validate the expectation that a more polarizable halogen atom is more likely to influence the solid-state assembly in ways to go beyond simple (and less directional) packing forces.

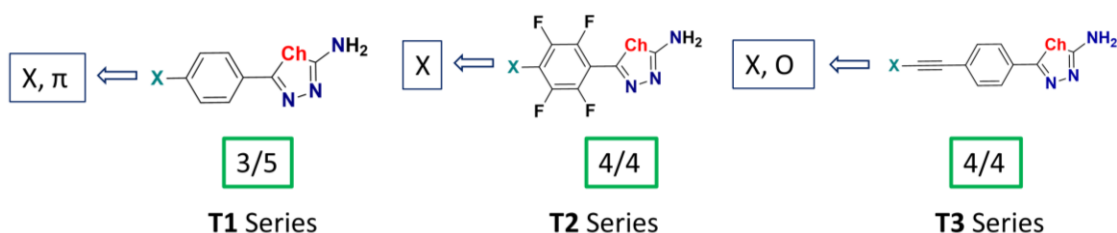


Figure 4.10 Postulated structural outcomes of halogen bonding.

Initially we postulated that the chalcogenodiazole derivatives should engage in either synthon A dimer formation or Synthon B or C with discrete or chain $N-H\cdots N$ hydrogen bonds. As postulated 77% of the structures obtained resulted in synthon A all of which also consisted of synthon B as well, and 23% only had synthon B and C in the structure arrangement. For all three series the highest and the second highest positive potentials were observed for the NH protons and for the **T1** and **T3** series, the N on the 3-position had the highest negative potential which explains the $R_2^2(8)$ HB dimer formation (synthon A) between $N-H\cdots N$. In the **T2** series the highest negative potential was changed to N on the 4-position while the second highest negative potential was seen for the 3-position which had resulted in a competing hydrogen bond formation that has prevented

the dimer formation for **T2-S-I** and **T2-Se-I**. A summary of these postulated outcomes is shown in Figure 4.11 and 4.12.

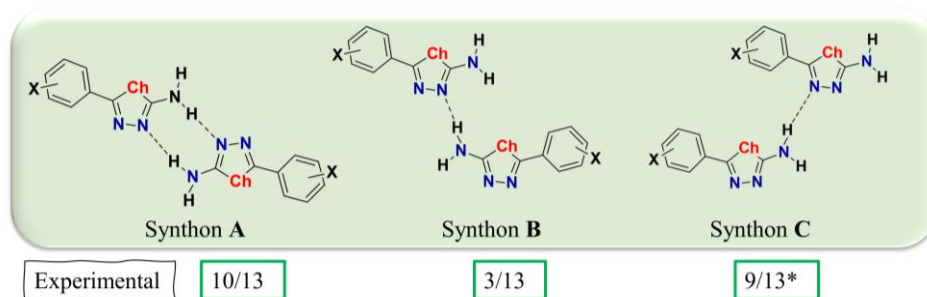


Figure 4.11 Summary of synthon outcomes of HB (*T3-S-I hydrate does not show Synthon C).

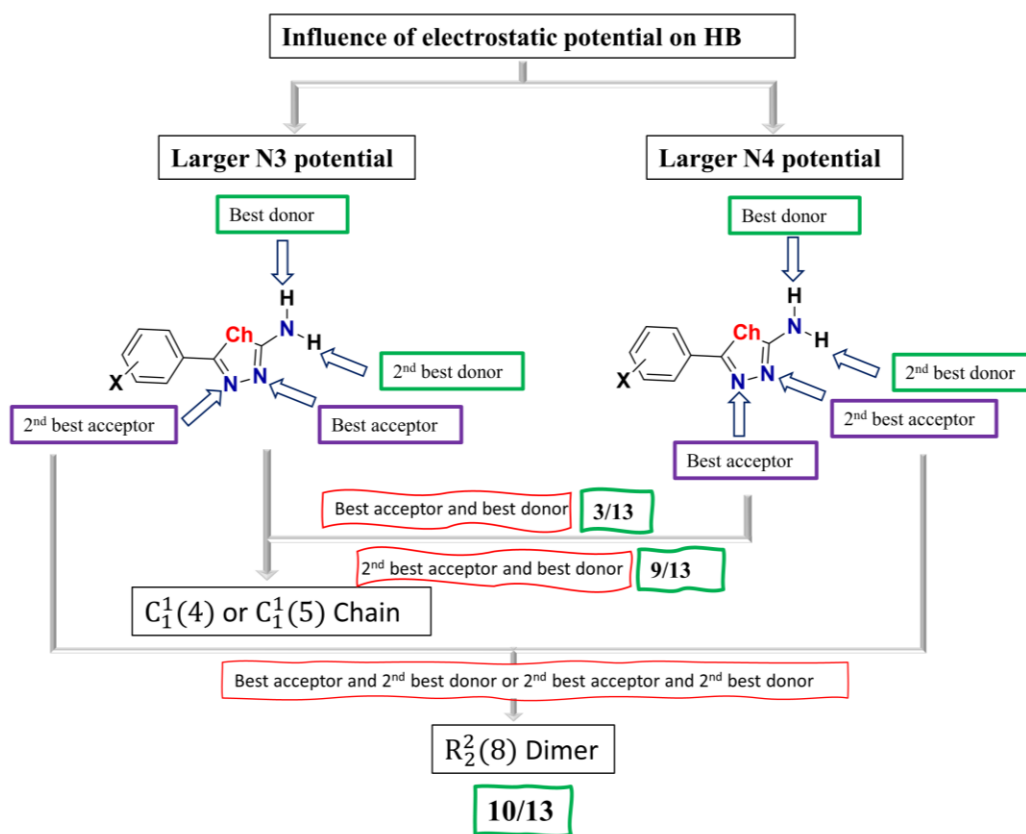


Figure 4.12 Postulated structural outcomes of hydrogen bonding for T1-T3 series based on electrostatic potentials.

A comparison of the frequency of occurrence of hydrogen, halogen, and chalcogen bonds in the crystal structures of these 1,3,4-chalcogendiazole (Table 4.5) shows that the former was the most prominent; HB exists in all the reported crystal structures and 10/13 exist as synthon A and 13/13 showed single hydrogen bond either as synthon B or C or both. Significant enhancement of the σ -hole electrostatic potentials of the halogens resulted in increased probability of the XB which resulted in 11/13 obtained structures having XBs. Of all the halogen bonding systems, 2/13 showed Type I XBs (excluding **T2-Ch-Br**), 2/13 showed Type II and 7/13 resulted in conventional XB. Despite the lack of noteworthy improvements to the σ -hole potentials, chalcogen bonding was present in 12/13 structure with the **T3-S-I** being the only exception. In the sulfur analogs, of the synthesized 1,3,4-chalcogendiazoles, most of them formed single ChB formation with the exception of **T2-S-I**. The structures of the selenium analogues in this study contained bifurcated ChB comprising both σ -holes. As a result of the substitution of sulfur with selenium, an additional chalcogen bond becomes structurally active and the supramolecular assembly proceeds along a different path.

Table 4.5 Summary of postulated structural outcomes

Series	NH...N dimer	NH...N chain	Ch...N	Ch...C(π)	X...C(π)	X...X	X...F	X...O
T1	4/5	5/5	3/5	4/5	1/5	2/5	n/a	n/a
T2	2/4	4/4	3/4	2/4	n/a	2/4	2/4	n/a
T3	4/4	3/4	1/4	3/4	1/4	n/a	n/a	3/4

Even though intermolecular hydrogen, halogen bonds and chalcogen bonds are the result of contributions from electrostatic, polarization, repulsion, and dispersion, it is helpful to note that

a relatively simplistic focus on the electrostatic component alone still offers valuable guidance for predicting which synthons are going to be more likely to appear in an extended structure. The increases in the electrostatic potential produce atoms that are more likely to form more prominent hydrogen, halogen and chalcogen bonds, respectively, which directly impacts their ability to more frequently deliver structure directing interactions in the solid state.

4.5 Conclusions

In summary, it is clear that atom-to-atom substitution and activation of the targets by electron withdrawing groups and sp-hybridization can lead to significant changes in crystal structures leading to a more structurally influential σ -holes. Despite the fact that hydrogen, halogen and chalcogen bonds comprise a variety of components, MEPs offer a simple way of mapping out electrostatic potentials in the 1,3,4-chalcogenadiazole systems.

The significance of the hydrogen bonding and the delicate balance between the hydrogen, halogen, and chalcogen bonding was clearly displayed in the unactivated two polymorphic structures of **T1-S-I**. The melting points of Form I and Form II only differed by 1–2 °C, implying that their lattice energies (and relative stabilities) are closely matched. Since Form I contains halogen and hydrogen bonds (chalcogen bonding was overshadowed by the hydrogen bonding), and Form II contains chalcogen and hydrogen bonds, we can surmise that the impacts on the stability and physical properties of the two σ -hole interactions are very similar.

The two activated series, **T2** and **T3** showed XBs in all the crystal structure arrangements which made them highly directional and a strong competitor to the hydrogen and chalcogen bonds. The sulfur species showed only one ChB in most cases and substituting the sulfur atom with selenium results in bifurcated ChB formation. The structural influence of chalcogen does not seem

to be singular and leads more towards a combined effect with hydrogen and halogen to deliver directionality.

Overall, this information can provide reliable guidelines for predicting which intermolecular interactions are going to be prominent in the solid state. By altering these electrostatic potentials through covalent means, the influence of σ -hole interactions (such as halogen and chalcogen bonds) can be controlled. Ultimately, this is of considerable practical importance when designing crystal engineering strategies that involve a combination of reversible non-covalent interactions.

4.6 References

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Chapter 5 - Cocrystals and salts : The structural landscape of multicomponent solids of chalcogenadiazoles

5.1 Introduction

The design and synthesis of co-crystals have become increasingly important aspects of pharmaceutical solid formulations to improve upon properties such as aqueous solubility, bioavailability, and chemical and mechanical stability. Currently there are nine FDA approved drugs on the market that are formulated as co-crystals, and four more are awaiting approval (Figure 5.1).^{1,2} In addition, it has been estimated that at least 50% of the drugs on the market are available as salts which shows how important multicomponent species are for the delivery of optimally active pharmaceutical substances.³ A multicomponent version of an active molecular species of a drug can improve its bulk physical properties without affecting the important pharmacological properties of the drug.^{3,4} Both co-crystallization as well as salt formations are achieved using FDA approved coformers and GRAS materials that can be combined with the active pharmaceutical ingredients (APIs).

Complementary functional groups, residing on the target and the coformer, respectively, are needed for the formation of co-crystals through intermolecular interactions. Therefore, an improved understanding of structural functional-group complementarity and enhanced molecular recognition events are needed to create more effective paths towards the assembly and synthesis of new co-crystals of high-value molecular solids.

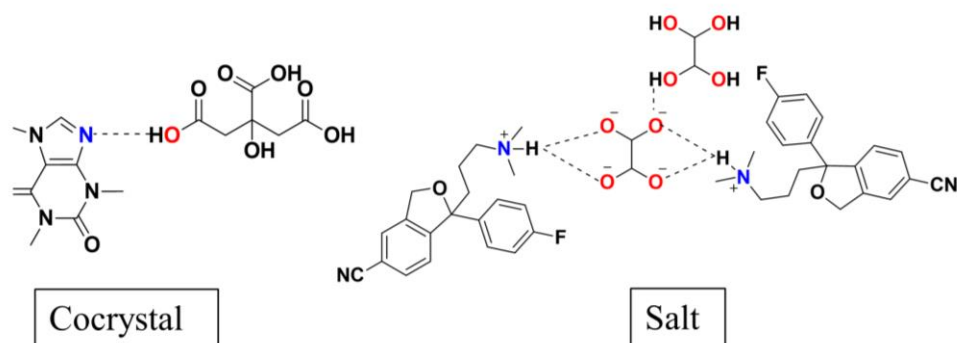


Figure 5.1 Intermolecular interactions of a cocrystal based FDA approved drug *Lexapro* and salt based drug *Cafcit*.

In Chapter 4, we successfully established the structural landscape of homosynthon of a library of “activated” and “unactivated” 1,3,4-chalcogenadiazole derivatives and the influence of electrostatic potential on the structural assembly.⁴ It was shown that 2-amino-1,3,4-chalcogenadiazole derivatives preferably forms hydrogen bond dimers with an $R_2^2(8)$, Synthon A, moiety through the heterocycle of the target and chains with $C_1^1(4)$ graph set. Considering the preferential formation of the hydrogen bonded dimers in the homosynthon solids, we wanted to determine the most efficient approach towards the synthesis of salts and cocrystals of the four unactivated compounds by using structural information from the CSD database (Figure 5.2).

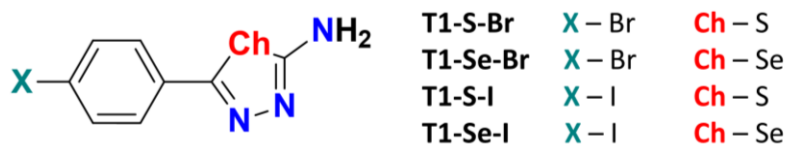


Figure 5.2 Target library used in synthesizing cocrystals and salts.

The CSD analysis was performed with ConQuest 2022.2.0 and to avoid having unreliable structures only the structures with R factor < 10%, no disorder, only organics, and single crystal

structures were used to mine the chalcogenadiazoles moiety containing crystal structures present in the CSD database. We found a total of 31 structures with the chalcogenadiazoles moiety and only 16% (5/31) were multicomponent systems where all the coformers were aromatic carboxylic acids (3 cocrystals and 2 salts). The molecular complementarity between the heteromeric target and the carboxylic acid coformer only results in the formation of primarily either synthon E or F which showed that in order to drive heteromeric synthons over homomeric synthons carboxylic acids provides a reliable avenue to explore (Figure 5.3).

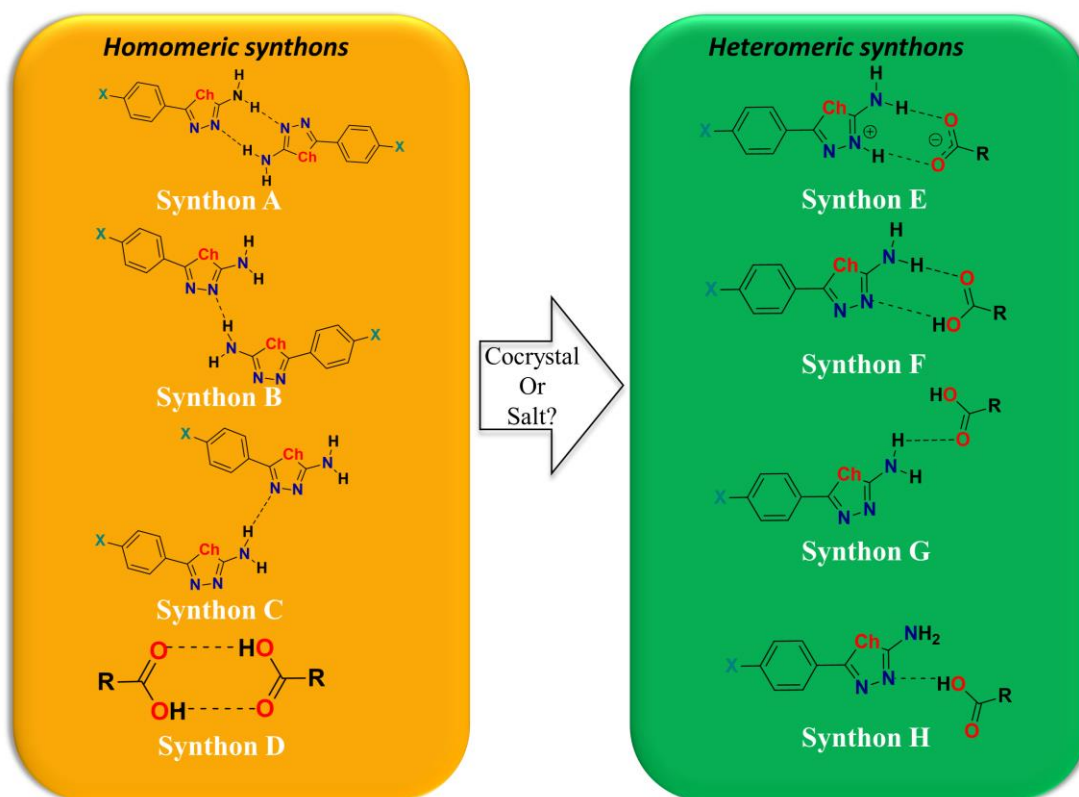


Figure 5.3 Postulated homomeric and heteromeric hydrogen-bond based synthons between chalcogenadiazole and carboxylic acids.

In this chapter we wanted to answer the following questions,

Question 1. What is the synthon preference of the heteromeric system of four unactivated chalcogenadiazoles with carboxylic acid coformers? To address this, a range of carboxylic acids,

both weak and strong along with APIs containing carboxylic acids listed below were used to perform a cocrystal screening (Figure 5.4).

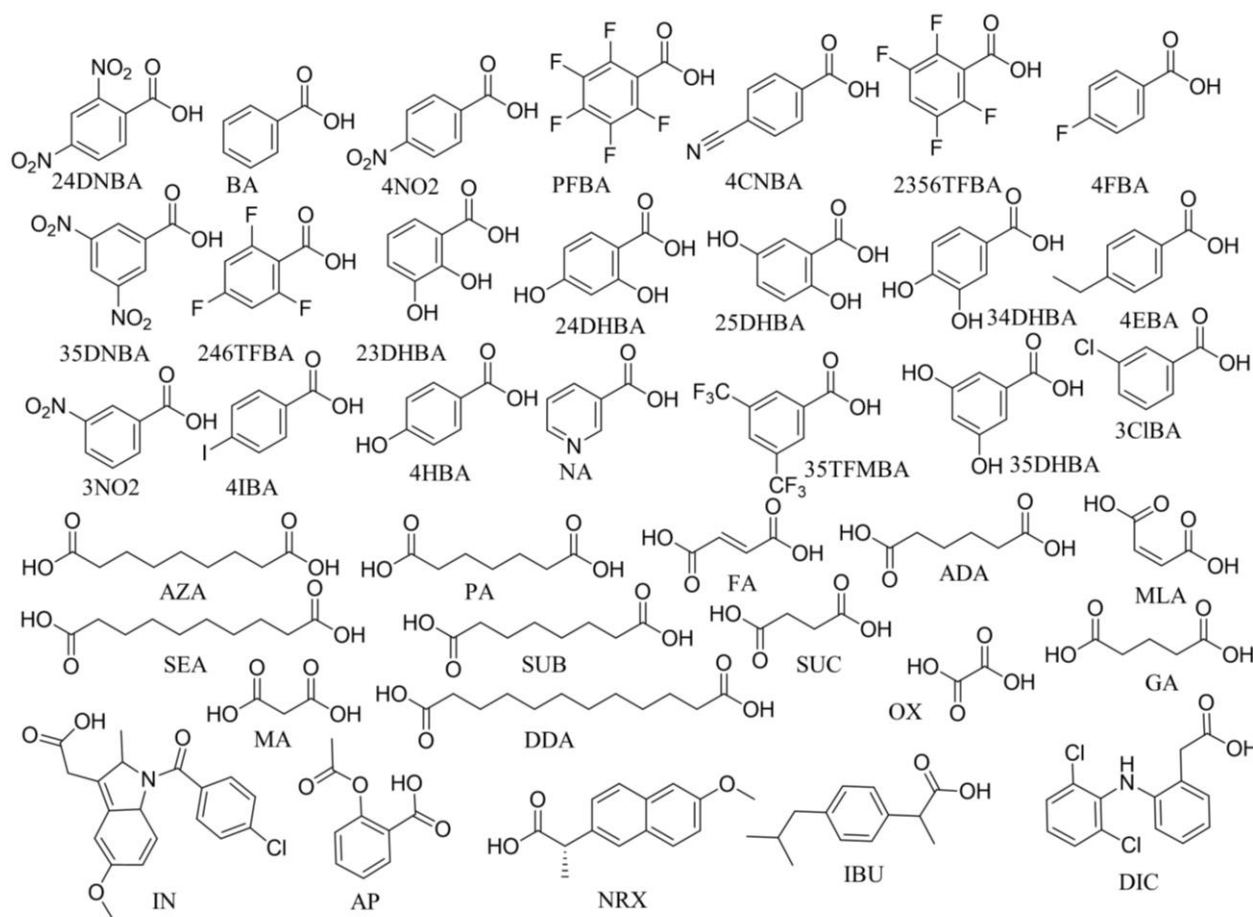


Figure 5.4 List of aromatic, aliphatic and API coformers used.

Question 2. Can we predict the proton transfer between the targets and coformers based on ΔpK_a rule, IR?

Question 3. Can we use computation analysis to predict the proton transfer in chalcogenadiazole derivatives?

Question 4. What is the effect of atom-to-atom replacement (selenium for sulfur) on the crystal structure arrangement of salts and cocrystals?

5.2 Experimental

5.2.1 General

T1-S-Br, **T1-Se-Br**, **T1-S-I**, **T1-Se-I** were synthesized based on previously reported procedures.⁴ All the aliphatic, aromatic, and pharmaceutical carboxylic acid coformers were purchased from commercially available sources and used without further purification. FT-IR spectra of co-crystal screening experiments were recorded with a Nicolet 380 FT-IR spectrophotometer using an attenuated total reflection (ATR) technique on a ZnSe crystal. Melting points were measured using TA instruments DSC Q20 differential scanning calorimeter. Hydrogen-bond energies were calculated using DFT with counterpoise corrected B3LYP/6-311++G** level of theory in vacuum. Single crystal X-ray diffraction data were obtained using a Rigaku XtaLAB Synergy-S with CuK α and MoK α sources.

5.2.2 Synthesis of cocrystals and salts

All four targets were put through a co-crystal screen using liquid-assisted grinding (LAG) in a drop of methanol against twelve aliphatic dicarboxylic acids, twenty-one aromatic acids, and five API carboxylic acids. In all 152 grinding experiments the reactants were mixed in 1:1 stoichiometric ratios, and the solid resulting from each reaction was characterized using IR spectroscopy to determine if a co-crystal or a salt had formed. The IR analysis focused on the positions of readily identifiable vibrational mode of C=O in carboxylic acids, with the corresponding bands in the resulting solids. Shifts greater than five wavenumbers were taken as an indication of co-crystal formation and the disappearance of the C=O stretch was considered to be a result of salt formation.

5.2.3 ΔpK_a calculation

The pK_a values for all the targets and the coformers were calculated using the pK_a prediction tool in *SPARC* online calculator with macro and micro options at 298 K.⁵ ΔpK_a was calculated using the following equation to predict the salt and cocrystal formation.^{6,7}

$$\Delta pK_a = [pK_{a(\text{protonated base})} - pK_{a(\text{acid})}]$$

5.2.4 Computational methods

Computational calculations were done for the neutral restrained and unrestrained heterosynthons for the six coformers that resulted in experimental salt or cocrystal systems. For these systems initial geometry optimization was done with Spartan'14⁸ program package with B3LYP/6-311++G** level of theory under vacuum with and without any constraints on bond lengths. For the coformers with large number of conformers, equilibrium geometry optimization was performed for the most common conformation that was observed for that compound in the CSD database. For the geometry optimized structures, hydrogen bond interaction energies (IE) between the dimers were calculated at the same level of theory similarly to Chapter 2. These IE were corrected for basis set superposition error (BSSE) using counterpoise method. The IE will be employed to establish the predictability of salt and cocrystal formation.

5.2.5 Quantitative measurement of proton transfer

The degree of proton transfer between the coformer Bronsted acid (HA) and the target Bronsted base (B) can generally be assessed based on the equilibrium constant under aqueous media. However, for the experimentally obtained solid-state multicomponent systems, we decided to use the ratio (Q) between the charge assisted interaction energy between the salt and its

conjugated cocrystal system to attempt to predict the possibility of the proton transfer between the acid and the base. Since the equilibrium between the product and the reactants is a result of interaction energies between the ionized species (Synthon E) and the neutral species (Synthon F) the equilibrium constant can be expressed as a ratio (Q) between the interaction energy of the salt (IE_{salt}) and the interaction energy of the cocrystal ($IE_{\text{cocrystal}}$). These calculations were done under both constrained bond lengths of standard neutron values of 1.018 Å for O-H, 1.015 Å for N-H and 1.036 Å for N^+-H and unconstrained systems as shown Figure 5.5 and 5.6.⁹

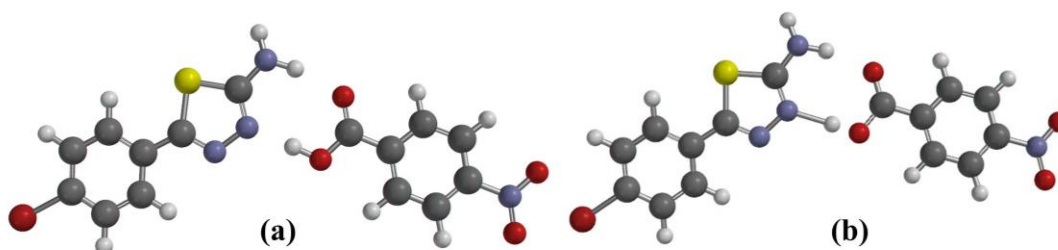


Figure 5.5 Screenshot showing the **T1-S-Br**+4-nitrobenzoic acid **(a)** cocrystal and **(b)** salt system used for optimization without any restrictions on bond lengths.

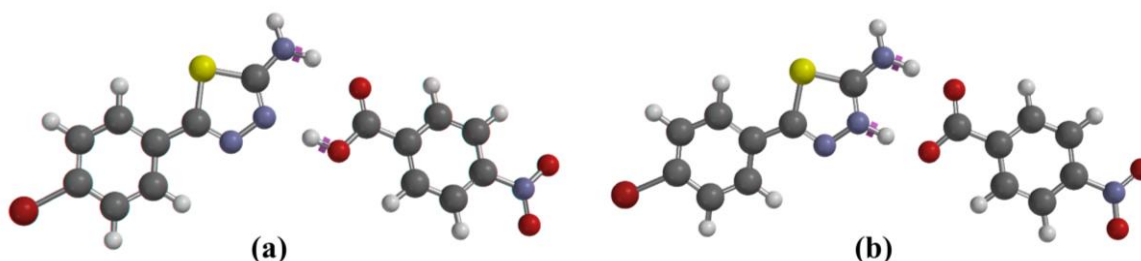


Figure 5.6 Screenshot showing the **T1-S-Br** + 4-nitrobenzoic acid **(a)** cocrystal and **(b)** salt system used for optimization with restrictions on bond lengths.

The magnitude of Q can potentially be used to assess the degree of proton transfer between the coformer Bronsted acid (HA) and the target Bronsted base (B) and determine the ‘tipping point’ between the formation of salt and the cocrystal systems.

5.2.6 Crystal growth

The mixtures obtained from the grinding experiments were dissolved in a minimum amount of methanol (1–2 ml) and heated followed by filtering through a cotton plug and kept in a vial for slow evaporation in order to obtain crystals suitable for single crystal X-ray diffraction. The details of the obtained crystals are summarized in Table 5.1.

Table 5.1 Solvents used for crystal growth and the crystal descriptions

Compound	Code	Solvent	Color and morphology	Melting point °C
5-(4-Bromophenyl)-1,3,4-thiadiazol-2-amine : 4-nitrobenzoic acid	T1-S-Br : 4NO2	Methanol	Colorless, irregular	204-206
5-(4-Iodophenyl)-1,3,4-thiadiazol-2-amine : 4-nitrobenzoic acid	T1-S-I : 4NO2	Dioxane/THF	Colorless, irregular	226-228
5-(4-Bromophenyl)-1,3,4-thiadiazol-2-amine : 4-nitrobenzoic acid	T1-Se-I : 4NO2	Methanol	Colorless, irregular	199-203
5-(4-Bromophenyl)-1,3,4-thiadiazol-2-amine : 2,4-nitrobenzoic acid	T1-S-Br : 24DNBA	Methanol	Yellow, plate	155-160
5-(4-Bromophenyl)-1,3,4-selenadiazol-2-amine : 2,4-nitrobenzoic acid	T1-Se-Br : 24DNBA	Methanol	Light yellow, plate	184-187
5-(4-Iodophenyl)-1,3,4-thiadiazol-2-amine : 2,4-nitrobenzoic acid	T1-S-I : 24DNBA	Methanol/THF	Light yellow, needle	158-163
5-(4-Iodophenyl)-1,3,4-selenadiazol-2-amine : 2,4-nitrobenzoic acid	T1-Se-I : 24DNBA	Methanol	Yellow, plate	190-192
5-(4-Bromophenyl)-1,3,4-selenadiazol-2-amine : 3,5-nitrobenzoic acid	T1-Se-Br : 35DNBA	Methanol	Colorless, Plate	204-206
5-(4-Iodophenyl)-1,3,4-thiadiazol-2-amine : 3,5-nitrobenzoic acid	T1-S-I : 35DNBA	Methanol	Yellow, irregular	219-222
5-(4-Iodophenyl)-1,3,4-selenadiazol-2-amine : 3,5-nitrobenzoic acid	T1-Se-I : 35DNBA	Methanol	Colorless, block	221-223
5-(4-Iodophenyl)-1,3,4-thiadiazol-2-amine : dodecanedioic acid	T1-S-I : DDA	Methanol	Colorless, needle	170-174
5-(4-Bromophenyl)-1,3,4-thiadiazol-2-amine : ibuprofen	T1-S-Br : Ibu	Methanol	Colorless, Plate	136-139
5-(4-Bromophenyl)-1,3,4-thiadiazol-2-amine : pentafluorobenzoic acid	T1-S-Br : PFBA	Methanol	Yellow, Plate	149-151
5-(4-Bromophenyl)-1,3,4-selenadiazol-2-amine : pentafluorobenzoic acid	T1-Se-Br : PFBA	Methanol	Yellow, Plate	160-162
5-(4-Iodophenyl)-1,3,4-thiadiazol-2-amine : pentafluorobenzoic acid	T1-S-I : PFBA	Methanol	Colorless, needle	165-167
5-(4-Iodophenyl)-1,3,4-selenadiazol-2-amine : pentafluorobenzoic acid	T1-Se-I : PFBA	Methanol	Colorless, irregular	170-172

5.3 Results

5.3.1 Cocrystal screening

Table 5.2 IR analysis of C=O stretches of the cocrystal screening

Type	Coformer	Code	Target				Success rate
			T1-S-Br	T1-Se-Br	T1-S-I	T1-Se-I	
Aromatic	3-Chlorobenzoic acid	3ClBA	✓	✓	✓	✓	100%
	3-Nitrobenzoic acid	3NO2	✓	✓	✓	✓	100%
	4-Cyanobenzoic acid	4CNBA	✓	✓	✓	✗	75%
	4-Iodobenzoic acid	4IBA	✗	✗	✗	✗	0%
	4-Ethylbenzoic acid	4EBA	✓	✓	✓	✓	100%
	4-Nitrobenzoic acid	4NO2	✓	✓	✓	✓	100%
	4-Hydroxybenzoic acid	4HBA	✓	✗	✗	✗	25%
	4-Fluorobenzoic acid	4FBA	✓	✗	✓	✓	75%
	2,3-Dihydroxybenzoic acid	23DHBA	✓	✓	✓	✓	100%
	2,4-Dihydroxybenzoic acid	24DHBA	✓	✓	✓	✓	100%
	3,5-Dinitrobenzoic acid	35DNBA	✓	✓	✓	✓	100%
	2,4-Dinitrobenzoic acid	24DNBA	✓	✓	✓	✓	100%
	2,5-Dihydroxybenzoic acid	25DHBA	✗	✓	✗	✓	50%
	3,4-Dihydroxybenzoic acid	34DHBA	✓	✓	✓	✓	100%
	3,5-Dihydroxybenzoic acid	35DHBA	✓	✓	✓	✓	100%
	3,5-(trifluoromethane)benzoic acid	35TFMBA	✗	✗	✓	✗	25%
	2,4,6-Trifluorobenzoic acid	246TFBA	✓	✓	✓	✓	100%
	2,3,5,6-Tetrafluorobenzoic acid	2356TFBA	✓	✓	✓	✓	100%
	Benzoic acid	BA	✓	✓	✓	✓	100%
	Nicotinic acid	NA	✓	✓	✓	✓	100%
	Pentafluorobenzoic acid	PFBA	✓	✓	✓	✓	100%
Aliphatic	Adipic acid	ADA	✓	✓	✓	✓	100%
	Azelaic acid	AZA	✗	✗	✓	✗	25%
	Dodecanedioic acid	DDA	✗	✓	✓	✓	75%
	Fumaric acid	FA	✓	✓	✓	✓	100%
	Glutaric acid	GA	✓	✓	✓	✓	100%
	Maleic acid	MLA	✓	✓	✓	✓	100%
	Malonic acid	MA	✓	✓	✓	✓	100%
	Oxalic acid	OX	✓	✓	✓	✓	100%
	Pimelic acid	PA	✓	✓	✓	✓	100%
	Sebacic acid	SEA	✓	✗	✓	✗	50%
	Suberic acid	SUB	✓	✓	✓	✓	100%

	Succinic acid	SUC	✓	✓	✓	✓	100%
API	Aspirin	AP	✓	✓	✓	✓	100%
	Diclofenac	DIC	✗	✗	✗	✗	0%
	Ibuprofen	IBU	✓	✓	✓	✓	100%
	Indomethacin	IN	✗	✗	✗	✓	25%
	Naproxen	NRX	✓	✓	✓	✓	100%
Positive			31/38	30/38	33/38	31/38	125/152
Success rate			81.5%	78.9%	81.5%	82%	82%

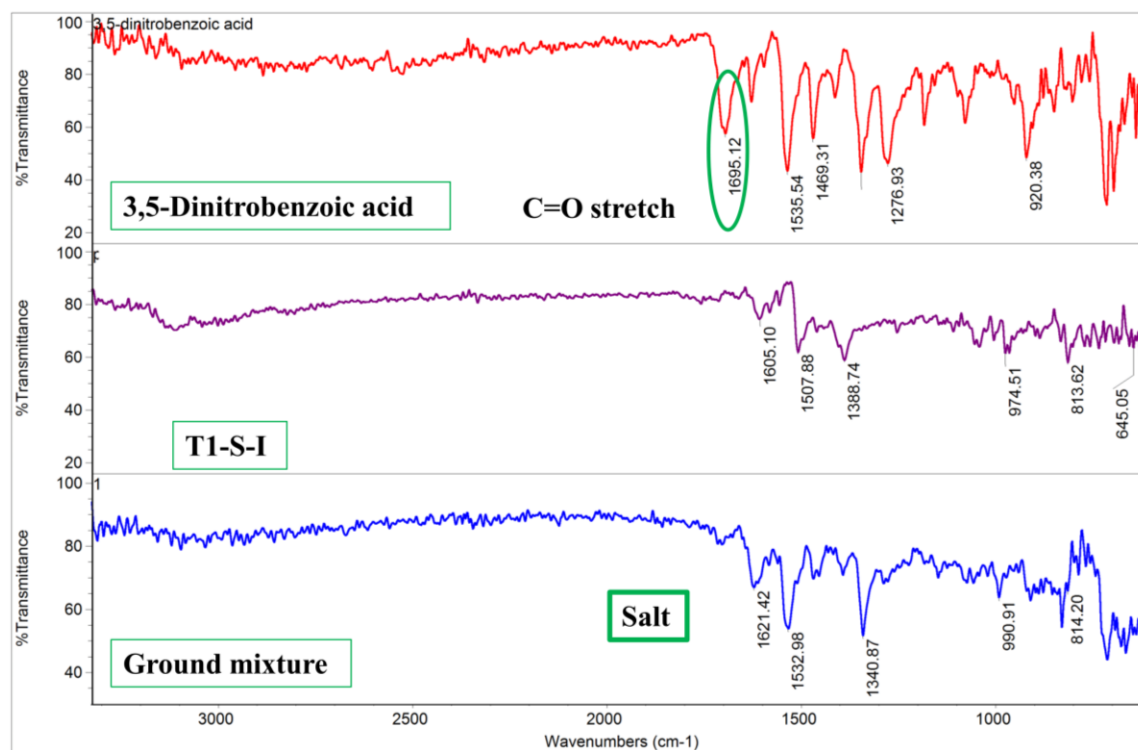


Figure 5.7 Comparison of IR spectra for (red) 3,5-dinitrobenzoic acid with the IR spectra of (purple) **T1-S-I** target against the (blue) ground mixture.

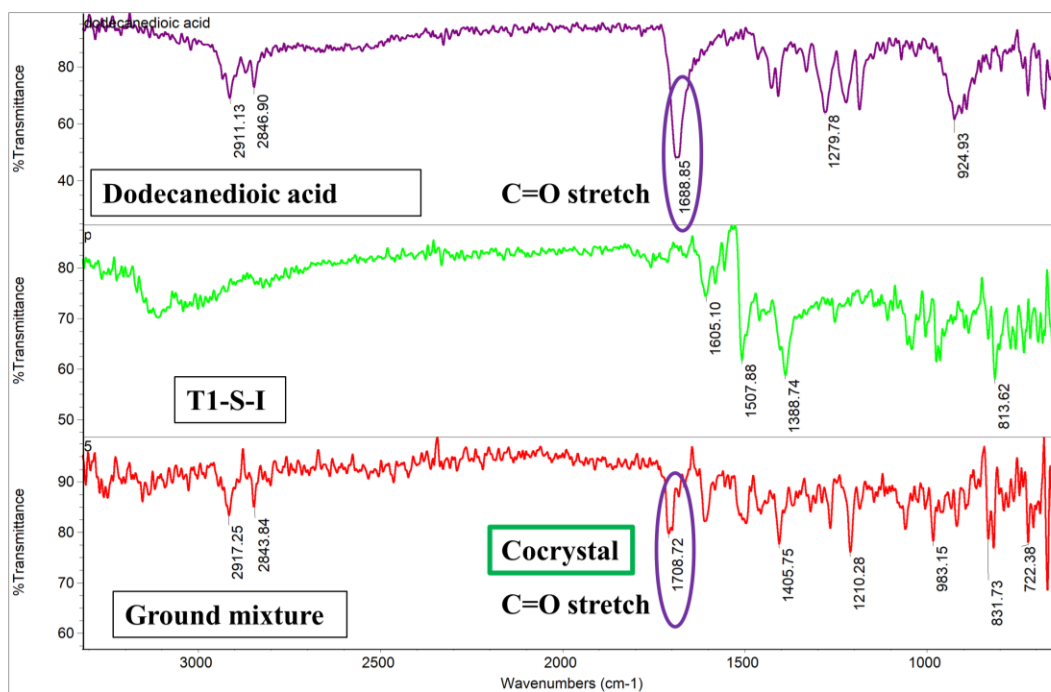


Figure 5.8 Comparison of IR spectra for (purple) dodecanedioic acid with the IR spectra of (green) **T1-S-I** target against the (red) ground mixture.

5.3.2 Crystal structures

5.3.2.1 Crystal structures of cocrystals

Single crystal XRD data for five cocrystals were obtained. All cocrystal structures observed gave rise to primarily $R_2^2(8)$ hydrogen bonded hetero dimer between the target $N-H\cdots O=C$ and the coformer carboxylic acid $O-H\cdots N$ in a 1:1 target/coformer stoichiometric ratio for the aromatic carboxylic acid. For the three 4-nitrobenzoic acid (**4NO2**) cocrystals sulfur targets crystalized in $C2/c$ symmetry and the selenium target in $Pbca$ space group. Interestingly, both sulfur targets were isostructural and had the same hydrogen-bonding interactions and chain $C_1^1(5)$ motif. In both S species, I and Br halogens had the same halogen bonding Type I and a conventional bifurcated interaction, $X\cdots X$ and $X\cdots O$, respectively. Chalcogen bonding (ChB) between $S\cdots O$ were present for both S targets. The only selenium cocrystal was formed with **T1-Se-I** which had the same

$R_2^2(8)$ motif but had discrete $D_1^1(2)$ N-H $\cdots$ N hydrogen bonds. Similarly, to the S, Se cocrystal had a bifurcated XB and a bifurcated Se $\cdots\pi$ ChB (Figure 5.9).

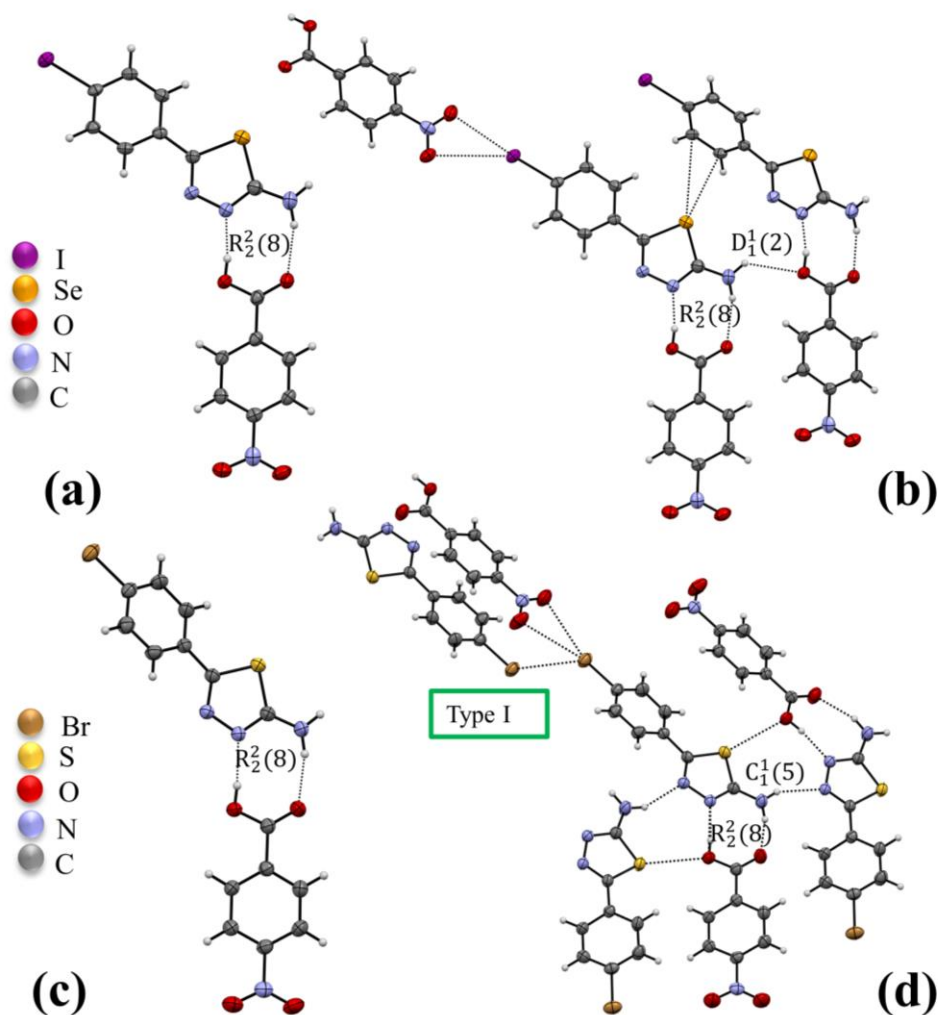


Figure 5.9 Crystals structure of **T1-Se-Br:4NO₂** in Pbca space group and **T1-S-Br:4NO₂**¹⁰ in C2/n space group (a) asymmetric unit (b) secondary interactions.

One cocrystal each, were obtained for **DDA** and **IBU** in a 1:1 stoichiometric ratio. Dodecanedioic acid formed a cocrystal with **T1-S-I** in a P21/c space group and had the $R_2^2(8)$ heteromeric hydrogen bonded motif and $C_1^1(5)$ NH $\cdots$ N chains. The iodine formed a Type I XB between X $\cdots$ X and the sulfur formed a bifurcated ChB between S $\cdots$ N and S $\cdots$ O. Only **T1-S-Br**

formed a cocrystal with ibuprofen and except for the lack of any XB from Br all other primary and secondary interactions obtained were the same.

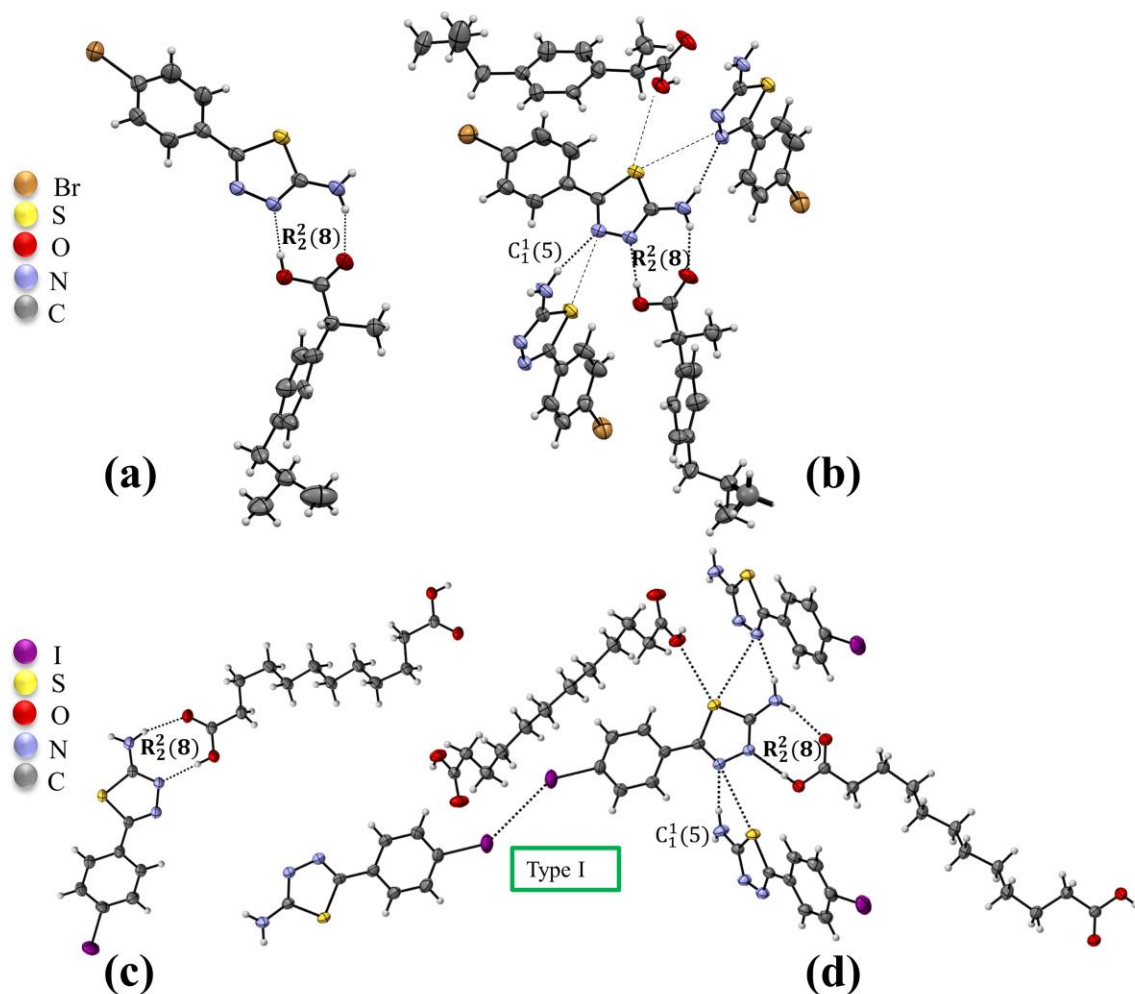


Figure 5.10 Crystals structure of **T-S-Br:IBU** in $Pca2_1$ space group and **T1-S-I:DDA** in $P21/c$ space group (a) asymmetric unit (b) secondary interactions.

5.3.2.2 Crystal structures of salts

A total of ten salt structures were obtained all with aromatic carboxylic acids in a 1:1 target/coformer stoichiometric ratio. Unlike in the case of cocrystals a proton transfer was observed between the COOH and the chalcogenadiazoles heterocycle leading to a charge assisted robust $R_2^2(8)$ ring motif formed between $N-H^+ \cdots O^-$ and $N-H \cdots O$. All the salts obtained with the

pentafluorobenzoic acid (**PFBA**) crystallized in $P 2_12_12_1$ space group regardless of the type of atom-to-atom substitution present and were isostructural. In addition to the primary HB motif there was discrete $D_1^1(2)$ N-H $\cdots$ O HB, S $\cdots$ O ChB and a Br $\cdots$ O Type II XB. Isostructural crystal structures were observed for the four salts obtained with 3,5-dinitrobenzoic acid (**35DN**) in $P21/c$ space group. Unlike the previous structures, these had additional $R_4^2(8)$ and $R_4^4(16)$ HB motif, a XB between Br $\cdots$ O-C and a ChB with S $\cdots$ O-N (Figure 5.11).

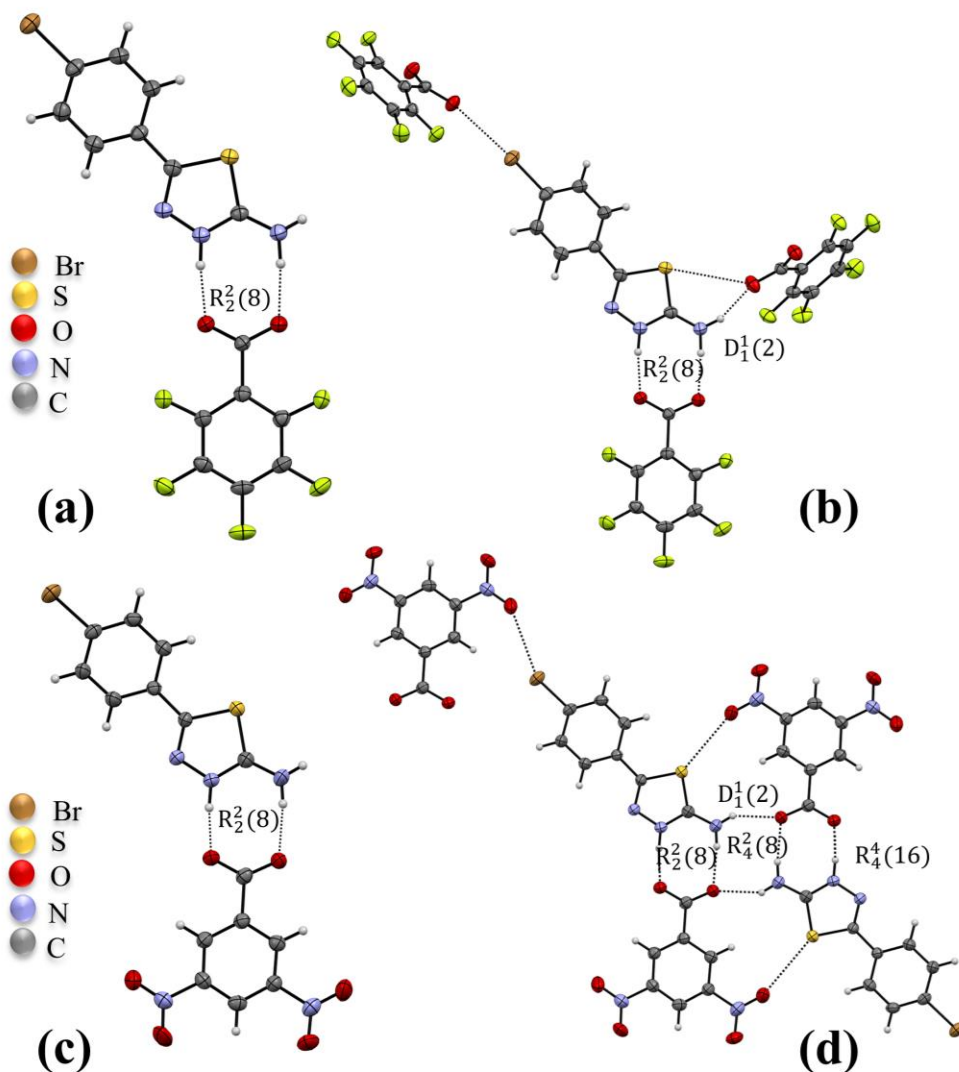


Figure 5.11 Crystals structure of **T1-S-Br:PFBA** in $P2_12_12_1$ space group and **T1-S-Br:35DNBA**¹¹ in $P21/c$ space group (a) asymmetric unit (b) secondary interactions.

The crystal structures of 2,4-dinitrobenzoic acid salts crystallized in either $P2_{1/n}$ or $P_{\bar{1}}$. Three structures, **T1-S-Br**, **T1-S-I** and **T1-Se-I** crystallized in $P2_{1/n}$ space group and both iodo species had a disordered methanol molecule which was masked for clarity. All three were isostructural and had $D_1^1(2)$ N-H $\cdots$ O-C HB motif, X $\cdots$ O-N XB and bifurcated S/Se $\cdots$ O-N ChB. The **T1-Se-Br** had a disordered benzene ring and crystallized in $P_{\bar{1}}$ space group that lacked any XB but contained bifurcated Se $\cdots$ O-N ChB and HB arrangement similar to **35DN** salts.

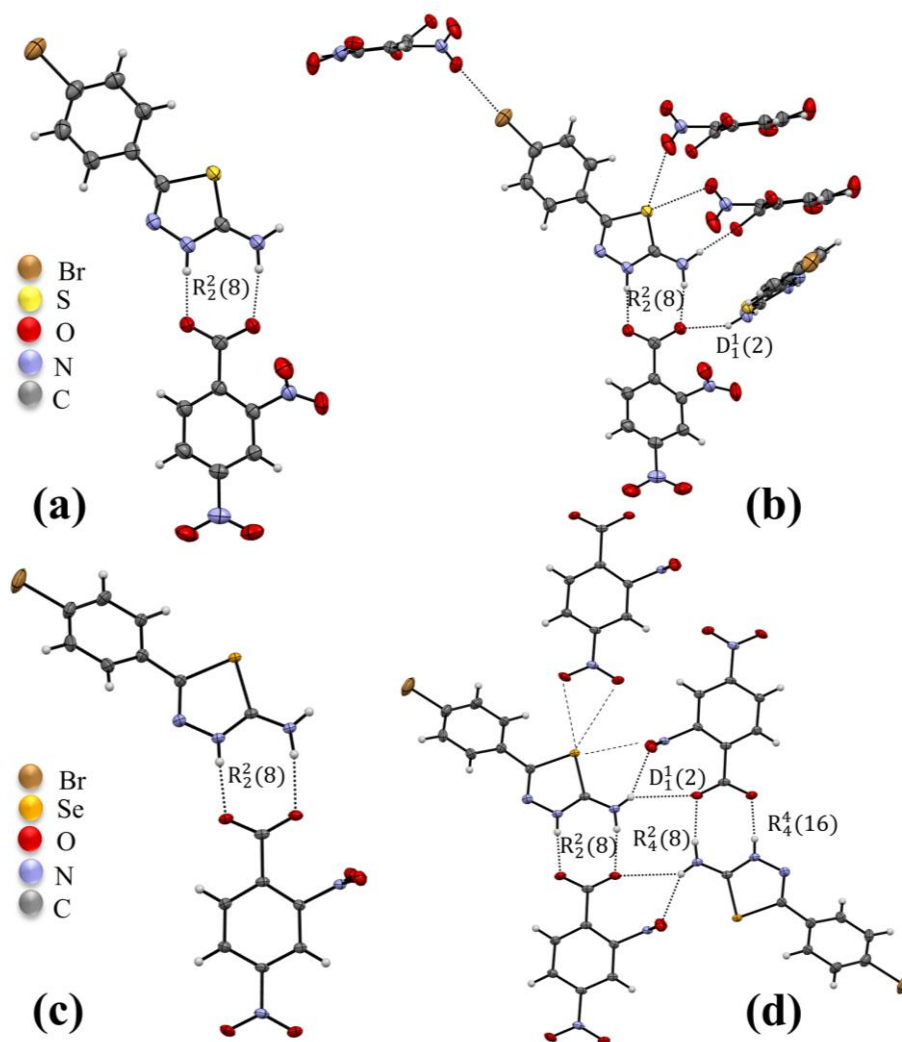


Figure 5.12 Crystals structure of **T1-S-Br:24DNBA** in $P2_{1/n}$ space group and **T1-Se-Br:24DNBA** in $P_{\bar{1}}$ space group (a) asymmetric unit (b) secondary interactions.

5.4 Discussion

5.4.1 Analysis of 1,3,4-chalcogenadiazole-carboxylic acid salt and cocrystal using

FT-IR

A heteromeric interaction between a carboxylic acid and 2-amino-1,3,4-chalcogenadiazole can either result in a salt or cocrystal which can be distinguished based on the specific stretches observed for target and the coformer. In general, free monomeric carboxylic acids have a strong C=O stretch around $1670\text{--}1710\text{ cm}^{-1}$ and when a cocrystal is formed this value shifts which is indicative of the disruption of the homomeric hydrogen bonds and the formation of heteromeric hydrogen bonds during co-crystallization (shifts > 4 or 5 cm^{-1} considered a positive result). For a salt due to transfer of the proton from the carboxylic acid to the target base the resulting COO^- anion lead to a strong asymmetric C-O stretch near $1650\text{--}1550\text{ cm}^{-1}$ and a weak symmetrical stretch around 1400 cm^{-1} .¹² The disappearance of the strong C=O stretch of a carboxylic acid is distinct feature of the salt formation when performing grinding experiments. The higher success rate of the interactions between the target and the coformer can be traced to molecular complementarity (Figure 5.13).

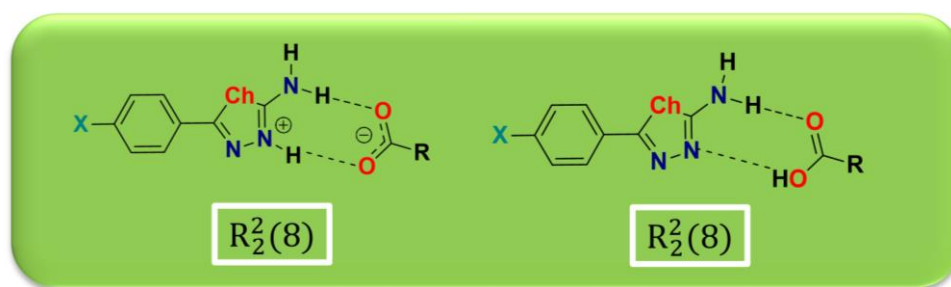


Figure 5.13 Molecular complementarity between heteromeric salt and cocrystal forms.

A summary of the analysis of IR spectra obtained for the specific salt and cocrystal screening is shown Figure 5.14. For the employed combination of carboxylic acids, only strong

aromatic carboxylic acids resulted in salts (19%), weaker aliphatic acids gave cocrystals (60-100%) and APIs also primarily produced cocrystals (60-80%).

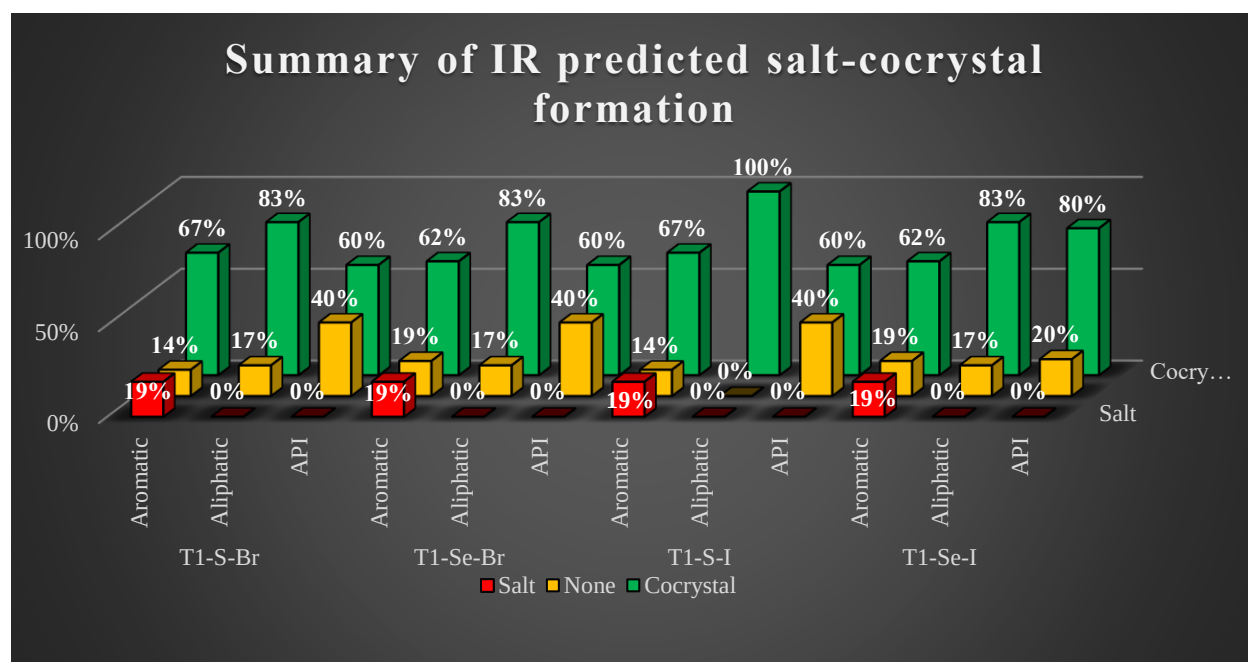


Figure 5.14 Summary of IR predicted salt and cocrystal formation with carboxylic acids.

5.4.2 Predicting salt and cocrystal using the ΔpK_a 'rule'

A common tool for predicting the proton transfer between target base and a coformer acid in crystal engineering is the ΔpK_a rule^{6,7}. In general, a proton transfer will occur when the pK_a difference between the acid and the conjugated acid is greater than 4 and a cocrystal will form when that value is less than -1. In-between 4 and -1 lies the salt-cocrystal continuum in which either a salt or a cocrystal could form. The dependency of the pK_a value on the solvent used and the specific target involved makes it difficult to predict the boundary between the salt and cocrystal.

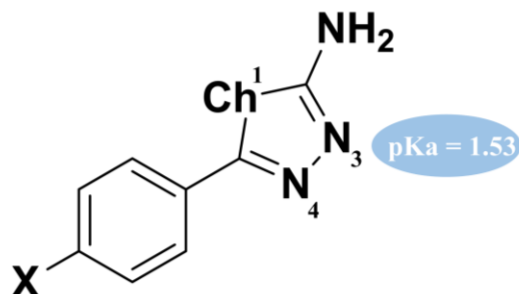


Figure 5.15 *SPARC* predicted average pKa value of the N3.

In this study, the pKa values calculated using *SPARC* is given in Table 5.3 along with the calculated Δ pKa values. For the four specified targets, formation of heteromeric dimer occurs through N3 acceptor, hence the pKa of that specific nitrogen was considered when calculating the Δ pKa. *SPARC* only allow calculations for S analogs and not Se, however for **T1-S-Br** and **T1-S-I**, the calculated pKa values were almost the same hence an average pKa value was used for all the targets when doing the Δ pKa calculation (Figure 5.15). For the four target molecules, the estimated Δ pKa differences suggest that 72% have a Δ pKa < -1 and 18% have $-1 < \Delta$ pKa < 4 and none have Δ pKa > 4. These data suggests that for 2-amino-1,3,4-chalcogenadiazole targets Δ pKa rule of thumb have proven to be invalid as the data suggest that majority of these should lead to cocrystals instead of salts even for extremely strong acids.

Table 5.3 *SPARC* calculated Δ pKa values

Type	Code	SPARC pKa	Δ pKa	Prediction
Aromatic	3CIBA	3.6	-2.07	Cocrystal
	3NO2	3.19	-1.66	Cocrystal
	4CNBA	3.35	-1.82	Cocrystal
	4IBA	3.65	-2.12	Cocrystal
	4EBA	4.2	-2.67	Cocrystal
	4NO2	3.21	-1.68	Cocrystal
	4HBA	4.17	-2.64	Cocrystal

	4FBA	3.79	-2.26	Cocrystal
	23DHBA	2.98	-1.45	Cocrystal
	24DHBA	3.22	-1.69	Cocrystal
	35DNBA	2.36	-0.83	Cocrystal/Salt
	24DNBA	1.78	-0.25	Cocrystal/Salt
	25DHBA	2.99	-1.46	Cocrystal
	34DHBA	4.08	-2.55	Cocrystal
	35DHBA	3.85	-2.32	Cocrystal
	35TFMBA	2.97	-1.44	Cocrystal
	246TFBA	2.19	-0.66	Cocrystal/Salt
	2356TFBA	1.7	-0.17	Cocrystal/Salt
	BA	4.03	-2.5	Cocrystal
	NA	1.86	-0.33	Cocrystal/Salt
	PFBA	1.46	0.07	Cocrystal/Salt
Aliphatic	ADA	4.65	-3.12	Cocrystal
	AZA	4.74	-3.21	Cocrystal
	DDA	4.45	-2.92	Cocrystal
	FA	3.17	-1.64	Cocrystal
	GA	4.21	-2.68	Cocrystal
	MLA	3.17	-1.64	Cocrystal
	MA	2.67	-1.14	Cocrystal
	OX	1.3	0.23	Cocrystal/Salt
	PA	4.41	-2.88	Cocrystal
	SEA	4.45	-2.92	Cocrystal
	SUB	4.43	-2.9	Cocrystal
	SUC	3.97	-2.44	Cocrystal
API	AP	3.63	-2.1	Cocrystal
	DIC	4.12	-2.59	Cocrystal
	IBU	4.53	-3	Cocrystal
	IN	4.66	-3.13	Cocrystal
	NRX	4.5	-2.97	Cocrystal

5.4.3 Determining proton transfer using ΔD_{C-O}

As observed with the FT-IR, differentiating between the COOH and COO⁻ functional groups can also be done based on the SC-XRD data. For the multicomponent salts and cocrystals with carboxylic acids the difference between the bond lengths of the two C-O bonds (ΔD_{C-O}) provides a useful parameter for determining the salt and cocrystal formation as it is an indication of the proton transfer between the heteromeric system. When the difference between C-O bond

lengths is less than 0.03 Å a salt is formed and when the difference is greater than 0.08 Å a cocrystal is formed. The ΔD_{C-O} values are summarized in the Table 5.4.

Table 5.4 Distribution of C-O bond lengths of single crystal structures obtained

Salt/Cocrystal	ΔD_{C-O} Å				Proton Transfer
	T1-S-Br	T1-Se-Br	T1-S-I	T1-Se-I	
35DNBA	0.018	0.002	0.021	0.012	Yes
PFBA	0.001	0.016	0.007	0.005	Yes
24DNBA	0.001	0.015	0.004	0.006	Yes
4NO2	0.092	-	0.088	0.083	No
DDA	-	-	0.109	-	No
IBU	0.118	-	-	-	No

5.4.4 Defining proton transfer based on the Q value

The third question in this study was directed towards identifying the different protocols that can be employed in determining the salt and cocrystal formation. So far FT-IR and ΔD_{C-O} satisfied the need of the predictability of the proton transfer in multicomponent systems with considerable accuracy. Optimization of the heteromeric system under unrestricted bond lengths led to lengthening of N-H bonds in a few systems, hence the restricted optimization and single point energy calculation was done. Analysis of the Q values using both restricted and unrestricted bond lengths of the heteromeric systems resulted in a two different outcome as shown in the table (calculated IE values are given in appendix E).

Table 5.5 Summary of calculated Q values without bond length restrictions

Salt/Cocrystal	ΔpK_a	$Q = IE_{\text{salt}} / IE_{\text{cocrystal}}$				Q prediction	Experimental result
		T1-S-Br	T1-S-I	T1-Se-Br	T1-Se-I		
35DNBA	-0.86	6.90	6.94	6.79	6.92	Salt	Salt
PFBA	0.07	6.98	6.97	6.91	6.98	Salt	Salt
24DNBA	-0.25	5.86	5.88	5.63	5.66	Salt	Salt
4NO2	-1.68	7.27	7.30	7.20	7.24	Cocrystal	Cocrystal
DDA	-2.92	7.75	7.83	7.71	7.70	Cocrystal	Cocrystal
IBU	-3	7.71	7.78	7.65	7.75	Cocrystal	Cocrystal

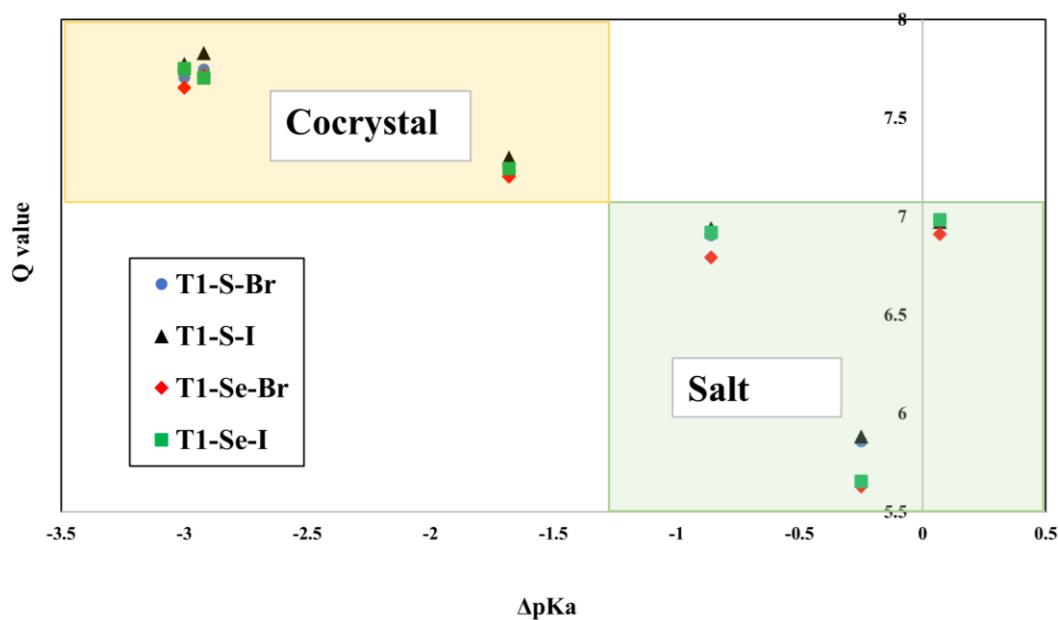


Figure 5.16 Summary of distribution of calculated Q values without bond length restrictions against ΔpK_a values.

Table 5.6 Summary of calculated Q values with bond length restrictions

Salt/Cocrystal	ΔpK_a	$Q = IE_{\text{salt}} / IE_{\text{cocrystal}}$				Q prediction	Experimental result
		T1-S-Br	T1-S-I	T1-Se-Br	T1-Se-I		
35DNBA	-0.86	5.86	5.87	5.72	5.87	×	Salt
PFBA	0.07	5.77	5.74	5.62	5.67	×	Salt
24DNBA	-0.25	5.69	5.73	5.58	5.59	×	Salt
4NO2	-1.68	5.89	5.88	5.73	5.76	×	Cocrystal
DDA	-2.92	5.92	5.95	5.78	5.75	×	Cocrystal
IBU	-3	5.91	5.87	5.76	5.83	×	Cocrystal

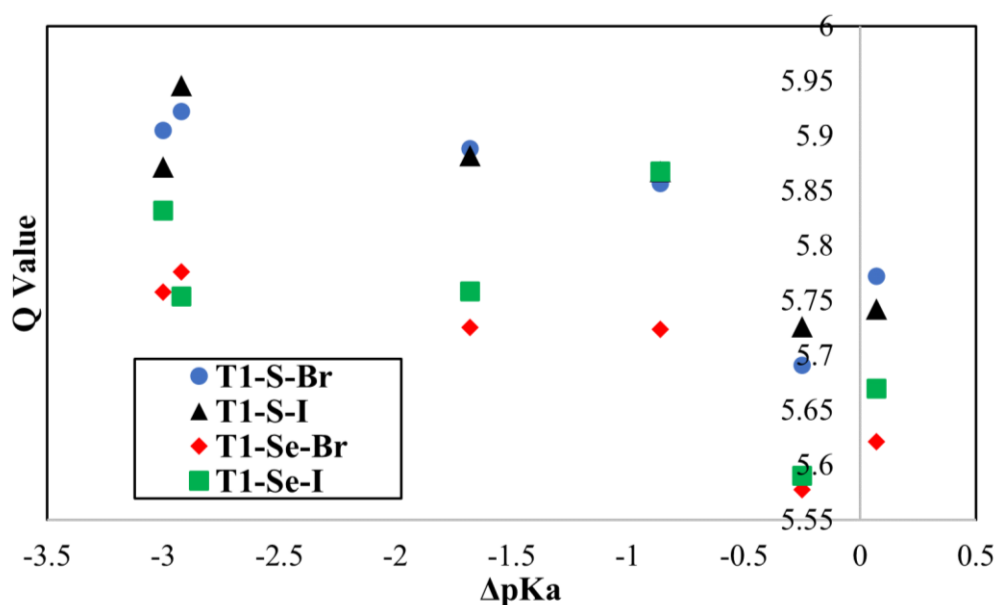


Figure 5.17 Summary of distribution of calculated Q values with bond length restrictions against ΔpK_a values.

The Q values based on unconstrained systems clearly show the tipping point of the proton transfer between the acid and the base which was determined to be “7.1”. Below the 7.1 lies the region of salt and above lies the domain of cocrystals. In the constrained systems Q values did not show a clear separation and a tipping point cannot be clearly recognized.

5.5 Conclusions

The use of carboxylic acid coformers for the cocrystal screening resulted in an overall success rate of 82% and individual success rate of 83.33%, 88% and 65% for aromatic, aliphatic and APIs respectively (Figure 5.18). Higher success rate in cocrystal screening was achieved by employing molecular complementarity which has a higher preference for heteromeric interactions over the homomeric interactions.

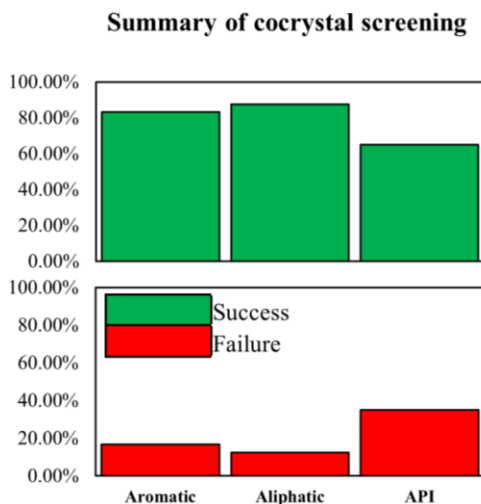


Figure 5.18 Success rate of co-crystallization experiments against aromatic, aliphatic and API carboxylic acids.

Analysis of the ΔpK_a values showed that 72% of these experiments should result in cocrystals while the rest was in the salt cocrystal continuum. However, the analysis of the crystal structures based on the $\Delta D_{C=O}$ in fact confirmed the proton transfer for strong aromatic acid and target pairs which suggest that the ΔpK_a rule doesn't correlate well with the predictability of proton transfer in 1,3,4-chalcogenadiazole systems. On the other hand, cocrystal screening experiments using FT-IR data succeeded in identifying the disappearance of the C=O stretch of acids around 1700 cm^{-1} for some systems that suggest a proton transfer while for the cocrystals only observable IR change was the shift in C=O stretch. Upon carrying out DFT calculation for the IE values and the Q values for the unrestricted systems a noticeable separation between the salt and cocrystal systems was visible which was identified as a cutoff point for the proton transfer process.

Finally, it was also observed that the atom-to-atom substitution has affected the crystal packing of salts and the cocrystals differently. All the salts obtained for **35DNBA**, **PFBA** were isostructural (with the exception of **24DNBA**) regardless of the halogen or the chalcogen atom

present in the target molecule however for the cocrystals of **4NO₂**, it was observed that atom-to-atom substitution has led to different crystal packing arrangements and the loss of isostructural properties between the S and Se species. For the **IBU** and **DDA**, only one cocrystal of each was obtained hence evidence of the atom-to-atom substitution affecting the crystal structure was not conclusive.

5.6 References

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Chapter 6 – Competition between chalcogen and halogen bonding in isostructural species

6.1 Introduction

The design of functional materials requires a solid understanding of the underlying intermolecular forces involved in the solid-state assembly of molecules.¹⁻⁴ In Chapter 4, we explored the structural landscape of the 2-amino-1,3,4-chalcogenadiazole derivatives and the balance between intermolecular interactions. The atom-to-atom substitution of these chalcogenadiazoles derivatives were successfully employed in altering the balance between hydrogen, halogen and chalcogen bonding.⁵ Physiochemical and biological properties of these derivatives can be related to molecular structures and unique abilities for forming a variety of structure directing intermolecular interactions.⁶ One of the many issues that can prevent potential pharmaceutically active species such as the chalcogenadiazoles derivatives studied in Chapter 4, from realizing their practical potential is a suboptimal aqueous solubility.^{7,8} In order to better understand how molecular structure directly connects to specific physical properties of the bulk materials, it is therefore critically important to fully explore the structural landscape of this family of compounds, Fig. 6.1.

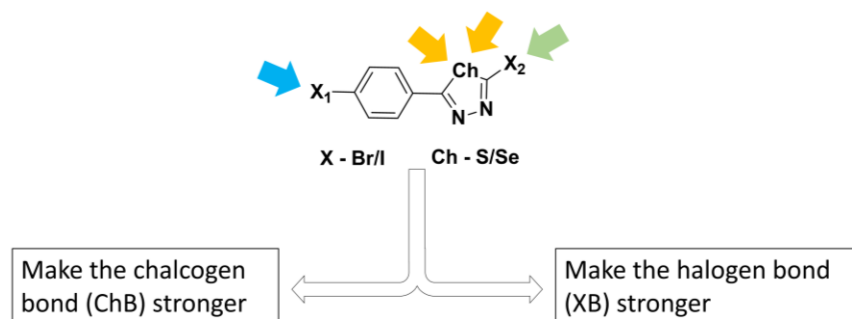


Figure 6.1 Depiction of the designed molecule and fine-tuning the balance between ChBs and XBs.

In order to map out the competing nature of the halogen and chalcogen bonds, a diverse set of targets were synthesized by substituting the amine group with halogen atom which prevents the hydrogen donor ability and creates the structural complexity to facilitate chalcogen and halogen bonding as intended. Through this strategy we built our target library; 2-iodo-5-(4-iodophenyl)-1,3,4-thiadiazole, **T1**, 2-bromo-5-(4-bromophenyl)-1,3,4-selenadiazole, **T2**, 2-bromo-5-(4-iodophenyl)-1,3,4-selenadiazole, **T3**, and 2-bromo-5-(4-iodophenyl)-1,3,4-thiadiazole, **T4**, 2-bromo-5-(4-bromophenyl)-1,3,4-thiadiazole, **T5**, Fig. 6.2.

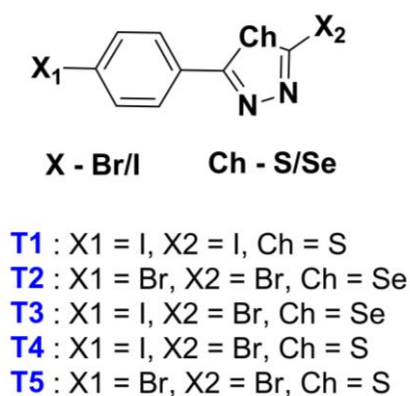


Figure 6.2 Synthesized target library.

By systematically contrasting and comparing the structural data for the compounds in this series we are trying to answer the following questions,

Question 1. How does changing the amine group into halogens affect the crystal structures?

Question 2. Can we alter and control the balance between chalcogen and halogen bonding?

Question 3. Can we use MEPs and energy frameworks to predict the directionality and the strength of these intermolecular interactions?

Question 4. How do these structural changes affect the physiochemical properties?

6.2 Experimental

6.2.1 General

Commercial reagents and solvents were purchased from commercially available sources and used without further purification. Melting points were measured using a TA instruments DSC Q20 differential scanning calorimeter. Nuclear magnetic resonance (NMR) data were measured on a Bruker Ascend 400 MHz spectrometer. The residual solvent peak was used as the internal reference for ^1H NMR. Single crystal X-ray diffraction data were collected using a Rigaku XtaLAB Synergy-S diffractometer and the structures were solved using Olex2⁹ with SHELXT¹⁰. All computational calculations were performed using Spartan14 software package.

6.2.2 Computational calculations

6.2.2.1 Molecular electrostatic potential maps

Molecular electrostatic potentials were calculated using Spartan14 Wavefunction. The compounds were sketched and saved using ChemDraw 12 and loaded into Spartan14¹¹ software followed by geometry optimization using density functional theory B3LYP hybrid functional and 6-311++G** basis set. A positive point charge in the vacuum was used as a probe against the surface to determine the positive and negative regions on the molecular surface. The electrostatic potentials are given in kJ/mol, and a negative number is representative of an electron-rich acceptor and a positive number of an electron-poor donor.

6.2.2.2 Energy frameworks calculations and Hirshfeld surface analysis

The crystallographic information file (cif) obtained by solving the single crystal X-ray diffraction data was used as the input file for CrystalExplorer17.5¹² software for performing energy

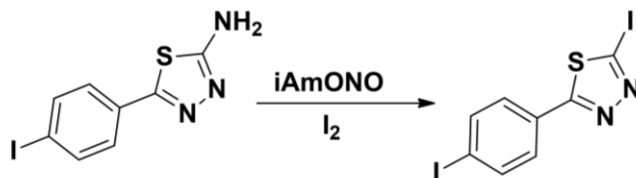
frameworks calculations. The interaction energies between molecules are calculated by first defining a sphere with a 3.80 Å radius around a center molecule and the fragments of all the molecules within that sphere were then completed and the energy frameworks calculation was performed using Tonto program and B3LYP/6-311G(d,p) level of theory for bromo derivatives and B3LYP/DGDZVP level of theory for iodo derivatives. The size and the color of the cylinders connecting the molecules represented the type and the magnitude of the interaction.

Hirshfeld surface is the visualization of the electron density of a molecule in a crystal structure which is partitioned into molecular fragments. It is derived from Hirshfeld's molecular weight function and determined based on the electron density of the molecule of interest (promolecule) and the influence of the surrounding molecules to provide information on intermolecular interactions.^{13,14} 2D fingerprint plots are obtained based on the Hirshfeld surface and provides a unique 'fingerprint' of the quantitative contributions of the intermolecular interactions. The information obtained from Hirshfeld surface on d_i showing the distance from the Hirshfeld surface to the nearest nucleus inside the surface and d_e representing the distance to the nearest nucleus outside the surface and mapping d_i with d_e , 2D fingerprint plots are obtained.¹³

Hirshfeld surfaces and fingerprint plots were generated using B3LYP/6-311G(d,p) level of theory for bromo derivatives and B3LYP/DGDZVP level of theory for iodo derivatives. The 2D fingerprint plots were recorded with d_i Vs d_e , expanded range, Isovalue : 0.5 and Quality : High.

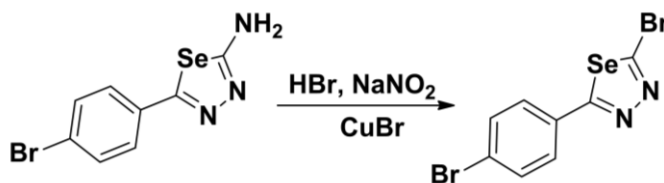
6.2.3 Synthesis

6.2.3.1 Synthesis of 2-iodo-5-(4-iodophenyl)-1,3,4-thiadiazole (T1)



The relevant 5-(4-iodophenyl)-1,3,4-thiadiazol-2-amine (ca. 1 mmol) was dissolved in acetonitrile (4 ml) and dichloromethane (1 ml), and the resulting solution cooled to 0 °C. To this, isopentyl nitrite (0.4 ml) was added, followed by the addition of iodine (1 mmol) in acetonitrile. Dimethylformamide (1–2 ml) was added to the mixture, which was stirred overnight. To this, saturated NaHSO₃ was added, and the product was extracted with dichloromethane (DCM). The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The crude product was washed with diethyl ether to obtain the pure product. The product was an orange solid. Yield 52%. Mp:182-187 ° C. ¹H NMR (400 MHz, DMSO-d₆) δ 7.94 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H).

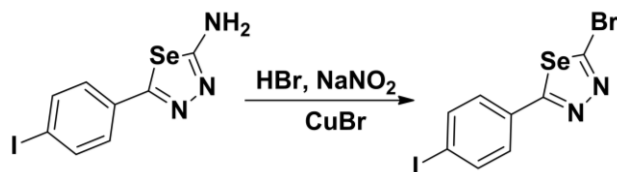
6.2.3.2 Synthesis of 2-bromo-5-(4-bromophenyl)-1,3,4-selenadiazole (T2)



The 5-(4-bromophenyl)-1,3,4-selenadiazol-2-amine (1 mmol) was added to a stirred solution of excess hydrobromic acid (15 mmol) at room temperature and water (2 ml) was added to the resulting slurry. This mixture was cooled to 0 °C in an ice bath and copper(I) bromide (1 mmol) was added. Sodium nitrite (1.2 mmol) was dissolved in water (2 ml) and added to the slurry dropwise, followed by stirring for another 30 min. The mixture was neutralized with saturated sodium bicarbonate and the product was extracted with DCM. The organic layer was dried, and

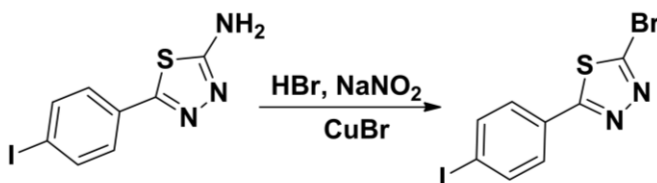
the product was purified with column chromatography. The pure product was orange solid. Yield 80%. Mp: 148-152 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 7.90 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H).

6.2.3.3 Synthesis of 2-bromo-5-(4-iodophenyl)-1,3,4-selenadiazole (T3)



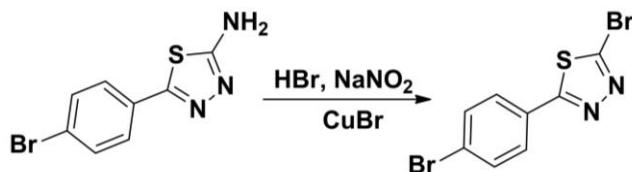
The 5-(4-iodophenyl)-1,3,4-selenadiazol-2-amine (1 mmol) was added to a stirred solution of excess hydrobromic acid (15 mmol) at room temperature and water (2 ml) was added to the resulting slurry. This mixture was cooled to 0 °C in an ice bath and copper(I) bromide (1 mmol) was added. Sodium nitrite (1.2 mmol) was dissolved in water (2 ml) and added to the slurry dropwise, followed by stirring for another 30 min. The mixture was neutralized with saturated sodium bicarbonate and the product was extracted with DCM. The organic layer was dried, and the product was purified with column chromatography. The pure product was a yellow solid. Yield 78%. Mp: 149-155 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 7.91 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H).

6.2.3.4 Synthesis of 2-bromo-5-(4-iodophenyl)-1,3,4-thiadiazole (T4)



The 5-(4-iodophenyl)-1,3,4-thiadiazol-2-amine (1 mmol) was added to a stirred solution of excess hydrobromic acid (15 mmol) at room temperature, and water (2 ml) was added to the resulting slurry. This mixture was cooled to 0 °C in an ice bath and copper(I) bromide (1 mmol) was added. Sodium nitrite (1.2 mmol) was dissolved in water (2 ml) and added to the slurry dropwise, followed by stirring for another 30 min. The mixture was neutralized with saturated sodium bicarbonate and the product was extracted with DCM. The organic layer was dried, and the product was purified with column chromatography. The pure product was a yellow solid. Yield 78%. Mp: 143-148 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 7.95 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H).

6.2.3.5 Synthesis of 2-bromo-5-(4-bromophenyl)-1,3,4-thiadiazole (T5)



The 5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine (1 mmol) was added to a stirred solution of excess hydrobromic acid (15 mmol) at room temperature and water (2 ml) was added to the resulting slurry. This mixture was cooled to 0 °C in an ice bath and copper(I) bromide (1 mmol) was added. Sodium nitrite (1.2 mmol) was dissolved in water (2 ml) and added to the slurry dropwise, followed by stirring for another 30 min. The mixture was neutralized with saturated sodium bicarbonate and the product was extracted with DCM. The organic layer was dried, and the product was purified with column chromatography. The pure product was an orange solid. Yield 67%. Mp: 133-138 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 7.91 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H).

6.2.4 Crystal growth

The targets were recrystallized from different solvents using slow evaporation to obtain singles crystals suitable for single crystal X-ray diffraction (SC-XRD), Table 6.1.

Table 6.1 Solvents used for crystal growth and crystal descriptions

Compound	Code	Solvent	Color and morphology	Melting point °C
2-iodo-5-(4-iodophenyl)-1,3,4-thiadiazole	T1	Dioxane	colorless, block	182-187
2-bromo-5-(4-bromophenyl)-1,3,4-selenadiazole	T2	Dioxane	orange, irregular	148-152
2-bromo-5-(4-iodophenyl)-1,3,4-selenadiazole	T3	THF	clear light yellow, plate	149-155
2-bromo-5-(4-iodophenyl)-1,3,4-thiadiazole	T4	THF	colorless, plate	143-148
2-bromo-5-(4-bromophenyl)-1,3,4-thiadiazole	T5	Ethyl acetate	orange, irregular	133-138

6.3 Results and Discussion

6.3.1 Single crystal structures

T1–T5 all crystallized in the space group *Pbca* and were isostructural. In the structure of **T1**, the I atom at the 2-position of the chalcogenadiazole ring forms a halogen bond (XB) in which the I atom in the para position of the arene ring acts as the XB acceptor, which leads to a zigzag arrangement in the crystal structure (Figure 6.3). This Type of XB is observed for all five targets. The para-halogen atoms display, in all cases except for **T1** and **T5**, short contacts with the π -electron cloud on the arene ring, as the molecular structure does not facilitate conventional XB formation. In **T1**, however, the geometrical features allow the para-I atom to form an XB with the π -electron cloud of the arene ring with a bond distance of 3.368(4) Å and an angle of 89.8(3)°, leading to a more compact crystal packing (Figure 6.4).

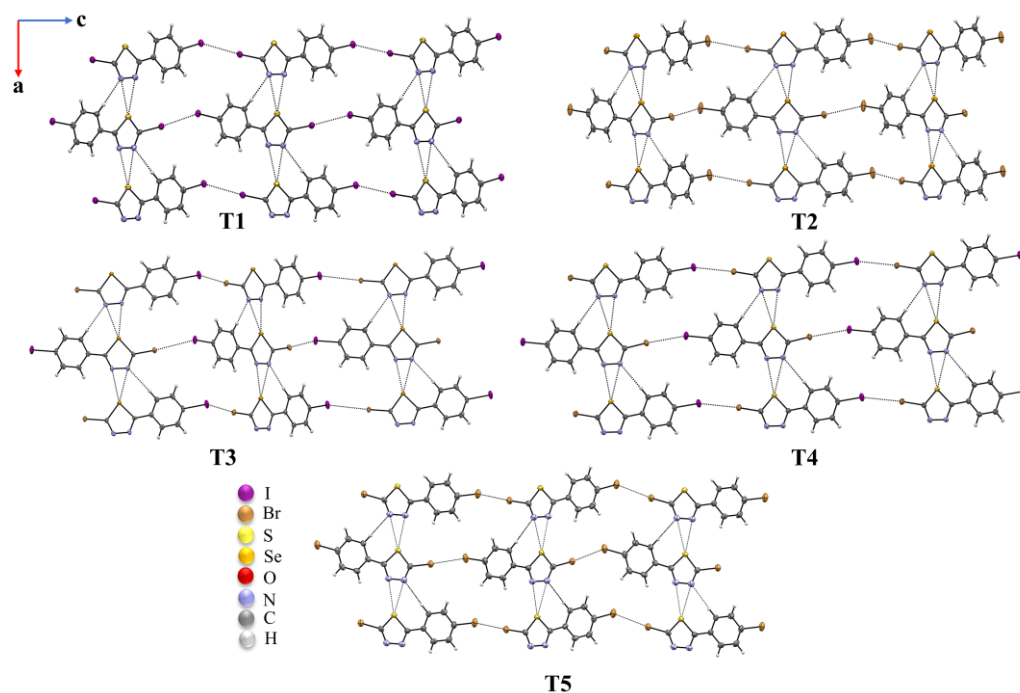


Figure 6.3 Significant noncovalent interactions shown in isostructural analogues **T1–T5**. The S and Se atoms both display chalcogen bonding (ChB) between the two N atoms.

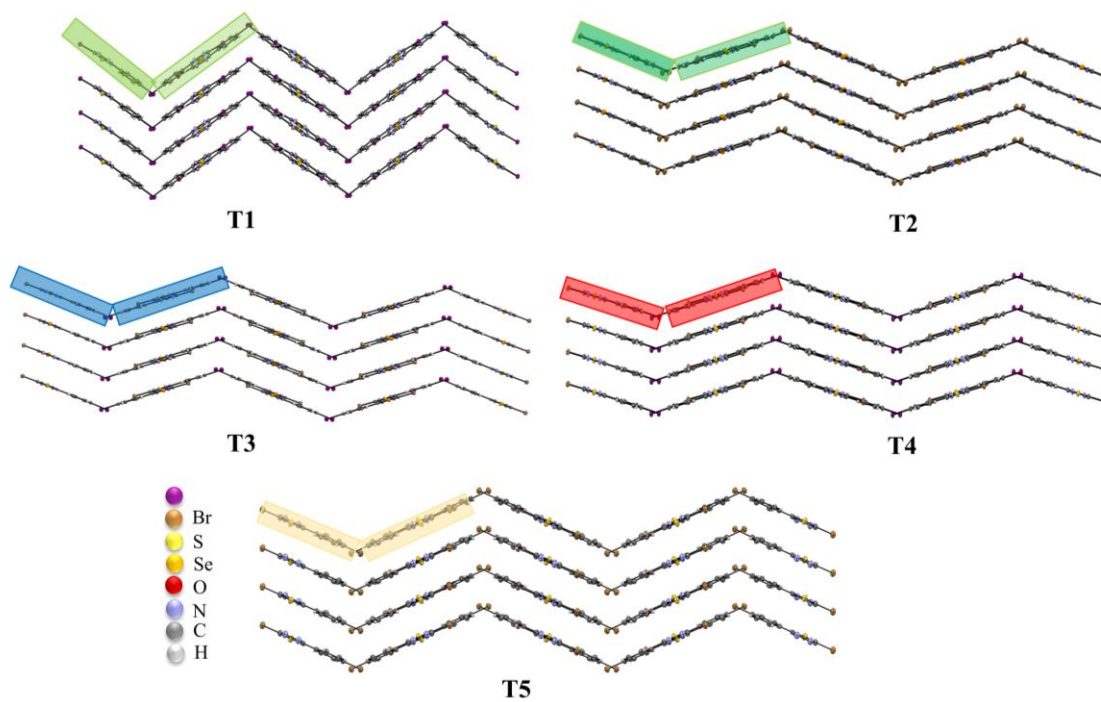


Figure 6.4 Crystal packing in **T1-T5**.

In all five targets, the S and Se atoms both displayed chalcogen bonding (ChB) to the two N atoms of the heterocycle, resulting in bifurcated interactions. In general, the more polarizable Se atom with a larger σ -hole showed shorter ChB bond distances compared to its less polarizable S counterpart. All relevant bond distances and angles are given in Table 6.2.

Table 6.2 Halogen and chalcogen bond geometries (Å, °)

Target	R-D...A	D...A (Å)	R-D...A (deg)
T1	I12...I13	3.747(6)	174.33(12)
	I13...C3	3.368(4)	89.8(3)
	S11...N8	3.147(4)	143.32(17)
	S11...N9	3.236(4)	155.25(17)
	C2-H2...N9	3.478(6)	117.3(3)
T2	Br12...Br13	3.468(10)	169.11(17)
	Se11...N8	3.060(5)	146.97(19)
	Se11...N9	3.123(5)	157.99(19)
	C2-H2...N9	3.690(8)	121.2(5)
T3	Br12...I13	3.623(7)	168.76(13)
	Se11...N8	3.050(3)	146.11(15)
	Se11...N9	3.129(3)	158.18(15)
	C2-H2...N9	3.696(6)	121.1(3)
T4	Br12...I13	3.614(7)	170.09(11)
	S11...N8	3.071(2)	147.59(12)
	S11...N9	3.153(2)	151.79(12)
	C2-H2...N9	3.646(4)	122.5(2)
T5	Br12...Br13	3.455(7)	171.18(13)
	S11...N8	3.127(4)	146.79(16)
	S11...N9	3.150(4)	152.06(16)
	C2-H2...N9	3.57(5)	119.9(3)

6.3.2 Molecular electrostatic potential maps

In Chapter 4 we used MEPs to determine σ -hole potentials, and we successfully evaluated their competing nature in many different 2-amino-1,3,4-chalcogenadiazole systems. In this study

the electrostatic potential maps were calculated and generated at the B3LYP/6-311G**++ level of theory using Spartan'14 for all targets. A summary of these results for **T1–T5** is shown in Figure 6.5.

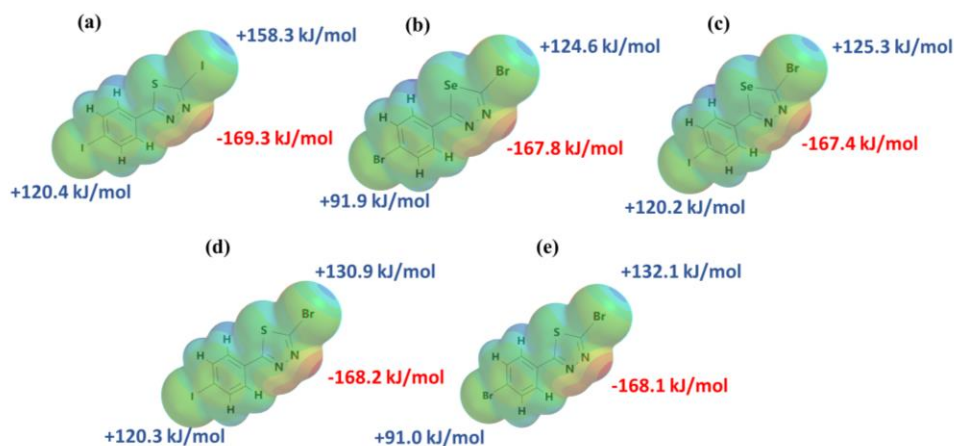


Figure 6.5 Molecular electrostatic potential surfaces of **T1–T5**.

Based on the MEPs, it was clear that the halogen atoms in the 2-position of the chalcogenadiazole ring presented a much larger σ -hole potential compared to those when the halogen atom was in the para position. Halogen atoms in the 2-position of the thiadiazole species had the highest σ -hole potential for both Br and I due to sulfur being more electronegative/electron withdrawing than the selenium atom. Among the chalcogen atoms, as expected, the more polarizable Se atom showed a larger positive σ -hole potential compared to the S atom. The two areas of positive electrostatic potentials were largely positioned directly opposite the C—Ch bonds, both near towards the 2-position halogen and the arene ring. The σ -hole closest to the arene ring contains an area of positive potential which has been overlapped with the positive potential of the C—H group, which is similar to what was observed in 2-amino-1,3,4-chalcogenadiazole derivatives in chapter 4 and the recent benzothiazolium species.¹⁵

The most negative electrostatic potential was observed for nitrogen in the 3-position which was therefore viewed as the best acceptor for a sigma-hole bond donor. The second and the third most negative potentials were observed for the lone pairs of the halogen atoms and the π electron cloud on the arene ring. XB formation was observed between the best donor and the second and third best acceptor while the ChB was between second best donor and the best acceptor.

6.3.3 Hirshfeld surface analysis

The Hirshfeld surfaces and fingerprint plots^{13,14} were generated for **T1–T5** using CrystalExplorer17.5 in order to identify the presence of any key intermolecular interactions driving the structural arrangement. Hirshfeld surface two-dimensional (2D) fingerprint plots showed major contributions arising from $I\cdots H/H\cdots I$ and $Br\cdots H/H\cdots Br$ contacts (16-17% per halogen atom), regardless of the structural positioning. The second largest contribution resulted from $C\cdots H/H\cdots C$ contacts (13-16%). However, with respect to the structure-directing interactions, they indicated that the most dominant interactions were halogen and chalcogen bonds. For **T1**, the halogen contacts observed were $I\cdots I$ (8%) and $I\cdots C/C\cdots I$ (8.2%), and for **T2** and **T5**, the dominant interactions were $Br\cdots Br$ (10.6%, 9.8% respectively) and $Br\cdots C/C\cdots Br$ (3.2% and 4.4%). For both **T3** and **T4**, there were $I\cdots Br/Br\cdots I$ (7.5 and 6.7%, respectively) and $I\cdots C/C\cdots I$ (1 and 1.8%) contacts. A comparison of the percentages of the all the main contributing contracts are shown in Figure 6.6.

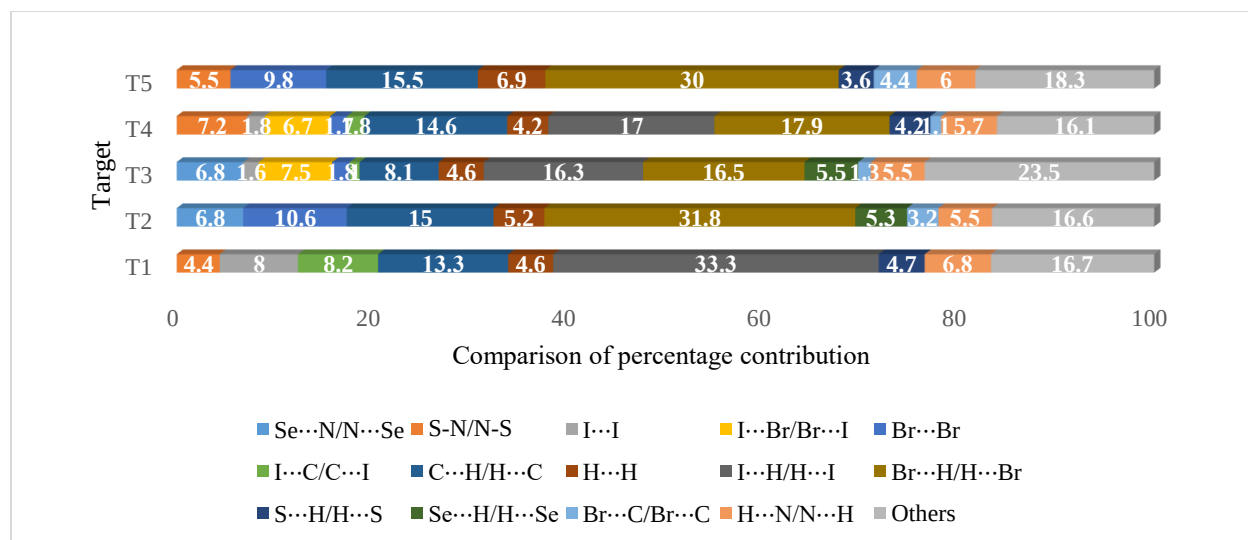


Figure 6.6 Comparison of all the major contributing interactions for targets **T1-T5**.

In the case of chalcogen bonding, **T1**, **T4** and **T5** they all showed $S\cdots N/N\cdots S$ (4.4%, 7.2% and 5.5% respectively), while **T2** and **T3** had $Se\cdots N/N\cdots Se$ (6.8 and 6.8%) contacts. These bifurcated ChB are directed more toward the N atoms; hence, the ChB configuration deviated slightly from an ideal ChB which forms along the $C-Ch$ axis. Interestingly, the only non σ -hole interaction present was $C-H\cdots N$ hydrogen bonding (HB) (6.8, 5.5, 5.8 and 6% for **T1**, **T2-T3**, **T4** and **T5** respectively), which was observed for all four targets (Figures 6.7 and 6.8).

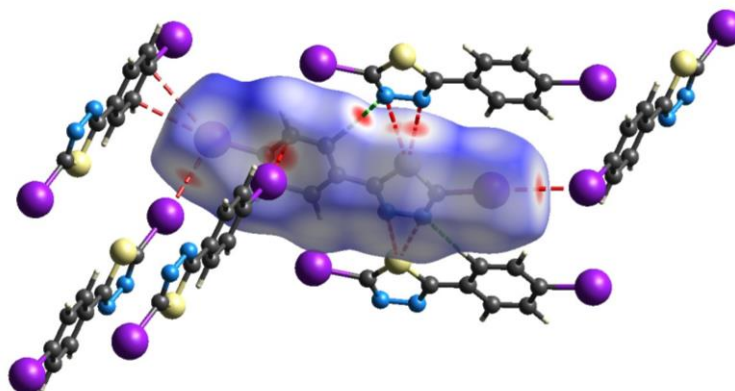


Figure 6.7 Hirshfeld surface mapped over d_{norm} for **T1**.

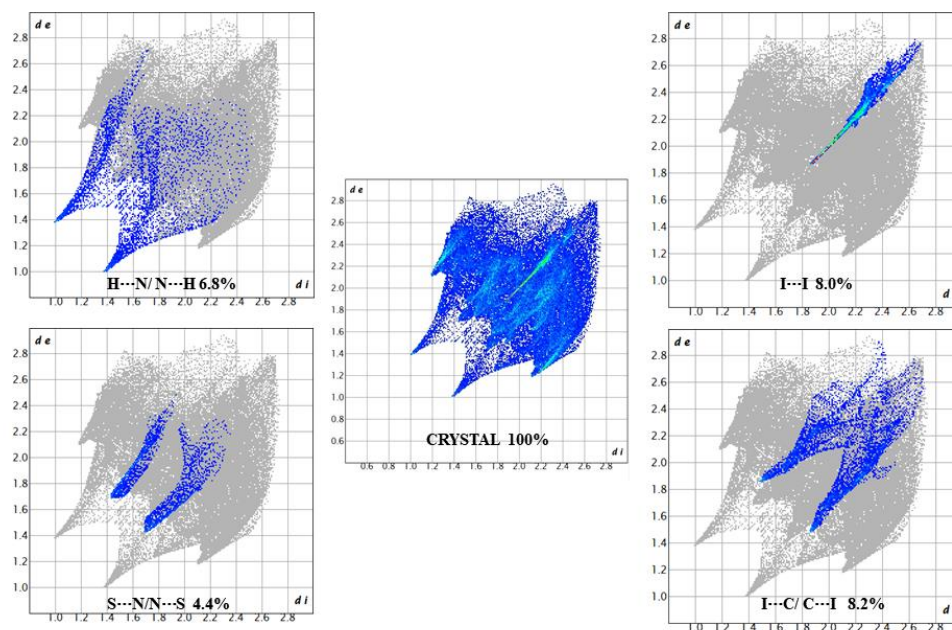


Figure 6.8 2D fingerprint plots of **T1** for the observed interactions.

Furthermore, the total Hirshfeld surfaces for **T1–T5** were very similar, except for the regions of XB interaction. For **T1**, **T2** and **T5** only one region was observed, as both halogen atoms present in the structure were the same, but as for **T3** and **T4**, there were mainly three regions of significance separated by the type of interactions, $I\cdots Br$, $Br\cdots I$, $I\cdots I$ or $Br\cdots Br$ (Figure 6.9).

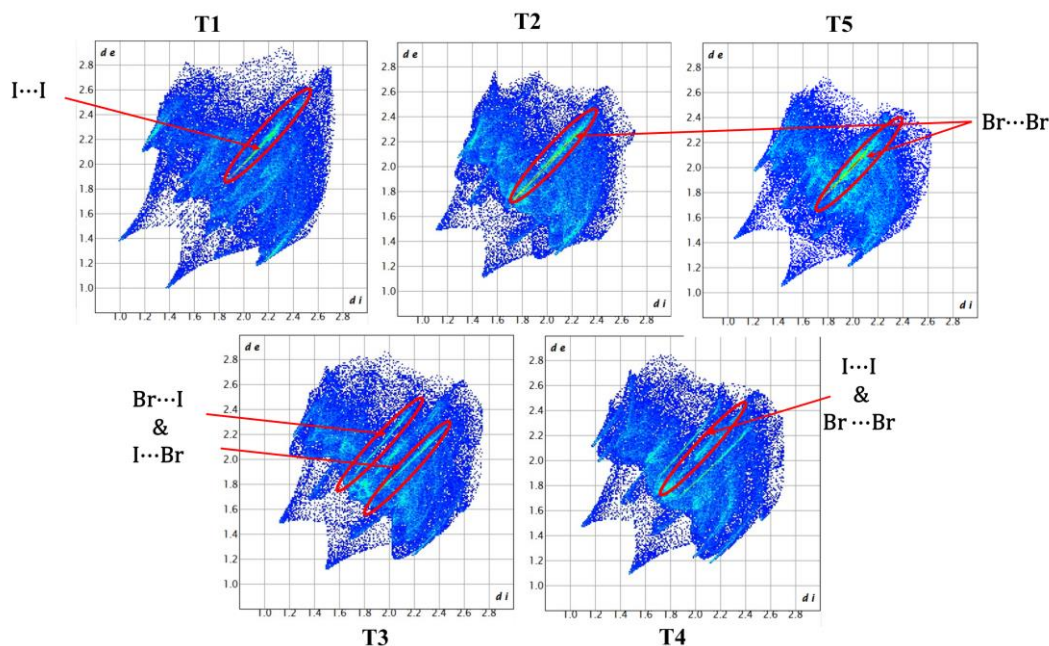


Figure 6.9 Hirshfeld surfaces of **T1-T5** highlighting the fingerprint regions of halogen bonding.

6.3.4 Energy frameworks

To further explore the competition between these noncovalent interactions, the energy frameworks for **T1-T5** were generated using built in TONTO program; B3LYP/6-311G(d,p)¹⁶ for **T2** and **T5** and B3LYP/DGDZVP¹⁶⁻¹⁸ for the other three iodine species. Based on the energy framework obtained for **T1**, the ChB is primarily a strong Coulombic interaction (Figure 6.10 and 6.11 wider cylinder) between the molecules when compared to the XB, which explains the interaction of the second-best donor with the best acceptor according to the MEPS. This confirms that the formation of the bifurcated ChB is likely more influential than the individual XBs that were formed (Figure 6.10).

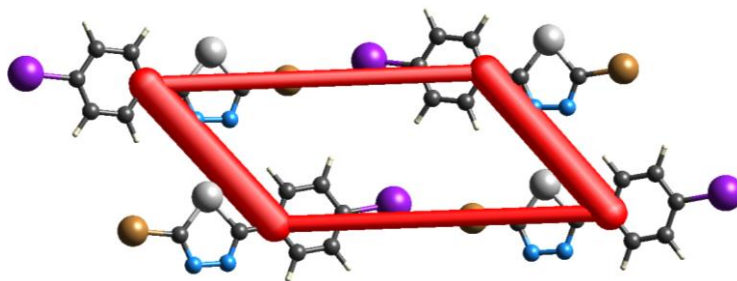


Figure 6.10 T1 Coulombic interaction difference between ChB and XB represented by the cylinder width.

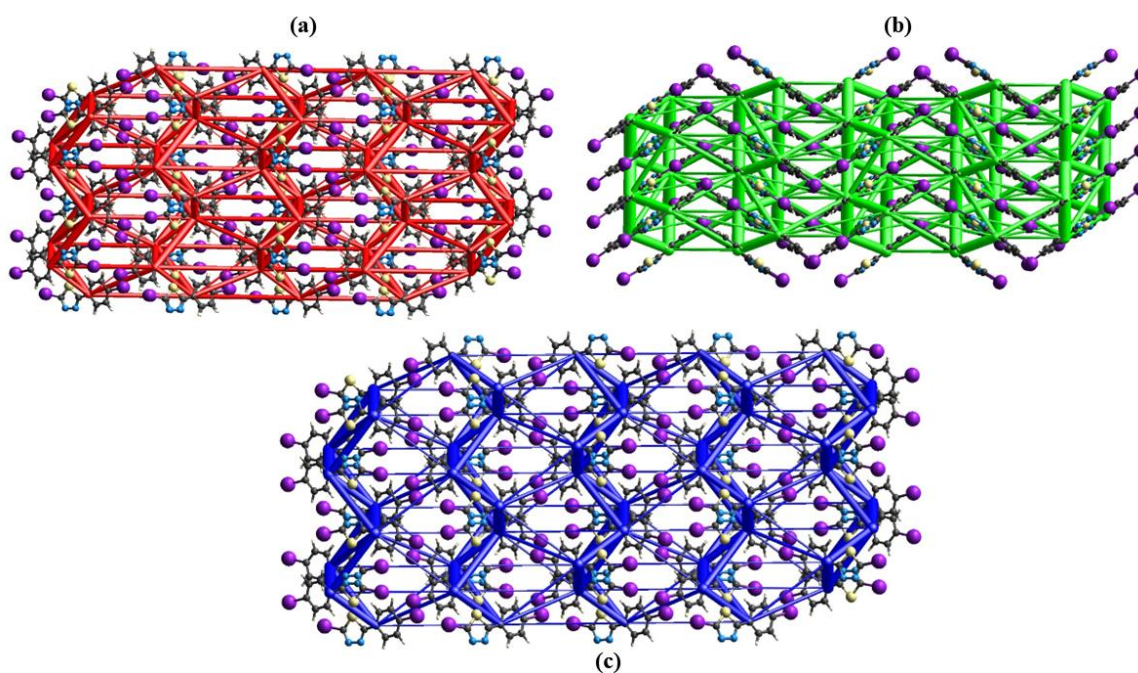


Figure 6.11 Energy framework calculations showing (a) the Coulombic interactions, (b) the dispersion interactions and (c) the total interaction energies of **T1**, in which the line thickness represents the relative strength of the energy component.

6.4 Conclusions

In this study, five isostructural chalcogenadiazole derivatives have been synthesized, characterized, and analyzed using SC-XRD, MEPs, and Hirshfeld surfaces. Changing the 2-amino group into a halogen removes the structural influence dominated by the hydrogen bonds in 2-

amino-1,3,4-chalcogenadiazole derivatives. Instead, it has generated a system primarily influenced by the σ -hole interactions.

In contrast to the 2-amino-1,3,4-chalcogenadiazole derivatives which had melting points above 200 °C, the melting points of the compounds in this study showed melting points between 100-200 °C which indicates the lower lattice energy and better solubility of σ -hole driven system over those controlled by hydrogen bonds.¹⁹

The MEP data showed that the halogen atoms at the 2-position of the chalcogenadiazole ring had a larger σ -hole than the para halogen atoms, which made them better XB donors with increased directionality. Hirshfeld surfaces showed a stronger structural influence for noncovalent interactions arising from I $\cdots$ I and Br $\cdots$ Br of **T1**, **T2** and **T5**, respectively, in comparison with **T3** and **T4**, where the two halogen atoms on opposite ends of the molecule were different. Overall, however, the relative percentage contribution of the I $\cdots$ Br/Br $\cdots$ I contacts of **T3** and **T4** was between those found in **T1**, **T2** and **T5**. Though MEPs predicted that the halogens with the larger σ -hole should form XB with the best-acceptor N atom, the diazo N atoms form ChBs with the second-best donor Ch instead of the halogen, forming bifurcated ChBs for all four structures, with the Se compounds, in general, showing shorter Ch $\cdots$ N contacts than the S compounds. Thus, it can be concluded that for these isostructural species, ChB is the more structurally influential interaction.

6.5 References

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Chapter 7 – Designing mechanically responsive crystals through controlled synthon design

7.1 Introduction

Crystalline materials have a degree of mechanical flexibility but when the applied external stimuli exceed the threshold of ‘buffering’ allowed by the system it results in brittleness. This threshold of buffer allowed for most crystalline materials is generally minute which is why crystals are generally regarded as brittle. Over the past decade, progress have been made in the territory of “soft” crystalline materials with pioneering work by Reddy and Desiraju, but the field remains in continuous development. The potential applications of these “soft” materials can aid in the advancement of flexible electronics^{1–5}, mechanical actuators⁶ and processability of pharmaceutical materials^{7,8}.

Mechanical responsiveness of crystal systems can be classified into three types: brittle, plastic, and elastic. When an external force is applied onto a crystal whether it breaks (brittle) or deforms to disperse that force, is dependent on not just the material itself but also on its crystal packing, structural corrugation, and the presence of anisotropic noncovalent interactions. When pressure is applied to a crystal, and it breaks or crumbles it is defined as a “brittle” system. If the crystal bends or deforms and can no longer return to its original form it is defined as “plastic” and if it returns to its original shape and orientation upon release of that external force it is defined as “elastic”, Fig. 7.1.

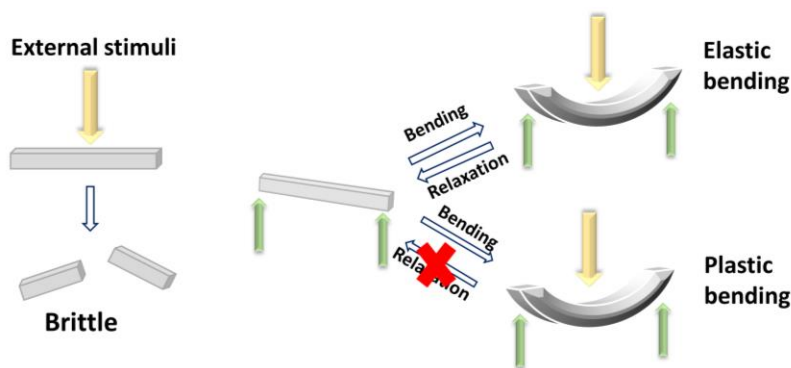


Figure 7.1 Types of mechanical responsiveness.

The structure-property relationship of flexible crystals has been examined over the past two decades with multiple systems which have shown that plastic bending is often associated with the presence of slip planes as well as anisotropy (strong interactions and weak interactions orthogonal to each other). The mechanism of elastic bending, however has been rationalized by three different hypotheses: i) interlocked crystal packing and isotropic interaction hypothesis ii) fibril lamella morphology hypothesis and iii) molecular movement hypothesis.⁹ The interlocked hypothesis correlates elasticity to molecular interlocking that prevents slippage and isotropic intermolecular interactions that provide a certain degree of freedom for the stress to be dissipated without damage to the crystal lattice.⁹ Presence of criss-cross slip-stacked molecular wires and the degree of movement between the stacked molecules were correlated with the elasticity in the fibril lamella hypothesis. In the molecular movement hypothesis, the slip-stacked molecules rotate reversibly from the inner arc to the outer arc at different angles to provide the mechanical flexibility of elastic crystals, Fig. 7.1 All three of these hypotheses have areas of overlap and areas of contradiction which suggests that when looking at these structures an overall assessment needs to be done to understand the underlying reasons of elasticity prior to using one hypothesis over the

others which also emphasize the fact that the number of examples of different elastically flexible systems are not enough and still there is a need to establish systematic development of such matter.

The design of flexible materials requires the presence of weak anisotropic intermolecular interactions such as hydrogen and halogen bonding in the crystal structures and the 2-amino-1,3,4-chalcogenadiazole derivatives that can form all three hydrogen, halogen, and chalcogen bonding interactions could provide a promising design strategy for creating flexible crystal systems. According to literature a few amide-substituted heterocyclic compounds^{10–12} have shown good mechanically flexibility which deemed to be a viable avenue of structural design modification for chalcogenadiazoles for developing flexible crystal systems hence, we decided to explore the possible structure property relationship of amide substituted chalcogenadiazole derivatives, Fig. 7.2.

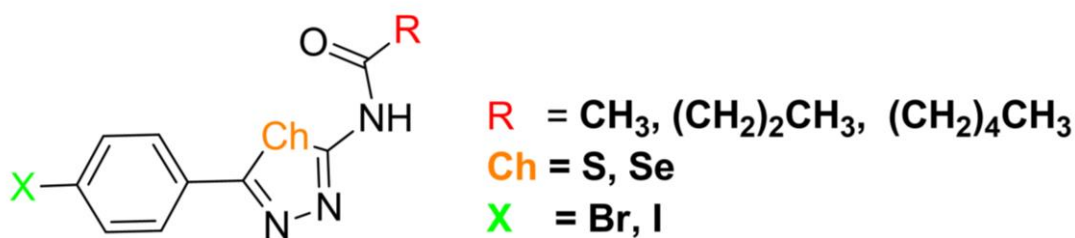


Figure 7.2 Target library.

In this study we are trying to answer the following questions,

Question 1. How do we synthesize and characterize these materials?

Question 2. What is the mechanical response of the synthesized crystal systems?

Question 3. What is the structure-property relationship with respect to mechanical behavior?

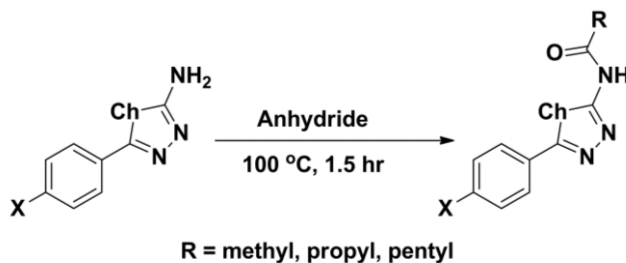
7.2 Experimental

7.2.1 General

Reagents were purchased from commercially available sources and used without further purification. All the solvents used were purchased from Fisher scientific and used without further purification. Melting points of the products were measured using a TA instruments DSC Q20 differential scanning calorimeter. ^1H NMR data were measured in a Bruker Ascend 400 MHz spectrophotometer. Single crystal X-ray diffraction data were collected using Rigaku XtaLAB Synergy-S diffractometer and the structures were solved using Olex2¹³ with SHELXT¹⁴. All computational calculations were performed using Spartan14¹⁵ software package.

7.2.2 Synthesis

General reaction scheme for amide synthesis



7.2.2.1 Synthesis of N-(5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)acetamide (SBr-Acetamide)

Previously synthesized 5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine (0.102 g) was dissolved in 2-5 ml of acetic anhydride in a 50 ml round bottom flask, and this was stirred for 1.5 h at 100 °C. Upon completion of the reaction the excess anhydride was removed by rotary evaporation and the product was purified by column chromatography. The product was a white

solid. Yield 92%. Mp: 310-318 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 12.66 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H), 2.22 (s, 3H).

7.2.2.2 Synthesis of N-(5-(4-bromophenyl)-1,3,4-selenadiazol-2-yl)acetamide (SeBr-Acetamide)

Previously synthesized 5-(4-bromophenyl)-1,3,4-selenadiazol-2-amine (0.110 g) was dissolved in 2-5 ml of acetic anhydride in a 50 ml round bottom flask, and this was stirred for 1.5 h at 100 °C. Upon completion of the reaction the excess anhydride was removed by rotary evaporation and the product was purified by column chromatography. The product was a yellow solid. Yield 81%. Mp: 349-353 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 12.79 (s, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 2.24 (s, 3H).

7.2.2.3 Synthesis of N-(5-(4-iodophenyl)-1,3,4-thiadiazol-2-yl)acetamide (SI-Acetamide)

Previously synthesized 5-(4-iodophenyl)-1,3,4-thiadiazol-2-amine (0.111 g) was dissolved in 2-5 ml of acetic anhydride in a 50 ml round bottom flask, and this was stirred for 1.5 h at 100 °C. Upon completion of the reaction the excess anhydride was removed by rotary evaporation and the product was purified by column chromatography. The product was a white solid. Yield 91%. Mp: 328-331 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 12.67 (s, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H), 2.22 (s, 3H).

7.2.2.4 Synthesis of N-(5-(4-iodophenyl)-1,3,4-selenadiazol-2-yl)acetamide (SeI-Acetamide)

Previously synthesized 5-(4-iodophenyl)-1,3,4-selenadiazol-2-amine (0.105 g) was dissolved in 2-5 ml of acetic anhydride in a 50 ml round bottom flask, and this was stirred for 1.5

h at 100 °C. Upon completion of the reaction the excess anhydride was removed by rotary evaporation and the product was purified by column chromatography. The product was a light grey solid. Yield 78%. Mp : 335-342 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 12.80 (s, 1H), 7.86 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 2.23 (s, 3H).

7.2.2.5 Synthesis of N-(5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)butyramide (SBr-Apropyl)

Previously synthesized 5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine (0.105 g) was dissolved in 2-5 ml of butyric anhydride in a 50 ml round bottom flask and stirred for 1.5 h at 100 °C. Upon completion of the reaction the excess anhydride was removed by rotary evaporation and the product was purified by column chromatography. The product was a yellow solid. Yield 84%. Mp : 292-296 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 12.66 (s, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 2.47 (m, 2H), 1.69 – 1.60 (m, 2H), 0.92 (t, J = 6.9 Hz, 3H).

7.2.2.6 Synthesis of N-(5-(4-bromophenyl)-1,3,4-selenadiazol-2-yl)butyramide (SeBr-Apropyl)

Previously synthesized 5-(4-bromophenyl)-1,3,4-selenadiazol-2-amine (0.103 g) was dissolved in 2-5 ml of butyric anhydride in a 50 ml round bottom flask and stirred for 1.5 h at 100 °C. Upon completion of the reaction, the excess anhydride was removed by rotary evaporation and the product was purified by column chromatography. The product was an orange solid. Yield 80%. Mp : 319-325 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 12.77 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 2.52 (m, 2H), 1.70 – 1.60 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H).

7.2.2.7 Synthesis of N-(5-(4-iodophenyl)-1,3,4-thiadiazol-2-yl)butyramide (SI-Apropyl)

Previously synthesized 5-(4-iodophenyl)-1,3,4-thiadiazol-2-amine (0.101 g) was dissolved in 2-5 ml of butyric anhydride in a 50 ml round bottom flask and stirred for 1.5 h at 100 °C. Upon completion of the reaction the excess anhydride was removed by rotary evaporation and the product was purified by column chromatography. The product was a white solid. Yield 97%. Mp : 308-312 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 12.65 (s, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 7.8 Hz, 2H), 2.47 (m, 2H), 1.64 (q, J = 7.2 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H).

7.2.2.8 Synthesis of N-(5-(4-iodophenyl)-1,3,4-selenadiazol-2-yl)butyramide (SeI-Apropyl)

Previously synthesized 5-(4-iodophenyl)-1,3,4-selenadiazol-2-amine (0.102 g) was dissolved in 2-5 ml of butyric anhydride in a 50 ml round bottom flask and stirred for 1.5 h at 100 °C. Upon completion of the reaction, the excess anhydride was removed by rotary evaporation and the product was purified by column chromatography. The product was a yellow solid. Yield 89%. Mp : 328-333 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 12.77 (s, 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.72 (d, J = 7.3 Hz, 2H), 2.50-2.52 (m, 2H), 1.65 (q, J = 7.8 Hz, 2H), 0.91 (t, J = 7.0 Hz, 3H).

7.2.2.9 Synthesis of N-(5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)hexanamide (SBr-Apentyl)

Previously synthesized 5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine (0.115 g) was dissolved in 2-5 ml of hexanoic anhydride in a 50 ml round bottom flask and stirred for 1.5 h at 100 °C. Upon completion of the reaction the excess anhydride was removed by air drying and the product was purified by column chromatography. The product was a light-yellow solid. Yield 98%. Mp : 252-257 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 12.65 (s, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 2.48-2.52 (m, 2H), 1.66 – 1.58 (m, 2H), 1.32 – 1.26 (m, 3H), 0.87 (t, J = 6.6 Hz, 3H).

7.2.2.10 Synthesis of N-(5-(4-bromophenyl)-1,3,4-selenadiazol-2-yl)hexanamide (SeBr-ApentyI)

Previously synthesized 5-(4-bromophenyl)-1,3,4-selenadiazol-2-amine (0.102 g) was dissolved in 2-5 ml of hexanoic anhydride in a 50 ml round bottom flask and stirred for 1.5 h at 100 °C. Upon completion of the reaction the excess anhydride was removed by air drying and the product was purified by column chromatography. The product was a yellow solid. Yield 92%. 285-290 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 12.76 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 2.48-2.54 (m, 2H), 1.63 (p, J = 7.0 Hz, 2H), 1.34 – 1.23 (m, 4H), 0.87 (t, J = 6.7 Hz, 3H).

7.2.2.11 Synthesis of N-(5-(4-iodophenyl)-1,3,4-thiadiazol-2-yl)hexanamide (SI-ApentyI)

Previously synthesized 5-(4-iodophenyl)-1,3,4-thiadiazol-2-amine (0.110 g) was dissolved in 2-5 ml of hexanoic anhydride in a 50 ml round bottom flask and stirred for 1.5 h at 100 °C. Upon completion of the reaction the excess anhydride was removed by air drying and the product was purified by column chromatography. The product was a white solid. Yield 91%. Mp : 263-268 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 12.65 (s, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 2.48 (m, 2H), 1.66 – 1.58 (m, 2H), 1.33 – 1.26 (m, 4H), 0.87 (t, J = 6.6 Hz, 3H).

7.2.2.12 Synthesis of N-(5-(4-iodophenyl)-1,3,4-selenadiazol-2-yl)hexanamide (SeI-ApentyI)

Previously synthesized 5-(4-iodophenyl)-1,3,4-selenadiazol-2-amine (0.104 g) was dissolved in 2-5 ml of hexanoic anhydride in a 50 ml round bottom flask, and this was stirred for 1.5 h at 100 °C. Upon completion of the reaction the excess anhydride was removed by air drying

and the product was purified by column chromatography. The product was a white solid. Yield 95%. Mp : 285-290 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 12.77 (s, 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 2.54 (m, 2H), 1.64 (p, J = 7.2 Hz, 2H), 1.29 (d, J = 3.4 Hz, 3H), 0.88 (t, J = 6.7 Hz, 3H).

7.2.3 Crystal growth and mechanical response

All crystals were grown using slow evaporation, and details of the solvents used, and the crystals obtained are summarized in Table 4.1. Mechanical response of the crystals were recorded by examining the bending nature of the crystals by using a needle or glue to keep the crystal stationary at one end and using a second needle to bend the crystal or using “three-point” bending system of a needle and a pair of forceps (Figure 7.3). For microscopic size crystals, they were immersed in Paratone oil to prevent damage to crystals and a needle was used to move the crystal against the viscous liquid or “three-point bending” system was used to test the flexibility. If the crystal broke upon bending it was termed brittle and when the applied pressure was removed if the crystal returned to its original position, it was termed elastic if it remained at the bent position, it was termed plastic.

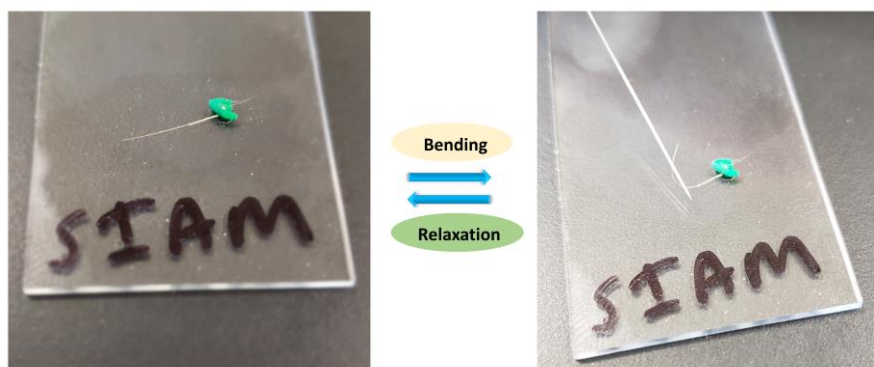


Figure 7.3 Elastic bending observed for **SI-Acetamide Form II**.

Table 7.1 Crystal description and the mechanical flexibility of the crystals

Compound	Code	Solvent	Color and morphology	Response to mechanical stress
N-(5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)acetamide	SBr-Acetamide	Ethy acetate/hexane	Yellow, Irregular	Elastic
N-(5-(4-bromophenyl)-1,3,4-selenadiazol-2-yl)acetamide	SeBr-Acetamide Form I	THF/Methanol	Yellow, Needle	Elastic
	SeBr-Acetamide Form II	THF/Dioxane/Nitromethane	Colorless, Needle	Brittle
N-(5-(4-iodophenyl)-1,3,4-thiadiazol-2-yl)acetamide	SI-Acetamide Form I	Chloroform	Colorless, Needle	Brittle
	SI-Acetamide Form II	Methanol/THF	Colorless, Needle	Elastic
N-(5-(4-iodophenyl)-1,3,4-selenadiazol-2-yl)acetamide	SeI-Acetamide	THF/Methanol	Colorless, Needle	Elastic
N-(5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)butyramide	SBr-Apropyl	THF	Colorless, Needle	Elastic
N-(5-(4-bromophenyl)-1,3,4-selenadiazol-2-yl)butyramide	SeBr-Apropyl	Methanol/THF	Light Yellow, Needle	Elastic
N-(5-(4-iodophenyl)-1,3,4-thiadiazol-2-yl)butyramide	SI-Apropyl	THF	Colorless, Needle	Elastic very thin needle
N-(5-(4-iodophenyl)-1,3,4-selenadiazol-2-yl)butyramide	SeI-Apropyl	THF/Dioxane	Colorless, Needle	Elastic
N-(5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)hexanamide	SBr-Apentyl	THF	Colorless, Plate	Brittle
N-(5-(4-bromophenyl)-1,3,4-selenadiazol-2-yl)hexanamide	SeBr-Apentyl	THF/Dioxane	Yellow, Plate	Brittle
N-(5-(4-iodophenyl)-1,3,4-thiadiazol-2-yl)hexanamide	SI-Apentyl	THF/Dioxane	Colorless, elongated Plate	Brittle
N-(5-(4-iodophenyl)-1,3,4-selenadiazol-2-yl)hexanamide	SeI-Apentyl	THF	Light Yellow, Needle	Elastic thin needle

7.3 Results and Discussion

7.3.1 Single crystal structures

In all 12 targets, including polymorphs thereof, the primary hydrogen-bond motif $R_2^2(8)$ was observed between the $\text{NH}\cdots\text{N}$ heterocyclic pocket (Figure 7.4 (a)). The second sphere of noncovalent interactions between the dimers were different for methyl analogues where $\text{Ch}\cdots\text{O}=\text{C}$ chalcogen bonding interactions were seen, whereas for propyl and pentyl targets a $\text{C}-\text{H}\cdots\text{O}=\text{C}$ $R_2^2(20)$ motif was found, Fig. 7.4 (c). All the relevant bond geometries are given in table 7.2.

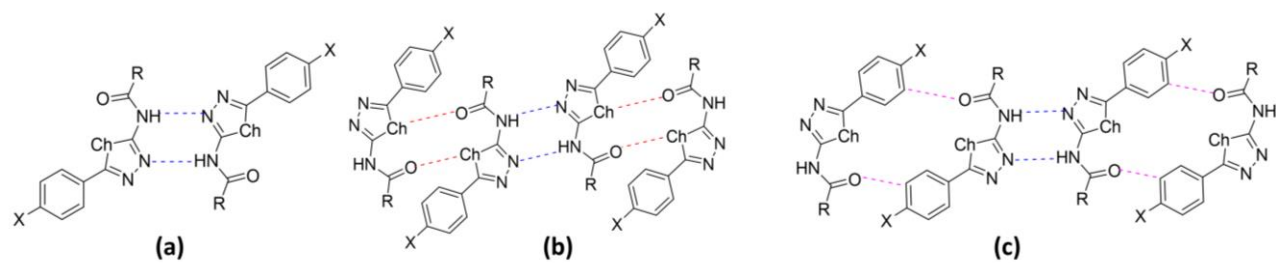


Figure 7.4 (a) Primary HB motif and (b) and (c) secondary ChB and HB.

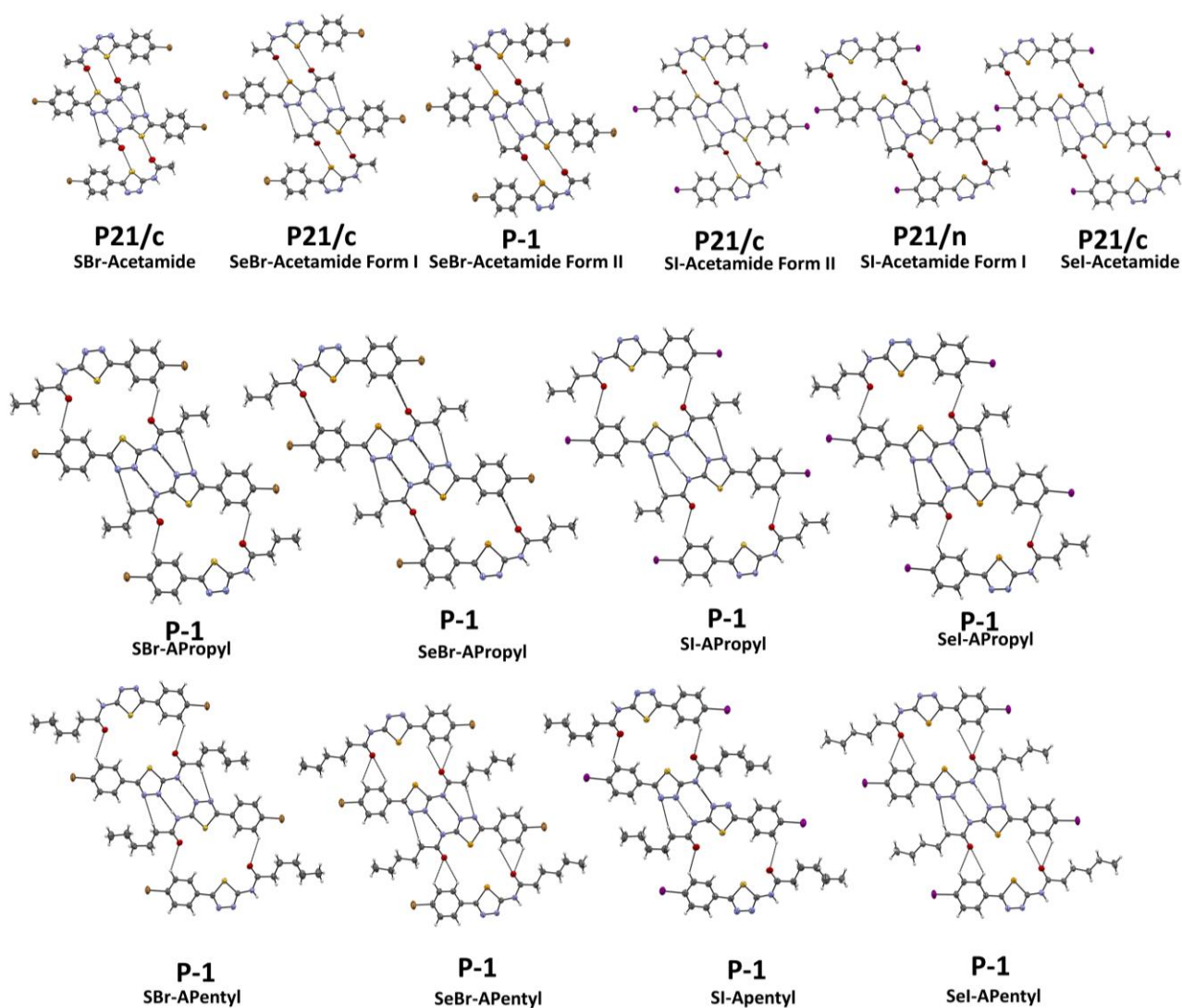


Figure 7.5 Dimer formation in all the obtained crystal structures.

Table 7.2 The relevant primary bond geometries in the target compounds

Compound	D-H/X/Ch...A	D/X/Ch...A (Å)	D-H/X/Ch...A (deg)
SBr-Acetamide	N006-H006...N005	2.864(7)	172.8(3)
	S002...O004	3.208(5)	154.8(2)
SeBr-Acetamide Form I	N12-H12...N9	2.869(4)	174.8(2)
	Se11...O14	3.126(3)	162.10(11)
SeBr-Acetamide Form II	N12-H12...N9	2.881(5)	172.3(2)
	Se11...O14	3.315(4)	167.12(11)
SI-Acetamide Form II	N12-H12...N9	2.877(7)	172.4(4)
	S11...O14	3.210(6)	154.9(2)
SI-Acetamide Form I	N12-H12...N9	2.883(3)	166.37(15)
	C3-H3...O14	3.234(4)	174.57(17)
SeI-Acetamide	N12-H12...N9	2.877(4)	169.3(2)
	C5-H5...O14	3.309(5)	175.8(3)
SBr-Apropyl	N12-H12...N9	2.880(4)	172.0(2)
	C5-H5...O17	3.354(5)	137.84(19)
SeBr-Apropyl	N12-H12...N9	2.869(4)	171.4(2)
	C5-H5...O17	3.315(5)	172.8(3)
SeI-Apropyl	N12-H12...N9	2.868(5)	175.5(2)
	C5-H5...O17	3.337(7)	134.9(3)
SI-Apropyl	N12-H12...N9	2.881(6)	172.7(3)
	C5-H5...O17	3.376(7)	136.5(3)
SBr-Apentyl	N32-H32...N49	2.897(4)	178.0(3)
	C45-H45...O39	3.313(4)	140.45(17)
	N12-H12...N9	2.909(4)	176.0(2)
	C5-H5...O19	3.483(4)	133.21(18)
	N52-H52...N29	2.887(4)	176.0(3)
	C45-H45...O39	3.313(4)	140.45(17)
SeBr-Apentyl	N11-H11...N9	2.880(5)	176.9(3)
	C5-H5...O13	3.354(6)	126.4(3)
SeI-Apentyl	N12-H12...N9	2.892(8)	176.8(4)
	C3-H3...O19	3.362(9)	128.5(5)
SI-APentyl	N11B-H11B...N9A	2.882(6)	174.9(3)
	C6B-H6B...O13A	3.344(6)	139.6(4)
	N11B-H11B...N9A	2.882(6)	174.9(3)
	C6B-H6B...O13A	3.344(6)	139.4(4)

7.3.2 Structure property relationships based on the secondary and tertiary noncovalent interactions

7.3.2.1 Methyl analogues

The methyl analogues of **SBr-Acetamide**, **SeBr-Acetamide** Form I and **SI-Acetamide** Form II crystallized in the P21/c space group and were isostructural. Analysis of the crystal packing showed all three having strong π - π stacking between the aromatic rings in an edge-to-edge fashion. The $R_2^2(8)$ HB dimers between $\text{NH}\cdots\text{N}$ are connected through $\text{Ch}\cdots\text{O}=\text{C}\text{ ChB}$ bonds and extends to form a 1D chain. The parallel 1D chains are stacked through previously discussed π - π stacking (Figure 7.6). Each 1D chain interlocks with surrounding chains through weak $\text{X}\cdots\text{CH}_3$ contacts, $\text{C-H}\cdots\text{X}$ and $\text{C-H}\cdots\pi$ hydrogen bonding interactions for all three compounds. These anisotropic interactions prevent slippage and allow the molecules to swing back to their original position upon removal of the external stimuli. The packing showed corrugated herringbone motifs hence these packing features correlate with elastic bending which was experimentally observed

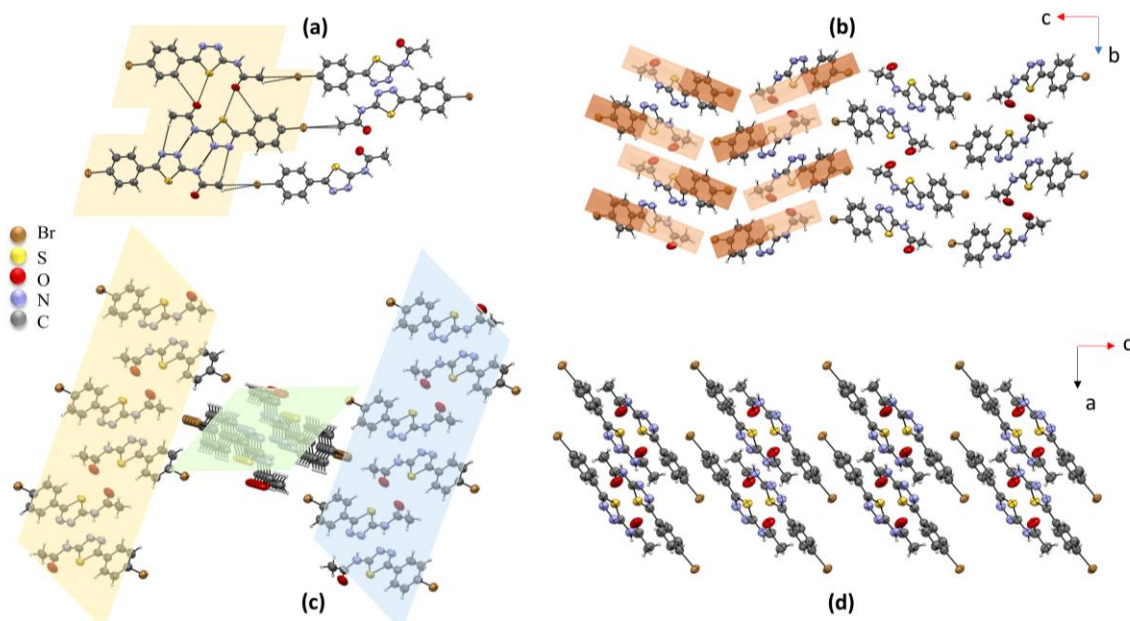


Figure 7.6 **SBr-Acetamide** packing features (a) 1D chain layer (b) interlocking pattern (c) packing in the b direction.

The **SeBr-Acetamide** Form II crystallized in the P-1 space group. The 1,3,4-selenadiazole ring and the benzene ring are arranged in a 9.84 Å dihedral angle which is larger than in the previous three structures. The HB dimeric molecules were connected through $\text{Ch}\cdots\text{O}=\text{C ChB}$ similarly to the previous structures and the HB 1D chains were interconnected through weak $\text{X}\cdots\text{CH}_3$ interactions leading a 2D layer of molecules almost on the same plane. These 2D layers undergo π - π stacking. The π stacked 2D layers lacks any corrugations and only shows parallel packing (Figure 7.7 (a) and (b)). Apart from the π stacking there were no other anisotropic interactions which correlated to the observed brittleness of the crystals.

In the case of **SI-Acetamide** Form I and **SeI-Acetamide** they both crystallized in P21/n and P21/c space group, respectively and were isostructural. Both lacked the $\text{Ch}\cdots\text{O}=\text{C ChB}$ observed for the previous four structures and instead showed $\text{C-H}\cdots\text{O}=\text{C}$ and HB interactions to form a 1D polymeric chain, Fig. 7.7 (c) and (d). These 1D chains were connected to surrounding chains through $\text{I}\cdots\pi$ halogen bonds and $\text{CH}_3\cdots\text{I}$ HB interactions. The crystal packing showed a herringbone motif and interlocked halogen bonding between molecular layers which prevents slippage and facilitates elastic flexibility. Based on that, both **SI-Acetamide** Form I and **SeI-Acetamide** should be elastic but when three-point bending was done these resulted in brittleness and elastic bending, respectively. This difference in mechanical response could be due to changes in interaction energies or packing densities.

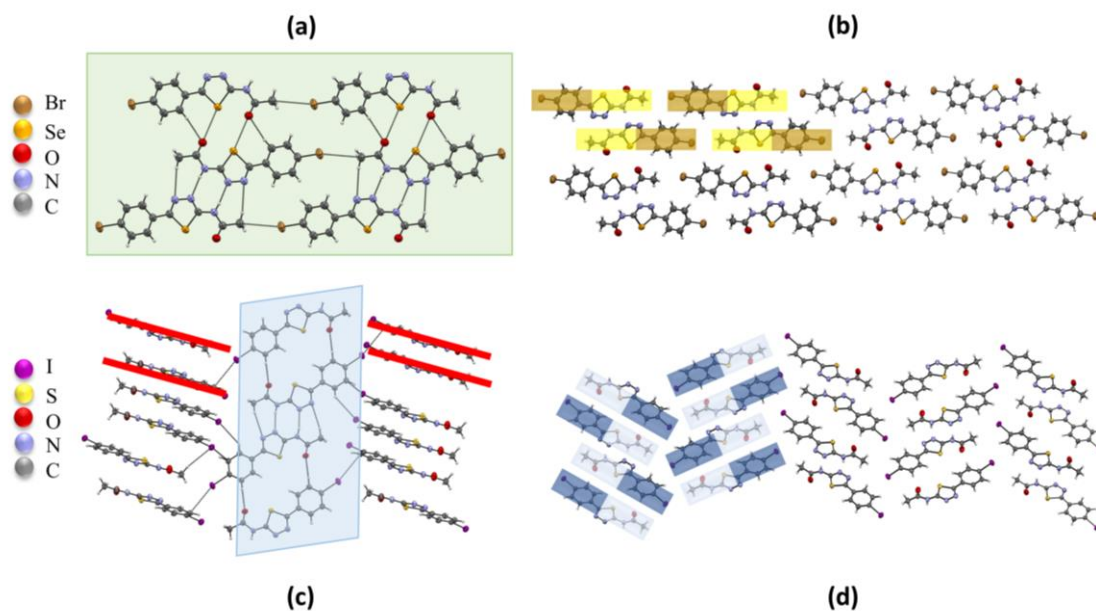


Figure 7.7 **SeBr-Acetamide** Form II **(a)** 2D chain **(b)** parallel packing and **SI-Acetamide** Form I **(c)** 1D chain arrangement **(d)** interlocked pattern.

7.3.2.2 Propyl analogues

All propyl analogues crystallized in P-1, and were isostructural and they all lacked the $\text{Ch} \cdots \text{O}=\text{C} \text{ ChB}$ that were observed in majority of the methyl analogues and instead the hydrogen-bonded dimers were connected through $\text{C}-\text{H} \cdots \text{O}=\text{C}$ hydrogen bonds similarly to those in **SeI-Acetamide** and **SI-Acetamide** Form I. However, unlike the two methyl analogues where 1D chains were formed, these propyl analogues form 2D layers by connecting the HB 1D layers through weak $\text{X} \cdots \text{CH}_3$ contacts, Fig. 7.8. The crystal packing showed parallel packing which should theoretically lead to shearing or breaking but since the polymeric chains were connected through anisotropic $\text{CH}_3 \cdots \text{X}$ rectangular $\text{R}_4^2(8)$ hydrogen bonds and interlayer π - π stacking leading to a certain degree of interlocked packing of the layers resulting in mechanical elasticity in all four crystals.

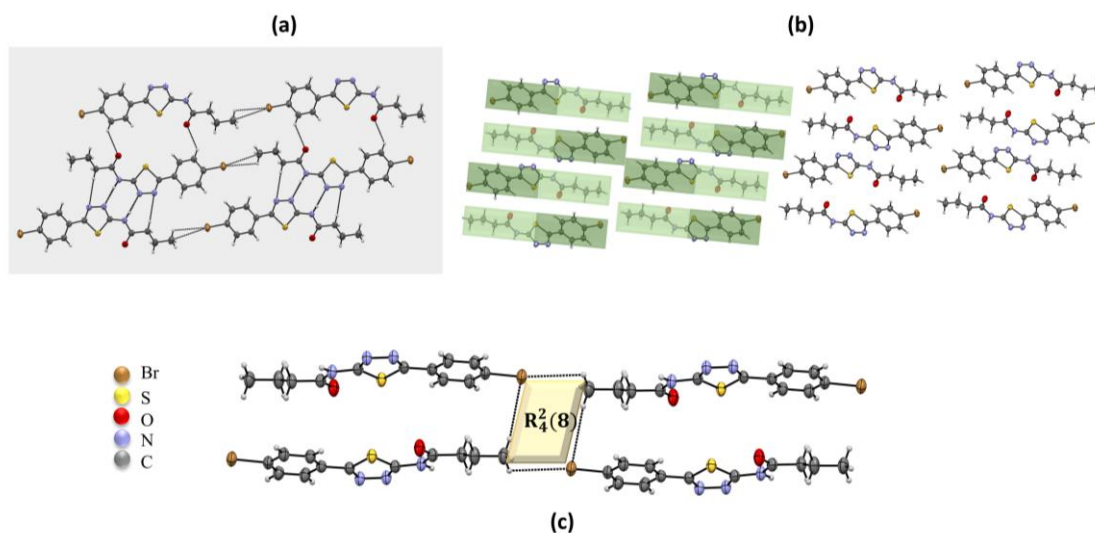


Figure 7.8 SBr-Apropyl (a) 2D plane (b) parallel packing (c) HB tetramer.

7.3.2.3 Pentyl analogues

The four crystal structures obtained for the pentyl targets all crystallized in the P-1 space group, but with different intermolecular interactions. The structure of **SBr-Apentyl** had a $Z' = 3$ and they all displayed hydrogen bonded dimeric units interacting through $\text{C-H}\cdots\text{O}=\text{C}$ HB to form a 1D polymeric chain. The polymeric units of the 1D chains were interacting through weak $\text{X}\cdots\text{CH}_3$ contacts to form 2D sheets. These 2D sheets display π - π stacking but no other interlayer interactions (Figure 7.9). The polymeric HB units were structurally isolated and the main differences between the methyl and propyl crystal packing is arising from the mechanical flexibility of the pentyl chain which showed a nonlinear conformation which had led to loss of coplanarity between the chain and the aromatic rings resulting a different morphology compared to all the other crystals obtained. The lack of herringbone packing motif and interlayer interactions has resulted in a brittle crystal.

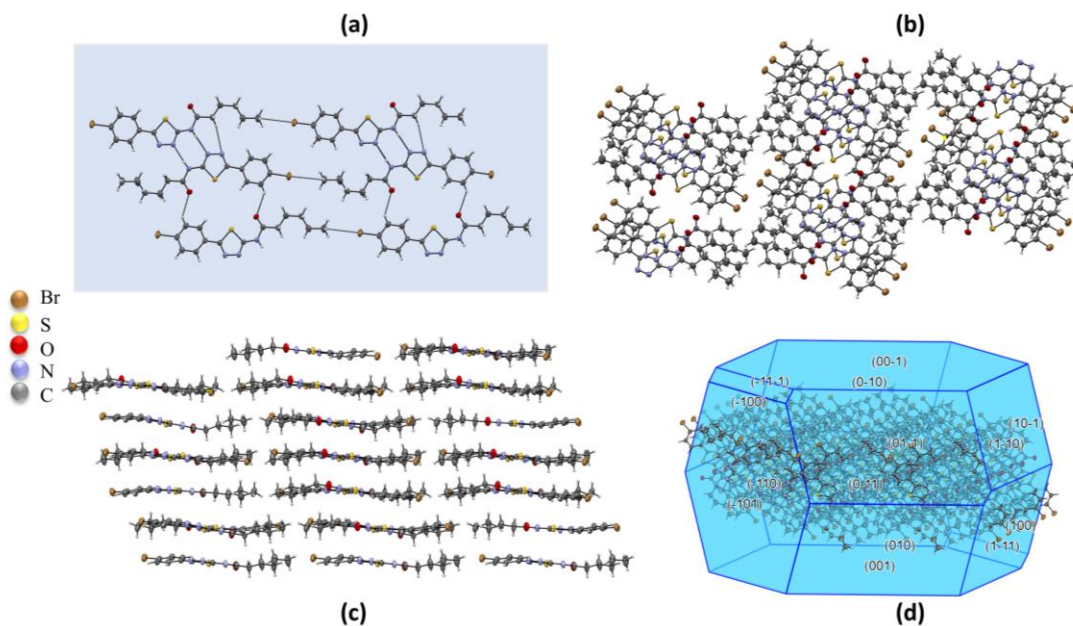


Figure 7.9 SBr-ApentyI (a) 2D layer (b) noncorrugated packing (c) packing side view (d) morphology.

In the case **SeBr-ApentyI** it had the same dimeric unit as previous, interacting through $\text{C-H}\cdots\text{O}=\text{C}$ HB to produce a 1D chain and there were no $\text{X}\cdots\text{CH}_3$ between the polymeric units leading to isolated polymeric chains. Unlike the aliphatic chain conformation observed for **SBr-ApentyI**, **SeBr-ApentyI** pentyl chain had a linear conformation. The polymeric units showed π - π stacking though the aromatic rings were not aligned and showed “slipped” packing. The pentyl carbon chain showed linear conformation which is coplanar with the aromatic rings. The crystal packing showed parallel packing motif and lacked corrugation which produced brittle crystals.

SI-ApentyI crystallized in the P-1 space group with two molecules in the asymmetric unit. Both molecules had the same dimeric unit interacting through $\text{C-H}\cdots\text{O}=\text{C}$ HB and there were no $\text{X}\cdots\text{CH}_3$ interactions. Instead, there were $\text{I}\cdots\text{I}$ Type I halogen bonds between the polymeric units to form a 2D sheet (Figure 7.10 and 7.11). The pentyl chain again showed a nonlinear conformation

which lacks coplanarity to the aromatic rings. There were no interlayer interactions, and it lacked the herringbone motif which resulted in mechanical brittleness.

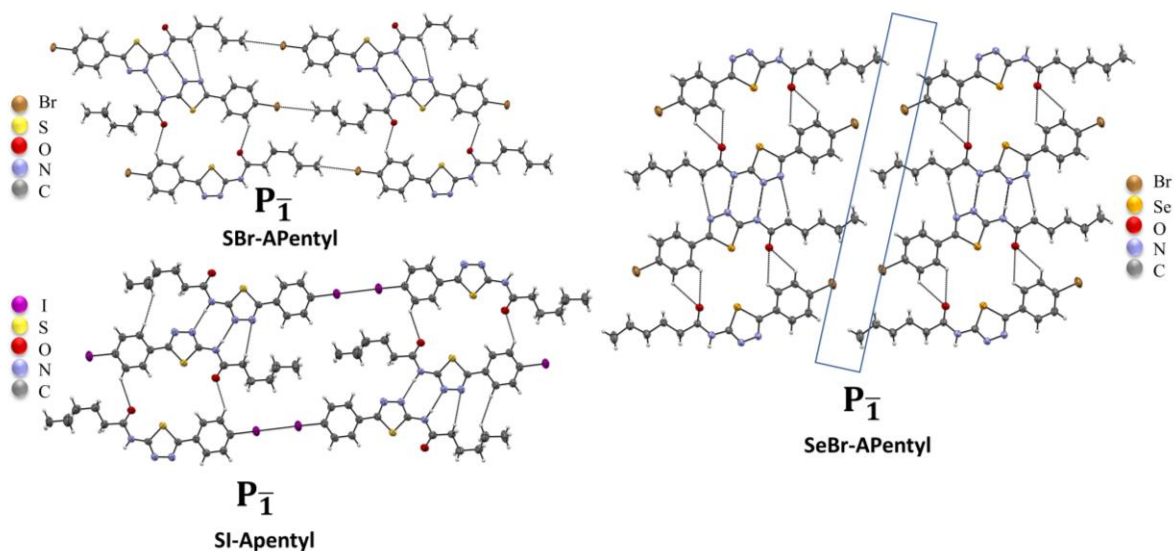


Figure 7.10 2D sheet formation of (a) SBr-APentyl (b) SeBr-APentyl (c) SI-APentyl.

SeI-APentyl had the hydrogen bonded dimeric unit interacting through $\text{C-H}\cdots\text{O}=\text{C}$ HB forming a 1D polymeric chain and these chains interact through anisotropic $\text{I}\cdots\text{I}$ Type I halogen bonding and $\text{CH}_2\cdots\text{I}$ hydrogen bonding interactions to form a 2D sheet. These 2D sheets showed strong π - π stacking. Though this lacked the herringbone motif, there were weak $\text{CH}_3\cdots\text{CH}_3$ interlayer interactions due to the linear conformation of adjacent pentyl chains which has led to interlocking. This produced the only elastic crystal in this family of compounds, (Figure 7.11). Though the **SI-Pentyl** had a similar packing and interactions to this, it lacked interlocking feature exclusive to the **SeI-APentyl** which explains why it was brittle. For **SeI-APentyl** two types of crystals were observed, thin and thick, both of which were the same type, however only the thinner crystals showed flexibility demonstrating that the thickness of crystals can potentially affect the flexibility.

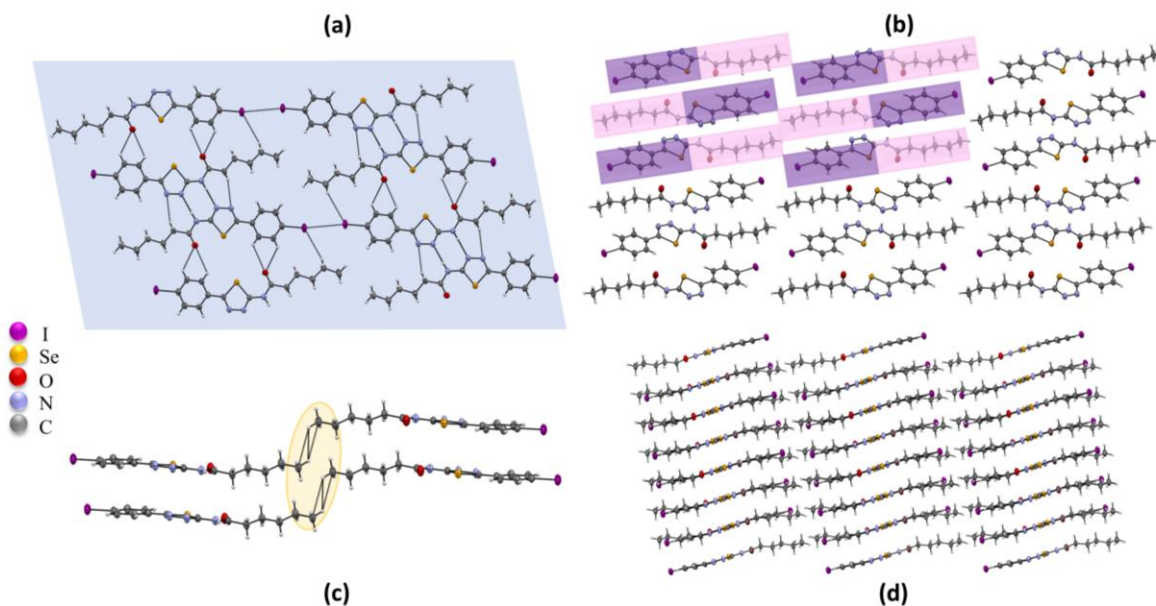


Figure 7.11 SeI-ApentyI (a) 2D layer (b) parallel interlocked packing (c) interlayer $\text{CH}_3 \cdots \text{CH}_3$ contact (d) packing.

7.4 Conclusions

Successful design and expansion of flexible crystal systems have been achieved by the use of amide functional group with substituted heterocyclic compounds. However, the nature of unpredictability of mechanical behavior still exists in few systems. The changes in conformational flexibility, crystal packing, crystal morphology and intermolecular interactions work in harmony to deliver the mechanical response of these systems.

For methyl analogues there were four flexible crystals all of which showed corrugated crystal packing along with anisotropic interlayer interactions which explained the elastic bending. There were only two brittle crystals and only **SeBr-Acetamide** Form II showed parallel packing and lack of anisotropic interlayer interactions that resulted in brittleness. Though **SeI-Acetamide** showed elastic flexibility, the isostructural **SI-Acetamide** Form I was brittle, which might be

associated with differences in the strength of the intermolecular interactions or packing density between the two species.

The propyl series was the only series of molecules which lead to elastic bending in every crystal. All these compounds lacked structural interlocking, which is generally a characteristic of elastic bending, however the presence of anisotropic interlayer interactions has resulted in elastic bending.

Pentyl series showed the highest number of brittle crystals, 3/4, due to structural nature of the pentyl carbon chain and crystal packing. There were two crystals with high Z' all of which were brittle and showed parallel packing. **SeI-Apentyl** showed mechanical flexibility even though it was parallel packed due to the interlocking between the methyl groups.

For these three series, larger alkyl chains seem to facilitate brittle systems while small to moderate size chains primarily results in elastic crystals. The thickness of the crystals also played a role in the mechanical response as it was observed that thinner crystals showed flexibility while thick crystals were brittle. None of the crystal systems that were designed showed any slip planes which resulted in zero plastic bending crystals. A summary of the mechanical responses along with a road map analysis is shown in Figure 7.12.

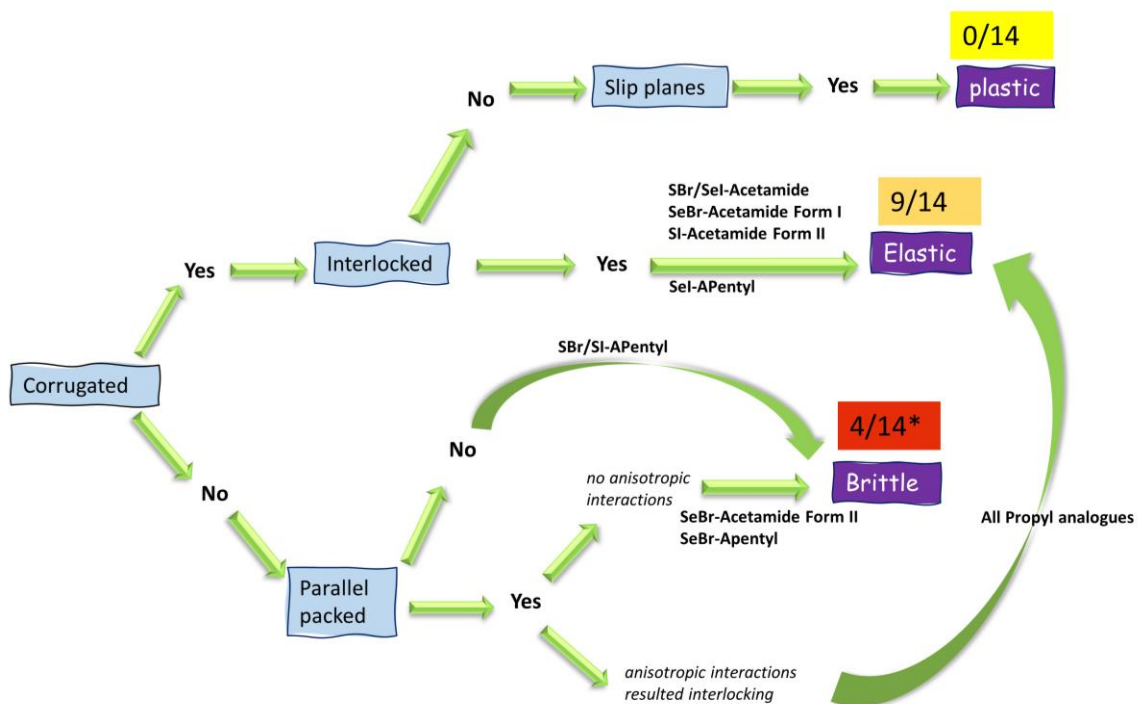


Figure 7.12 A summary of analysis of the mechanical response of the crystals of amide derivatives (* **SI-Acetamide** brittle interlocked system was excluded).

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Chapter 8 – Host-guest chemistry of chalcogen-bond based cavitands

8.1 Introduction

Supramolecular containers are synthetic species designed to provide an isolated and confined space for various applications from chemicals to pharmaceuticals.^{1,2} This field of molecular containers started in 1982 with the discovery of “cavitands” by Cram, which are resorcin[4]arenes based molecular containers.³ The field of synthetic molecular containers have since been progressed significantly over the past 40 years to include various macromolecules such as cyclodextrins⁴, calix[n]arenes⁵ and pillar[n]arenes⁶ with a variety of usages including molecular recognition⁷, catalysis⁸, drug delivery⁹ and encapsulation^{1,10}.

In this study we wanted to explore cavitand molecular containers due to the versatility of functionalization. The self-assembly of molecular containers into discrete capsules or guest recognition and encapsulation by cavitands have been achieved with the use of intermolecular interactions such as hydrogen bonding (HB)¹¹, metal coordination¹², halogen bonding (XB)^{13,14} and most recently with chalcogen bonding (ChB)^{15,16}. Similar to XBs, ChBs have become useful tools for constructing functional cavitands and molecular capsules with strong self-assembly features. In this chapter we wanted to further explore the applicability of tunable and versatile ChBs in the context of cavitand host-guest assembly.

Functionalization of resorcin[4]arene cavitands can be achieved at four main stages of the bottom-up assembly of the synthesis. First, the selection of the backbone that makes up the basic skeleton of the cavitand can eventually determine the functionalization at the upper rim of the cavitand.^{17,18} Second, changes to the ‘feet’ can be done to achieve varying level of solubility to even include functional groups capable of attaching to a substrate. The third sequence of changes

can be done at the bridging groups in which it can be changed from methyl and ethyl bridges^{19,20} to even include octanitro cavitands²¹ that determine the width and even functionality of the cavitand. The fourth and the final change can be performed post synthetically at the upper rim of the cavitand depending on the desired use and the application.^{22,23} The basic skeleton of the cavitand used in this study involves methylene bridges, pentyl feet and resorcinol backbone with halogen atoms at the upper rim of the cavitand which can be functionalized to achieve selective ChB based host-guest interactions (Figure 8.1). Therefore, in this study we have selected two families of chalcogen-bond donor cavitands with a deeper upper rim and a wider upper rim (Figure 8.2).

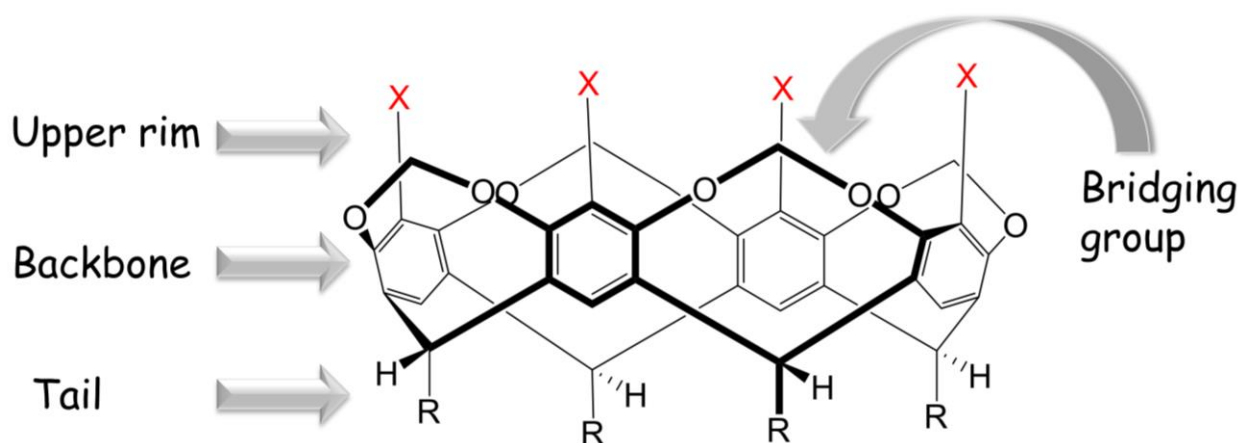


Figure 8.1 Schematic of the basic structure of a cavitand.

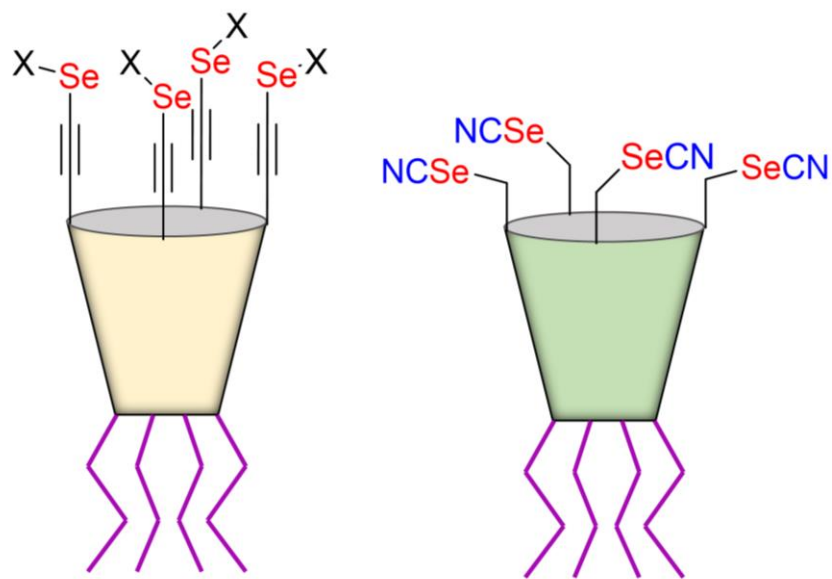


Figure 8.2 Schematic of the proposed deep cavitand (left) and the wider cavitand (right).

Cavitands are versatile molecular containers which can encapsulate guest molecules in several different binding modes as shown in Figure 8.3. In this study we wanted to specifically develop cavitands which can drive host-guest interaction at the upper rim of the cavitand through chalcogen-bonding interactions. For this purpose, we designed three specific targets molecules, Figure 8.4.

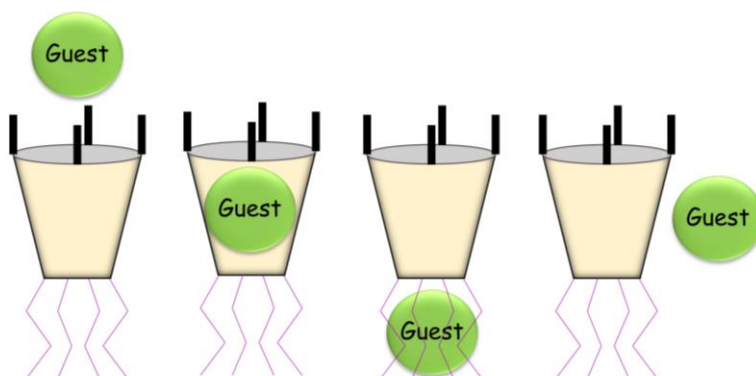


Figure 8.3 Representation of some possible host-guest binding modes.

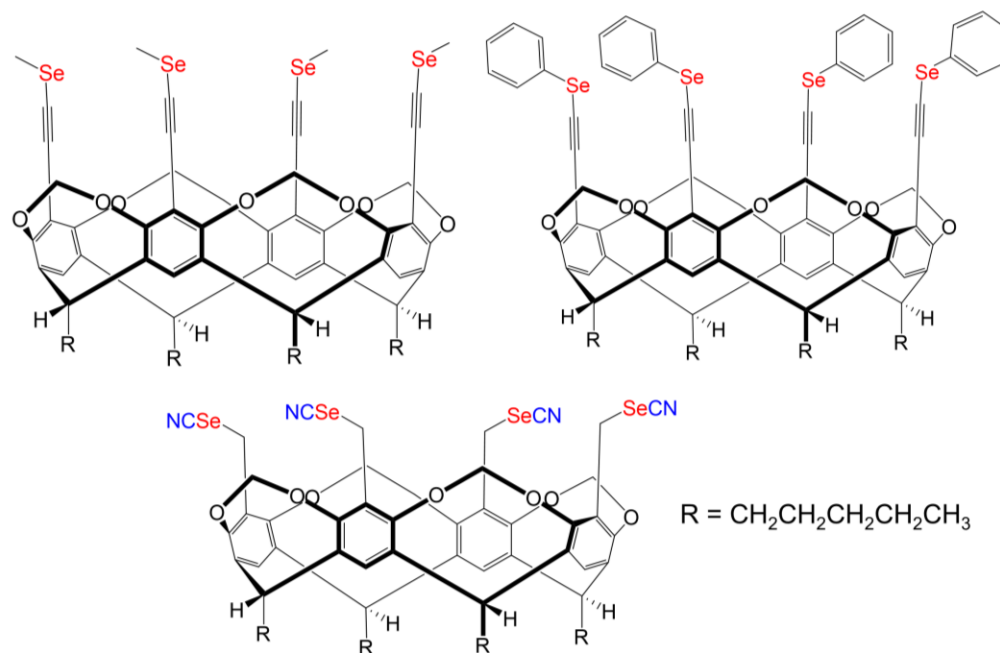


Figure 8.4 Target library.

A series of guest molecules with varying degrees of flexibility, electron donor ability and steric bulk were chosen to explore the possibility of the host-guest interactions driven by ChB interactions. The list of guest molecules selected is given in Figure 8.5.

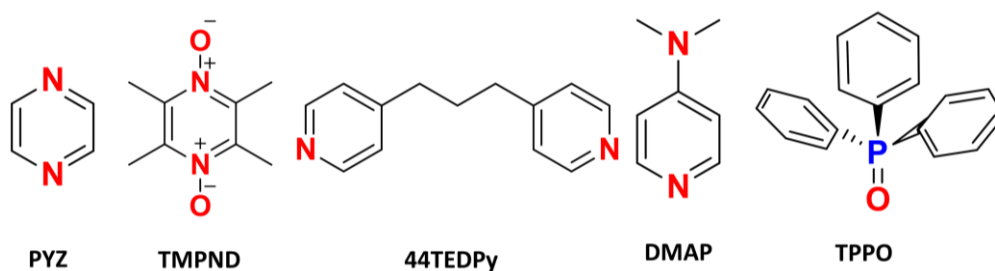


Figure 8.5 Selected list of guest molecules for solution studies.

In this study wanted to answer the following questions,

Question 1. How can we synthesize, characterize, and crystallize the host cavitands?

Question 2. Can we predict the host-guest interactions using molecular electrostatic potentials?

Question 3. How can we determine the origin of host-guest interactions?

Question 4. What dictates the host-guest interactions in the liquid phase? Is it coulombic attraction, geometrical features, or charge transfer?

8.2 Experimental

8.2.1 General

Reagents and solvents were purchased from commercially available sources and used without further purification. Melting points were measured using a TA instruments DSC Q20 differential scanning calorimeter. Nuclear magnetic resonance (NMR) data were measured on a Bruker Ascend 400 MHz spectrometer using either chloroform (CDCl_3) or dimethylsulfoxide (DMSO-d_6). The residual solvent peak was used as the internal reference for ^1H NMR. For ^{77}Se NMR the selenium peak was referenced against the residual solvent peak in its corresponding ^1H NMR spectrum.

8.2.2 Synthesis

The target cavitands were synthesized using modified procedures of the previously reported synthetic schemes.^{17,18,24}

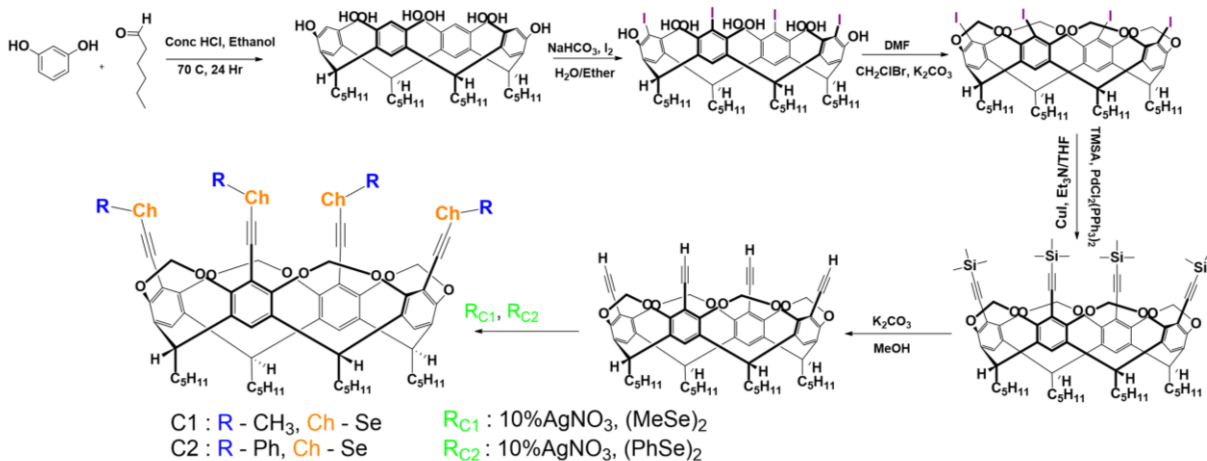


Figure 8.6 Overall synthetic scheme for the selenium methyl, selenium phenyl cavitand synthesis.

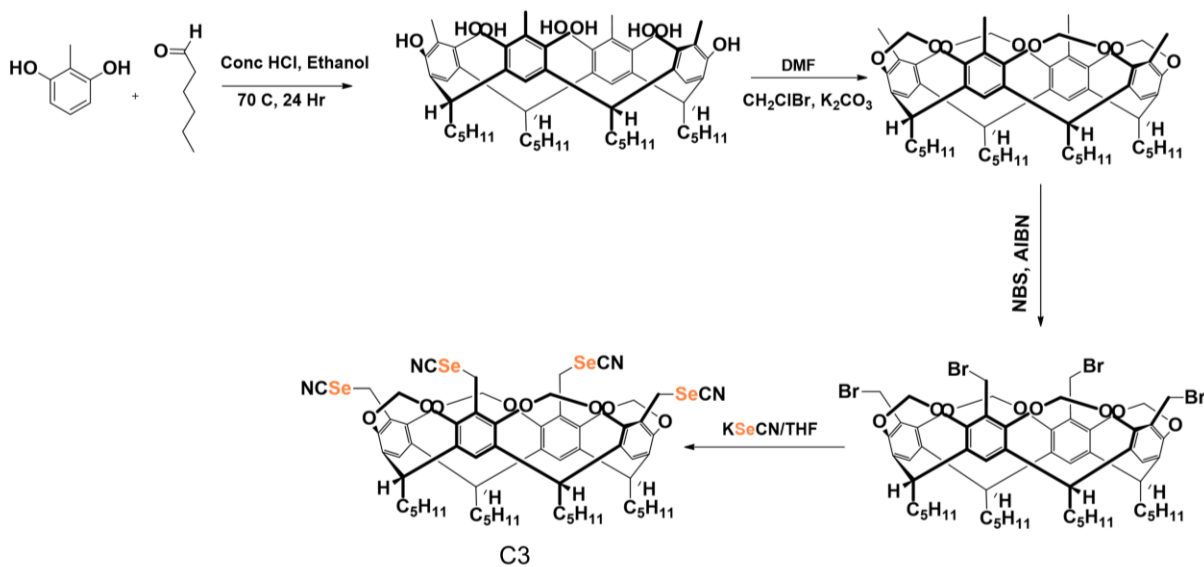


Figure 8.7 Overall synthetic scheme for the selenocyanato **C3** cavitand synthesis.

8.2.2.1 Synthesis of C-pentylcalix[4]resorcinarene

To a solution of resorcinol (100.00 g, 0.900 mol) in ethanol (900 ml) was added hexanal (91.00 g, 0.900 mol). The mixture was cooled to 0 °C under a N₂ atmosphere. Then conc. HCl (145

ml) was added dropwise over 15 minutes. A condenser was attached, and the mixture heated to 70 °C for 24 hours. The reaction mixture was allowed to cool to room temperature, and then diluted with 1 L water. The dark brownish precipitate formed which was filtered using a fritted Buchner funnel and washed with hot water until neutral pH and air dried. The product was dried in an oven at 100 °C for removal of excess water or solvents to yield the pure product. Yield 95 %. M.p. > 280 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 8.87 (s, 8H), 7.15 (s, 4H), 6.15 (s, 4H), 4.21 (t, J=7.6Hz, 4H), 2.03 (m, 8H), 1.16-1.25 (m, 24H), 0.83 (t, J = 6.4Hz, 12 H).

8.2.2.2 Synthesis of C-pentyltetraiodocalix[4]resorcinarene

To a solution of C-pentylcalix[4]resorcinarene (20.00g, 0.0260 mol) in a 1:1 mixture of water and diethyl ether (100 ml), NaHCO₃ (9.83 g, 0.117 mol), and I₂ (26.42g, 0.104 mol) were added. The solution was stirred overnight at room temperature. Following Buchner filtration, the precipitate was washed with cold ethanol. The pure product was collected as a white solid. Yield 31%. M.p. > 280 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 9.31 (s, 8H), 7.50 (s, 4H), 4.29 (s, 4H), 2.27 (s, 8H), 1.28 (m, 24H), 0.85 (s, 12H).

8.2.2.3 Synthesis of C-pentyltetraiodocavitand

C-pentyltetraiodocalix[4]resorcinarene (5.33 g, 4.20 mmol) was dissolved in DMF (80 ml) in a 250 ml round bottom flask. To this solution mixture CH₂ClBr (21.73 g, 0.168 mol) and K₂CO₃ (10.43 g, 0.0750 mol) was added, and the mixture was stirred at 85 °C for overnight under N₂. After neutralization with HCl 2%, a precipitate formed; following Buchner filtration, the resulting crude product was purified by column chromatography to obtain the white pure product. Yield 88%. M.p. > 280 °C. ¹H NMR (400 MHz, Chloroform-d) δ 7.05 (s, 4H), 5.96 (d, J = 7.4 Hz, 4H), 4.84

(t, J = 8.1 Hz, 4H), 4.31 (d, J = 7.4 Hz, 4H), 2.18 (m, 8H), 1.39-1.30 (m, 24H), 0.91 (d, J = 7.1 Hz, 12H).

8.2.2.4 Synthesis of C-pentyltetra((trimethylsilyl)ethynyl)cavitand

C-pentyltetraiodocavitand (1.62 g, 1.23 mmol) was dissolved in trimethylamine and THF mixture and degassed by bubbling N₂ through the reaction mixture for 10-15 min. TMS-acetylene (6.15 mmol, 0.98 ml), PdCl₂(PPh₃)₂ (0.086 g, 0.123 mmol) and CuI (0.047 g, 0.246 mmol) were added to the mixture. The resulting mixture was refluxed at 70- 80 ° C overnight under N₂ atmosphere. The reaction was monitored using TLC. Upon completion the solvent was evaporated using rotary evaporator and the residue was purified by column chromatography to obtain the pure product. Yield 77%. M.p. > 280 °C. ¹H NMR (400 MHz, Chloroform-d) δ 6.97 (s, 4H), 5.84 (d, J = 7.3 Hz, 4H), 4.77 (t, J = 7.9 Hz, 4H), 4.51 (d, J = 7.2 Hz, 4H), 2.16 (m, 8H), 1.34 (s, 24H), 0.89 (s, 12H), 0.19 (s, 36H).

8.2.2.5 Synthesis of C-pentyltetra(ethynyl)cavitand

C-pentyltetra((trimethylsilyl)ethynyl)cavitand (1.467 g, 0.0012 mol) and potassium carbonate (1.34 g, 0.00976 mol) were stirred in methanol at room temperature for 6 hrs. Upon completion the solvent was removed by rotavap, and the solid was dissolved in diethyl ether and washed with water. The organic layer was dried using anhydrous magnesium sulfate and the solvent was removed via rotavap to obtain the pure product. Yield 79%. M.p : > 280 °C. ¹H NMR (400 MHz, Chloroform-d) δ 7.05 (s, 4H), 5.93 (d, J = 7.3 Hz, 4H), 4.79 (t, J = 8.1 Hz, 4H), 4.52 (d, J = 7.3 Hz, 4H), 3.31 (s, 4H), 2.18 (s, 8H), 1.34 (s, 24H), 0.90 (s, 12H).

8.2.2.6 Synthesis of C-pentyltetra((methylselanyl)ethynyl)cavitand (C1)

C-pentyltetra(ethynyl)cavitand (0.228 g, 0.250 mmol) was dissolved in dichloromethane (5 ml) in a 100 ml round bottom flask. This was stirred and AgNO₃ (10% mol/mol, 0.0169 g, 0.100 mmol) was added followed by the addition of dimethyl diselenides (0.094 g, 0.500 mmol). Septum was placed on the round bottom and the mixture was stirred at room temperature under air overnight. The solvent was evaporated, and the crude was purified by column chromatography. This was further recrystallized to obtain the pure product. Yield 68%. Mp : > 280 °C. ¹H NMR (400 MHz, Chloroform-d) δ 6.96 (s, 4H), 5.87 (d, J = 7.2 Hz, 4H), 4.75 (t, J = 8.0 Hz, 4H), 4.45 (d, J = 7.2 Hz, 4H), 2.35 (s, 12H), 2.14 (s, 8H), 1.32 (s, 24H), 0.89 (s, 12H).

8.2.2.7 Synthesis of C-pentyltetra((phenylselanyl)ethynyl)cavitand (C2)

C-pentyltetra(ethynyl)cavitand (0.228 g, .250 mmol) was dissolved in dichloromethane (5 ml) in a 100 ml round bottom flask. This was stirred and AgNO₃ (10% mol/mol, 0.0169 g, 0.100 mmol) was added followed by the addition of diphenyl diselenide (0.156 g, 0.500 mmol). A septum was placed on the round bottom and the mixture was stirred at room temperature under air overnight. The solvent was evaporated, and the crude was purified by column chromatography. The crude was purified by column chromatography to obtain the pure product. Yield 77%. M.p : > 280 °C. ¹H NMR (400 MHz, Chloroform-d) δ 7.56 (d, J = 7.2 Hz, 4H), 7.31 – 7.21 (m, 16H), 7.18 (d, J = 7.2 Hz, 4H), 7.02 (s, 4H), 5.77 (d, J = 7.3 Hz, 4H), 4.80 (t, J = 8.0 Hz, 4H), 4.48 (d, J = 7.2 Hz, 4H), 2.20 (s, 8H), 1.37 (s, 24H), 0.92 (s, 12H). ⁷⁷Se NMR (76 MHz, Chloroform-d) δ 282.22.

8.2.2.8 Synthesis of C-pentyltetramethylresorcin[4]arene

To a solution of 2-methylresorcinol (10.00 g, 0.0800 mol) in ethanol (90 ml) hexanal (8.1 g, 0.0810 mol) was added. The solution was cooled to 0 °C under N₂ atmosphere. Then conc. HCl (14.5 ml) was added dropwise over 15 minutes. The reaction mixture was refluxed at 70 °C for 12 hr. The reaction mixture was allowed to cool to room temperature, and then diluted with water. A dark brownish precipitate formed which was filtered using a fritted Buchner funnel and washed with hot water until neutral pH and air dried. The product dried in oven at 100 °C for removal on excess water or solvents. Yield 90 %. M.p : >280 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 8.65 (s, 8H), 7.25 (s, 4H), 4.20 (t, J = 7.6Hz, 4H), 2.22 (m, 8H), 1.95 (s, 12H), 1.16-1.25 (m, 24H), 0.85 (t, J = 6.4Hz, 12 H).

8.2.2.9 Synthesis of C-pentyltetramethylcavitand

To a stirred solution of C-pentyltetramethylresorcin[4]arene (5.00 g, 6.50 mmol) in DMF (200 ml) K₂CO₃ (18.5 g, 0.0130 mol) and CH₂BrCl 10.09 ml, 0.0780 mol) was added. The solution was heated at 70 °C for 24 h. The reaction mixture was then poured into cold ice water and the brown solid was collected by suction filtration. The crude product was purified through column chromatography. Yield 48%. M.p : >280 °C. ¹H NMR (400 MHz, Chloroform-d) δ 6.98 (s, 4H), 5.88 (d, J = 4Hz, 4H), 4.76 (t, J = 8Hz, 4H), 4.26 d, J = 4Hz, 4H), 2.20 (m, 8H), 1.95 (s, 12H), 1.16-1.25 (m, 24H), 0.90 (t, J = 6.4Hz, 12 H).

8.2.2.10 Synthesis of C-pentyltetra(bromomethyl)cavitand

Dry C-pentyltetramethylcavitand (2.65 g, 3.05 mmol) and AIBN (119 mg, catalytic amount) was dissolved in 170 ml of degassed CCl₄. Then NBS (2.71 g, 15.2 mmol) was added under dark conditions, and the reaction mixture was refluxed overnight. The reaction was

monitored by TLC. After completion the solid precipitate was filtered off and CCl_4 was evaporated to yield white product. Yield 61%. M.p. $>280^\circ\text{C}$. ^1H NMR (400 MHz, Chloroform- d) δ 7.31 (s, 4H), 6.02 (d, $J = 4\text{Hz}$, 4H), 4.77 (t, $J = 8\text{Hz}$, 4H), 4.56 (d, $J = 4\text{Hz}$, 4H), 4.41 (s, 8H), 2.20 (m, 8H), 1.30-1.43 (m, 24H), 0.90 (t, $J = 8\text{Hz}$, 12 H).

8.2.2.11 C-pentyltetra(selenocyanatomethyl)cavitand (C3)

The C-pentyltetra(bromomethyl)cavitand (0.200 g, 0.170 mmol) was dissolved in THF and KSeCN (0.118 g, 0.816 mmol) was added to this reaction mixture and stirred and refluxed at 80°C for overnight under N_2 . The progress of the reaction was monitored using TLC and upon completion the solvent was removed by rotavap and purified by column chromatography. Yield 89%. M.p $> 280^\circ\text{C}$. ^1H NMR (400 MHz, Chloroform- d) δ 7.14 (s, 4H), 6.00 (d, $J = 7.1\text{ Hz}$, 4H), 4.73 (s, 4H), 4.37 (d, $J = 7.1\text{ Hz}$, 4H), 4.17 (s, 8H), 2.19 (d, $J = 6.5\text{ Hz}$, 8H), 1.39 (m, 24H), 0.89 (t, $J = 7.0\text{ Hz}$, 12H).

8.2.3 Molecular electrostatic potential maps

Molecular electrostatic potentials were calculated using Spartan14 Wavefunction. The host compounds were sketched using ChemDraw 12 without the pentyl feet in order to minimize the computational time required and this was saved and loaded into Spartan14 software followed by conformer distribution analysis using molecular mechanics using MMFF. The hundred most stable conformers were then subjected to a geometry optimization using semi-empirical calculations using PM6 level of theory. The ten most stable conformers were then saved and subjected to Hartree-Fock calculations using 3-21G basis set. Finally, the most stable conformer was then geometry optimized and analyzed for the molecular electrostatic potential map using density

functional theory and B3LYP hybrid functional and 6-311++G** basis set. For the small guest molecules, the optimization was performed at the same B3LYP /6-311++G** level of theory. A positive point charge in the vacuum was used as a probe against the surface to determine the positive and negative regions on the molecular surface. The electrostatic potentials presented herein are given in kJ/mol and a negative number is representative of an electron rich acceptor and a positive number of an electron poor donor.

8.2.4 NMR titration experiments

A solution of 0.5 ml of 40 mM of the host cavitand (**C3**) and 1 ml of 0.2 M guest compound was prepared. The guest was added to the host solution in the NMR tube in 0.25 equivalence (25 μ l) increments and analyzed using ^1H NMR and ^{77}Se NMR. Control experiments were done for host and the guest solution to rule out the possible influence of dilution effects.

8.3 Results

8.3.1 Molecular electrostatic potential maps

The electrostatic potentials of the most noticeable positive and negative regions of the host and the guest molecules were calculated at B3LYP/6-311**G++ at iso=0.002. The molecules explored in this study are summarized in Figure 8.8 and 8.9.

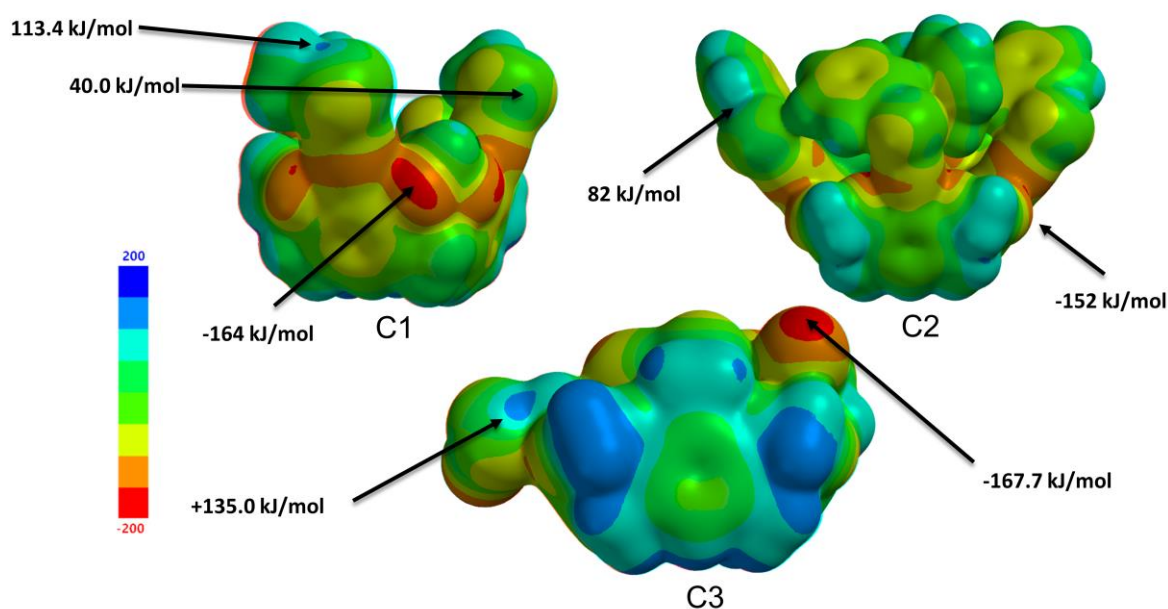


Figure 8.8 MEPs of the cavitands synthesized with the highest positive and negative potentials observed for each target.

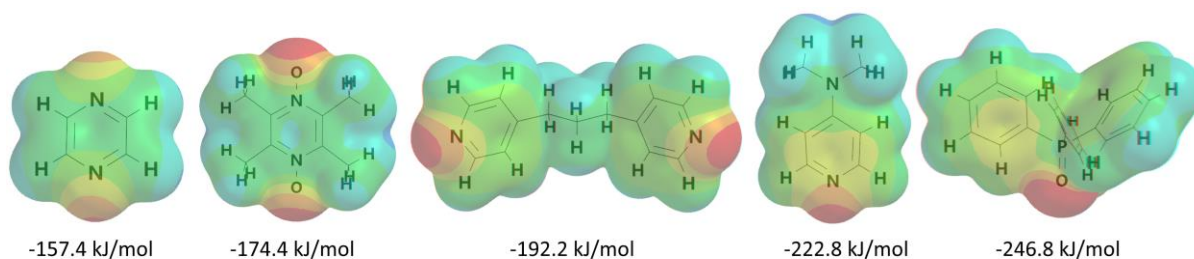


Figure 8.9 A summary of the electrostatic potentials observed for the select guest molecules.

8.3.2 CSD analysis

MEPs give an overview of the most probable interactions between the host and the guest in the gas phase but to add more validation towards the selection of the conformers and the relevant synthons formation in the solid state, an analysis of the potential interactions between chalcogen-bond donor groups used in this study and the geometrical features of possible ChBs in both homomeric and heteromeric systems were conducted using CSD. During the analysis, only crystal

structures with $R < 0.5$, non-disordered, nonionic, organic, and single crystal structures were considered.

8.3.3 NMR titrations

A summary of the positive and a negative NMR titration experiment between the host and the guest molecules are illustrated in Figures 8.10 to 8.14.

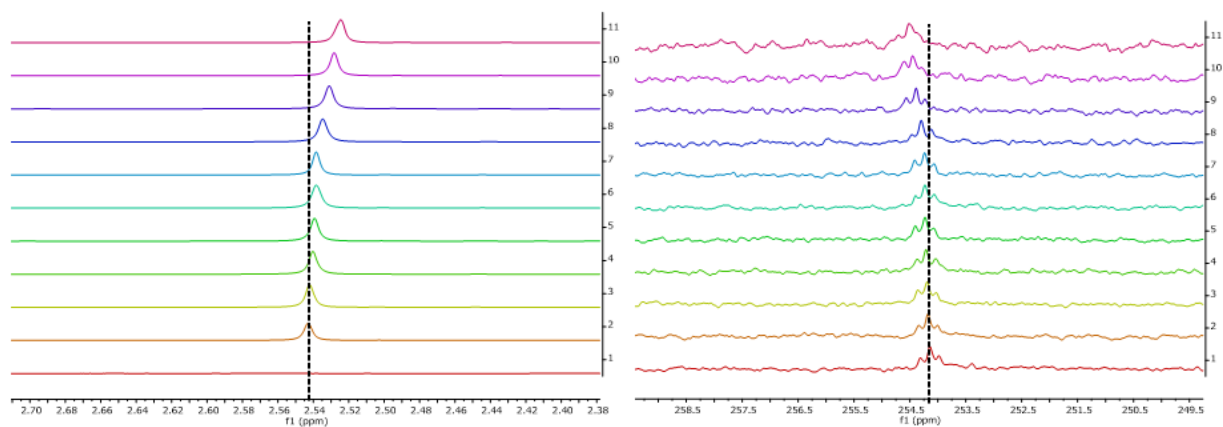


Figure 8.10 ^1H and ^{77}Se NMR titration experiment for **C3** host with **TMPND** guest.

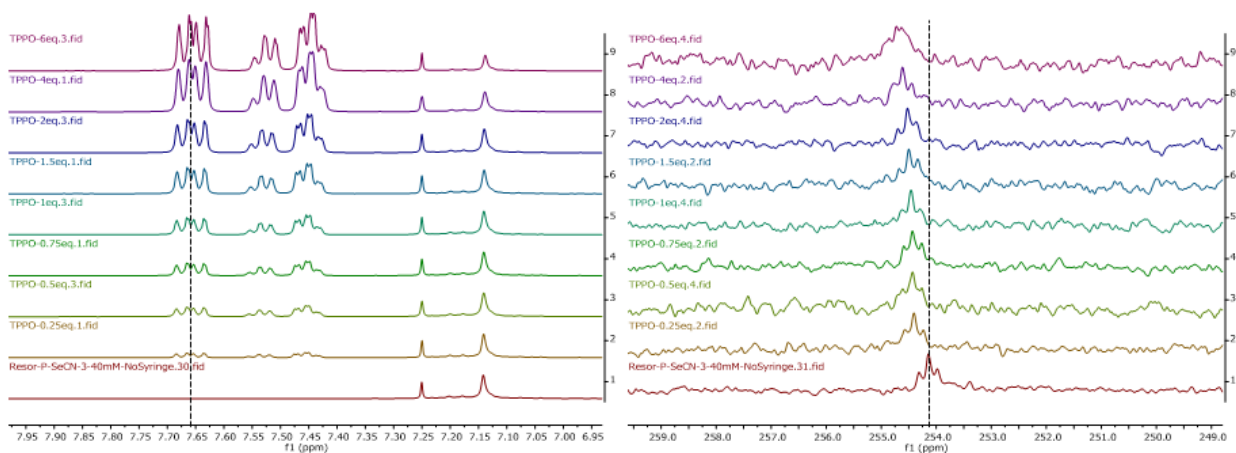


Figure 8.11 ^1H and ^{77}Se NMR titration data for **C3** host with **TPPO** guest.

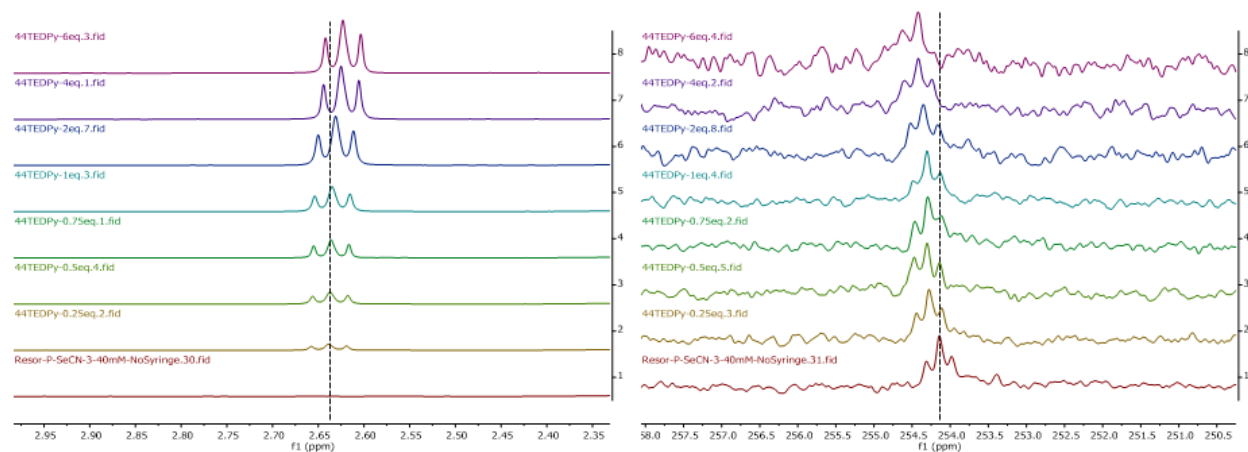


Figure 8.12 ^1H and ^{77}Se NMR titration data for **C3** host with **44TEDPy**.

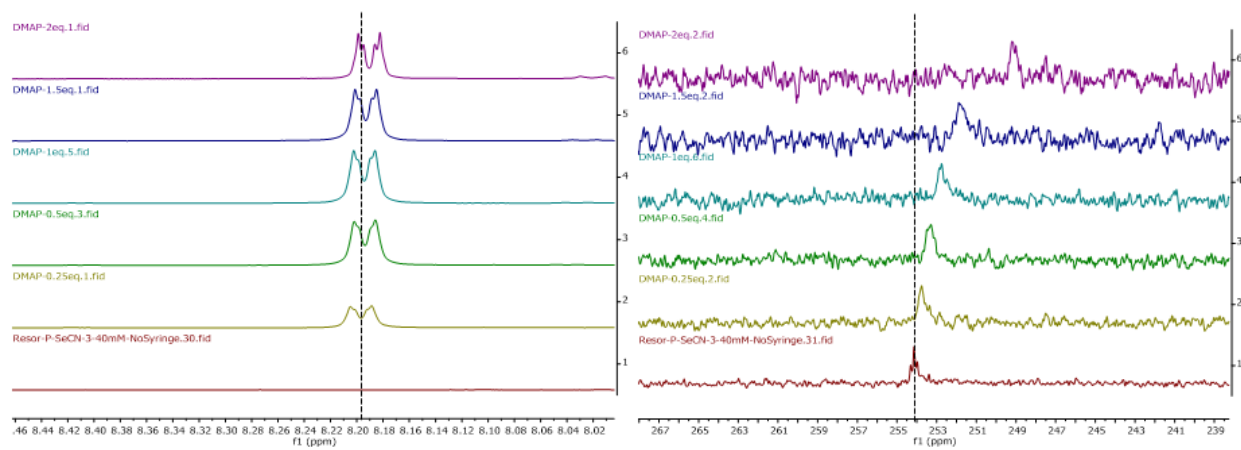


Figure 8.13 ^1H and ^{77}Se NMR titration data for **C3** with **DMAP**.

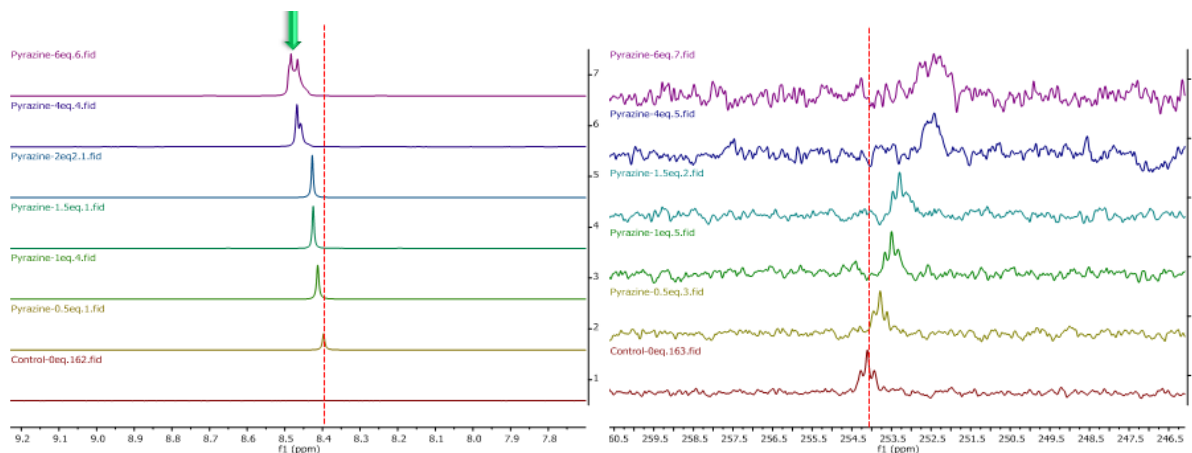


Figure 8.14 ^1H and ^{77}Se NMR titration data for **C3** host with **PYZ** guest.

8.4 Discussion

8.4.1 Molecular electrostatic potentials

MEPs calculated for the **C1-C3** hosts showed an increased σ -hole potentials in the order of **C2** < **C1** < **C3** with lowest σ -hole potential value being 82 kJ/mol and the highest +135.0 kJ/mol. Unlike the molecules seen in chapter 2 and 3, only the σ -hole directly opposite to the sp -hybridized $\text{C}\equiv\text{C}$ show a significant positive potential which indicates that for these hosts only one specific ChB is likely. Based on what was observed in chapter 2 and 3, the Coulombic attractions took place between the most positive potential, the σ -hole, and the most negative potential. Based on this we could drive heteromeric host-guest interactions by employing guest molecules with larger negative potentials. Since the σ -hole potential is directly related to the interaction energies we decided to only examine the **C3** host which had the highest σ -hole for performing initial host-guest interaction analysis.

The selected guest molecules differed in multiple aspects including steric bulk, torsional flexibility and, most importantly, electrostatic potentials, to improve our understanding of the influence of multiple factors driving the host-guest interactions through ChB. Since the guest

molecules were expected to act as chalcogen-bond acceptors, the most negative potential of the guest was analyzed which showed significant increase in the negative values in the order of **PYZ** < **TMPND** < **44TEDPy** < **DMAP** < **TPPO**.

8.4.2 Conformational flexibility of the C3

In order to analyze the rotational flexibility of **C3**, which was used for the solution studies, rotational energy calculation was performed using Spartan14 at HF/3-21G level of theory using a model small molecule to limit the computational time. The resulting energy profile showed the possible conformers of the model system which can reasonably be applied to the cavitand systems as well. The highest energy conformer was observed for the conformation where SeCN group is in a syn-periplanar orientation with the benzene ring and the lowest energy was obtained when it was anti-periplanar with the benzene ring (Figure 8.15). This showed the wide range of flexibility observed in this type to functional groups in solid-state.

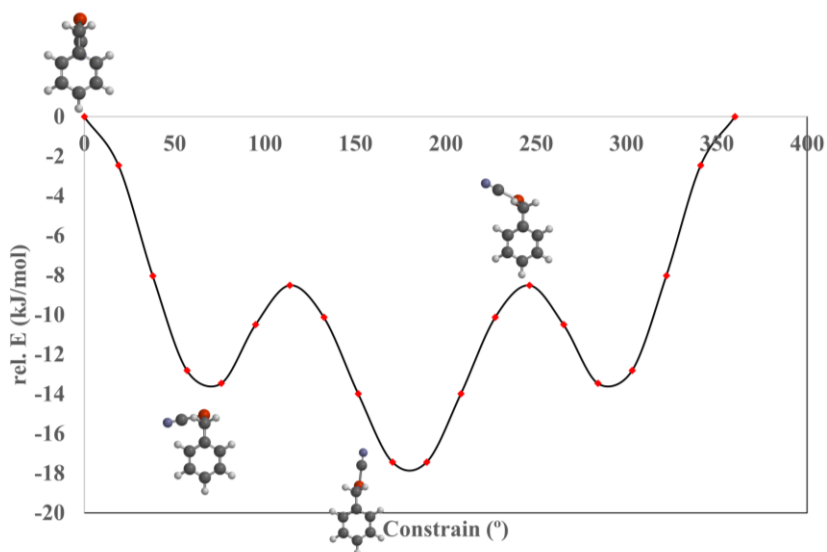


Figure 8.15 Graph of torsional strain energy change with respect to dihedral angle of the model system.

8.4.3 CSD analysis

MEPs provides an overview of potential guest acceptors and synthons along which we can drive host-guest interactions with **C3** using ChB as the driving force. However, to also explore existing data from the solid-state regarding possible synthons of the host-guest interactions, a CSD search was done. Due to the rotational flexibility multiple orientations of this SeCN was observed but the specific type of ChB interactions this selenocyanato group can form were found to be of only three types (Figure 8.16).

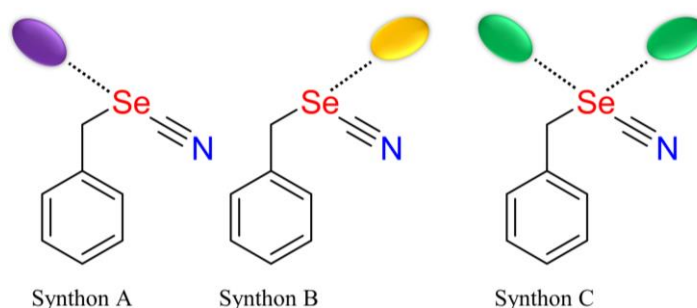


Figure 8.16 Plausible synthon assembly with the host functional group and the guests.

The two possible interactions that can form along the C-Se bond and the five selected guests were the $\text{Se}\cdots\text{N}$ and $\text{Se}\cdots\text{O}$ ChB interactions with N/O acceptor site on the guest molecule. The CSD search found 44 single crystal structures having 117 instances of $\text{Se}\cdots\text{N/O}$ ChB. Only 15 were crystal structures of multicomponent systems with $\text{Se}\cdots\text{N/O}$ interactions between a target chalcogen-bond donor and a N/O based guest acceptor. A summary of these synthons and their geometrical features are given in Figure 8.17.

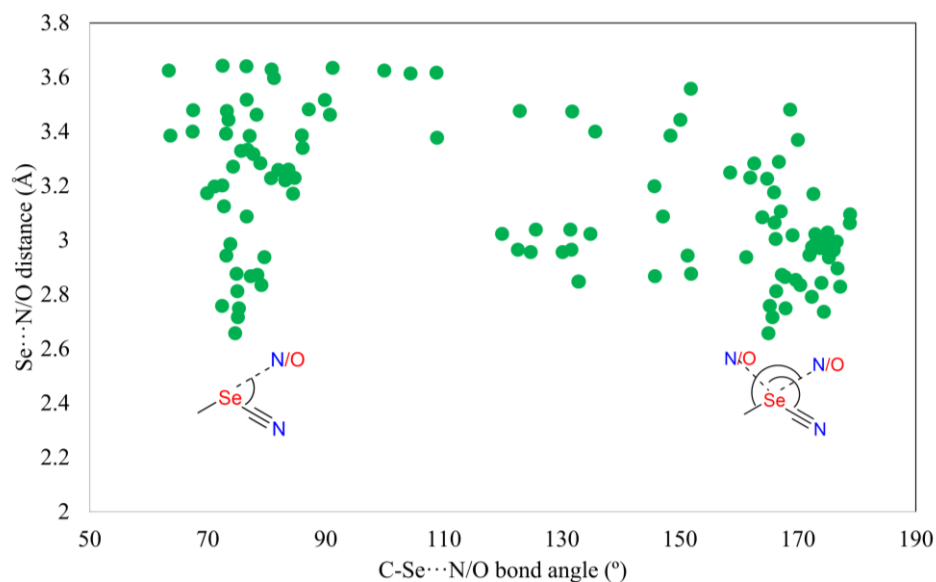


Figure 8.17 A summary of the geometrical features of the plausible synthons within the CSD database.

8.4.4 Solution phase ChB characterization

The computational calculations and solid-state structural data suggested the possibility of several ChB synthons with the selected guests, but can they form a similar ChB synthon in the solution phase?

Noncovalent interaction such as XB have been used in both solid-state and solution based applications over the past decade, in comparison ChB have predominantly been investigated in the solid-state. The characterization of the ChB in solution phase has been scarcely studied and the existing literature only consists of very few studies that was used to detect chalcogen bonding in solution. The existing data showed that it is possible to use multinuclear NMR titration^{25–28}, UV-Vis²⁹, IR^{30,31} and isothermal calorimetry (ITC)²⁹ for the solution based studies. To detect ChB driven host-guest assembly by **C3**, as an initial characterization we used NMR active ⁷⁷Se. The

sensitivity of ^{77}Se towards its chemical environment would make it easier to detect the specific ChB interactions expected.

8.4.4.1 NMR titrations

NMR titration studies with **C3** and the 2,3,5,6-tetramethylpyrazine 1,4-dioxide (**TMPND**) showed upfield ^1H NMR shifts of the methyl groups indicating shielding, and the ^{77}Se NMR showed downfield shift which is an indication of deshielding. The NMR shifts were initially suspected to be due to host-guest interaction, however, when the **TMPND** guest was titrated with a blank sample for the control experiment without the host it resulted in the same upfield shift as in the control experiment. Control experiment with just the host also showed the same downfield shifts which indicates that these shifts were purely due to dilution effects. The higher steric bulk and the lower negative electrostatic potential on the oxygen atom compared to the other guests used, make this guest a less likely candidate for host-guest interactions through ChB.

The solution studies with the triphenylphosphine oxide (**TPPO**) and **C3** showed no sign of ^1H NMR shift of the guest molecule however the same upfield ^{77}Se shift of the host as before was seen during the titration. The control experiment performed showed the same result as previous which confirms that there was no ChB driven host-guest assembly even though **TPPO** had the highest negative potential among all the guests used. The large steric bulk of three phenyl rings make this guest an unlikely candidate for host-guest binding with **C3** system.

The most rotationally flexible molecule of all the guest molecules used was the 4,4'-trimethylenedipyridine (**44TEDPy**) which had a moderately high negative potential that could result in ChB driven host-guest assembly. Though a downfield and a upfield shifts were observed for the ^1H and ^{77}Se NMR respectively, they were both a result of dilution effects.

The fourth guest molecule used was dimethyl aminopyridine (**DMAP**) and the titration did not show any noticeable changes to the protons on the guest molecules, however the ^{77}Se NMR showed an upfield chemical shift which was completely opposite to the previous three solution studies. The presence of the upfield ^{77}Se shift is an indication of shielding of the selenium atom that occurs as a result of the donation of the electron density from the guest molecule towards the host molecule when forming a ChB. A similar observation was made during a recent ^{125}Te NMR titration study of diphenyl ditelluride derivatives with triphenyl phosphine oxide³² nevertheless these observations provide the first evidence of a ChB driven host-guest assembly in this family of compounds.

The fifth and the final guest molecule studied was the pyrazine (**PYZ**) which had the lowest negative potential with no flexibility or steric hindrance. The solution study with the ^1H NMR showed downfield shifts of the pyrazine protons that indicates shielding and at four equivalences of the guest, the NMR started to split into two peaks. NMR splitting implied the slow exchange rate between the bound and the free guest and the upfield shift of the ^{77}Se reconfirms the ChB driven host-guest interaction between the **C3** and **PYZ**.

Overall, the titration experiments showed chemical shift changes upto 0.18 and 1.39 (1:1 **PYZ:C3** mixture) ppm for ^1H and ^{77}Se NMR respectively. The NMR solvent, CDCl_3 , used showed no competition towards the host-guest binding during the NMR titration experiment.

8.4.5 Evidence towards the nature of ChB

The nature of the ChB is still under debate but can be attributed to the electrostatic, dispersion, polarization, repulsion and charger transfer components which work in tandem to direct and strengthen the ChB. The MEPs of the **C3** and the guest molecules implies a coulombic

approach during the ChB formation however, the inability of the highest negative potential bearing **TPPO** and **44TEDPy** to interact with **C3** suggests that there are structural influences such as steric and conformational features that affects the host guest interaction in this series. The upfield shift of the ^{77}Se NMR signal provides evidence towards charge transfer component in which the lone pair electrons on the guest interacts with the σ^* orbital of the Se-C bond resulting in a $n \rightarrow \sigma^*$ charge transfer (Figure 8.18). Interestingly, out of the five guests used none of the guests with oxygen donors showed host-guest interactions which showed the preference of the soft selenium Lewis acid to interact with soft nitrogen Lewis base over oxygen following HSAB theory.

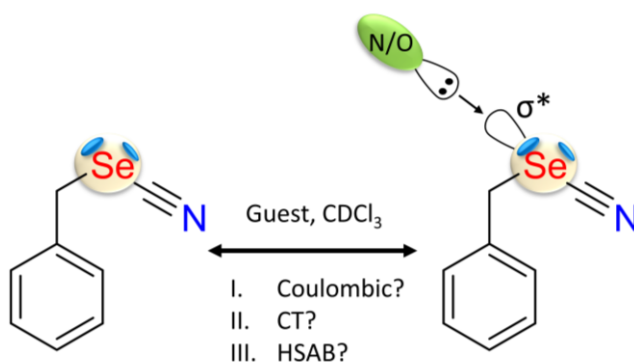


Figure 8.18 Schematic of the host-guest interactions with the unoccupied σ^* orbital of the chalcogen-bond donor.

8.5 Conclusions

We have successfully synthesized chalcogen functionalized resorcin[4]arene based cavitands for chalcogen-bond driven host-guest assembly. Though we lack solid-state structural data for the three targets synthesized, this provides more avenues for developing much stronger chalcogen-bond donor cavitands for studying not just host-guest chemistry but also supramolecular heteromeric capsule assembly driven by ChBs (Figure 8.19).

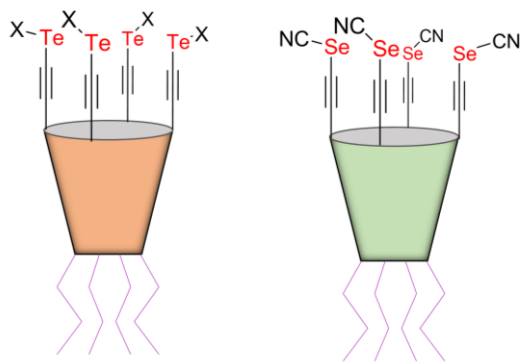


Figure 8.19 Schematic of a more "activated" chalcogen-bond donor cavitand.

MEPs predicted the coulombic attraction between the chalcogen-bond donor and the guest and showed the presence of the single σ -hole opposite to the Se-C bond. The CSD analysis resulted in three possible solid-state ChB synthons that could result during the host-guest assembly driven by chalcogen bonding.

The solution based studies using ^{77}Se NMR titrations confirmed the chalcogen-bond driven host-guest interactions for **PYZ** and **DMAF** based on the upfield ^{77}Se NMR shifts. This behavior of the solution based ChB matches with the charge transfer nature of the σ -hole interactions.

8.6 References

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Appendix B – Additional information for Chapter 2

Table B.1 Crystallographic information for the target crystal structures

Code	4Py	4CN	4NO2	35DN
Formula moiety	C ₈ H ₇ N Se	C ₁₀ H ₇ N Se	C ₉ H ₇ N O ₂ Se	C ₉ H ₆ N ₂ O ₄ Se
Empirical formula	C ₈ H ₇ N Se	C ₁₀ H ₇ N Se	C ₉ H ₇ N O ₂ Se	C ₉ H ₆ N ₂ O ₄ Se
Molecular weight	196.11	220.13	240.12	285.12
Color, Habit	Colorless, irregular	Colorless, needle	Orange, irregular	Orange, plate
Crystal system	monoclinic	triclinic	triclinic	orthorhombic
Space group, Z	P 2 ₁ /c, 4	P -1, 2	P -1, 2	P 2 ₁ 2 ₁ 2 ₁ , 4
a, Å	7.2141(3)	5.32630(10)	6.9311(4)	5.72550(10)
b, Å	5.5542(2)	9.1435(2)	7.0573(2)	11.35670(10)
c, Å	20.2334(7)	9.6724(2)	10.2804(3)	15.9304(3)
α, °	90	105.206(2)	93.681(3)	90
β, °	94.582(4)	93.326(2)	102.877(4)	90
γ, °	90	94.012(2)	106.191(4)	90
Volume, Å ³	808.13(5)	452.020(17)	466.47(3)	1035.84(3)
Density, g/cm ³	1.612	1.617	1.71	1.828
T, °K	220.00(10)	170.00(10)	170.00(10)	140.00(10)
Crystal size, min x mid x max	0.02×0.054×0.061	0.02×0.03×0.3	0.02×0.02×0.4	0.03×0.14×0.38
X-ray wavelength, Å	1.54184	1.54184	1.54184	1.54184
μ, mm ⁻¹	5.641	5.122	5.186	4.972
Trans min / max	0.80073/ 1.00000	0.70205/1.00000	0.56921/1.00000	0.45847 /1.00000
θ _{min} , °	4.38	4.753	4.453	4.782
θ _{max} , °	77.62	77.366	77.118	77.527
Reflections				
collected	7128	9610	5883	13280
independent	1698	1908	1922	2185
observed	1576	1853	1732	2153
R _{int}	0.0296	0.0356	0.0254	0.0356
Threshold expression	> 2σ(I)	> 2σ(I)	> 2σ(I)	> 2σ(I)
No. parameters	92	137	119	146
No. restraints	0	0	0	0
R ₁ (observed)	0.078	0.0291	0.0344	0.0323
wR ₂ (all)	0.2172	0.0782	0.0952	0.0922
Goodness of fit (all)	0.9924	1.098	1.055	1.095
ρ _{max} , ρ _{min} , e Å ⁻³	1.4658, -1.1587	0.783, -0.614	0.458, -0.464	0.635, -0.827

Completeness to 2θ limit	0.9884	0.993	0.977	0.998
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Table B.2 Target Vmax and Vmin potentials and Hammet parameters

Target	σ_1 potential kJ/mol	σ_2 potential kJ/mol	Vs, min	Hammet $\sigma_{p/m}$
B1	113	40	-90.3	0.00
4F	121	47	-82.2	0.06
4Py	144	74	-185	0.44
4CN	152	84	-185	0.66
4NO2	161	90	-169.5	0.78
35DN	175	105	-135	$0.71 \times 2 = 1.42$

Appendix C – Additional information for Chapter 3

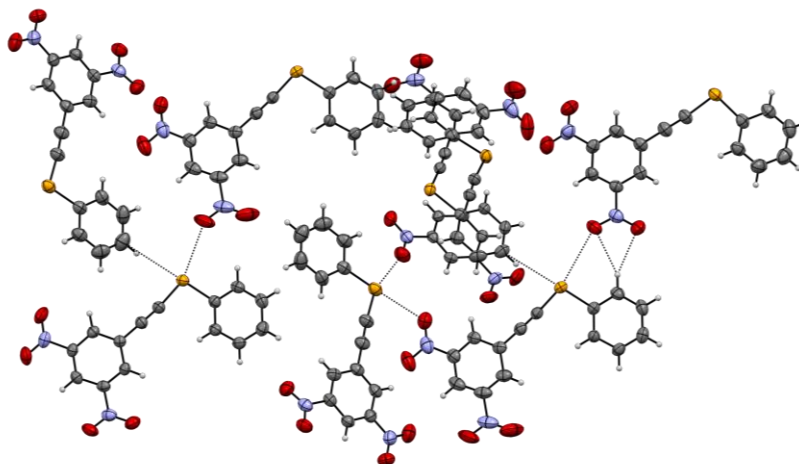


Figure C.1 35DN-Ph structure with three symmetrically unique molecules

Table C.1 Crystallographic information for the target crystal structures

Code	4Br-Ph	4CN-Ph	4NO ₂ -Ph	35DN-Ph
Formula moiety	C ₁₄ H ₉ Br Se	C ₁₅ H ₉ N Se	C ₁₄ H ₉ N O ₂ Se	C ₁₄ H ₈ N ₂ O ₄ Se
Empirical formula	C ₁₄ H ₉ Br Se	C ₁₅ H ₉ N Se	C ₁₄ H ₉ N O ₂ Se	C ₁₄ H ₈ N ₂ O ₄ Se
Molecular weight	336.08	282.19	302.18	347.18
Color, Habit	Colorless, irregular	Colorless, plate	Yellow, plate	Colorless, irregular
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic
Space group, Z	P 2 _{1/n} , 4	P 2 _{1/n} , 4	P 2 _{1/n} , 4	P 2 _{1/c} , 12
a, Å	7.20718(10)	5.95283(12)	7.4680(3)	7.6210(3)
b, Å	5.81264(9)	7.79755(19)	6.13080(19)	32.5170(17)
c, Å	28.9328(4)	25.7920(7)	27.0323(9)	16.4980(6)
α, °	90	90	90	90
β, °	90.7737(12)	95.046(2)	91.214(3)	97.473(4)
γ, °	90	90	90	90
Volume, Å ³	1211.97(3)	1192.56(5)	1237.39(7)	4053.7(3)
Density, g/cm ³	1.842	1.572	1.622	1.707
T, °K	150.00(10)	293(2)	210.00(10)	293(2)
Crystal size, min x mid x max	0.103×0.38×0.8	0.021×0.075×0.166	0.006×0.04×0.05	0.02×0.042×0.091

X-ray wavelength, Å	0.71073	1.54184	1.54184	1.54184
μ , mm ⁻¹	6.362	4.034	4.055	3.945
Trans min / max	0.66587/1.00000	0.83671/1.00000	0.01769/1.00000	0.79361/1.00000
θ_{min} , °	2.806	3.368	3.27	2.718
θ_{max} , °	29.259	76.515	77.522	77.806
Reflections				
collected	31212	3575	4114	40331
independent	4328	3575	4114	8515
observed	3799	3366	3688	6900
R _{int}	0.0221	0.056	0.055	0.0521
Threshold expression	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$
No. parameters	145	155	164	568
No. restraints	0	0	0	0
R ₁ (observed)	0.0262	0.0568	0.049	0.0429
wR ₂ (all)	0.0481	0.1452	0.133	0.0948
Goodness of fit (all)	1.118	1.147	1.058	1.048
ρ_{max}, ρ_{min} , e Å ⁻³	0.486, -0.486	0.403, -0.578	0.376, -0.474	0.799, -0.600
Completeness to 2 θ limit	0.917	0.98	0.97	0.983

Table C.2 Crystallographic information for the target crystal structures

Code	4Cl-Te	4Br-Te	4CN-Te	4Py-Te	4NO ₂ -Te	35DN-Te
Formula moiety	C ₁₄ H ₉ Cl Te	C ₁₄ H ₉ Br Te	C ₁₅ H ₉ N Te	C ₁₃ H ₉ N Te	C ₁₄ H ₉ N O ₂ Te	C ₁₄ H ₈ N ₂ O ₄ Te
Empirical formula	C ₁₄ H ₉ Cl Te	C ₁₄ H ₉ Br Te	C ₁₅ H ₉ N Te	C ₁₃ H ₉ N Te	C ₁₄ H ₉ N O ₂ Te	C ₁₄ H ₈ N ₂ O ₄ Te
Molecular weight	340.26	384.72	330.83	306.81	350.82	395.82
Color, Habit	Colorless, block	Colorless, needle	Yellow, needle	Colorless, plate	Yellow, plate	Orange, irregular
Crystal system	monoclinic	monoclinic	Monoclinic	Triclinic	monoclinic	Triclinic
Space group, Z	P 2 ₁ , 2	P 2 ₁ , 2	P 2 _{1/n} , 4	P -1, 2	P 2 ₁ , 2	P -1, 2
a, Å	7.27450(10)	7.4148(2)	14.3088(3)	5.8169(2)	4.98542(6)	7.40070(9)
b, Å	5.82070(10)	5.80562(17)	4.88289(9)	8.1272(2)	22.5396(3)	9.23166(11)
c, Å	14.7186(3)	14.9396(6)	17.8477(3)	12.1467(2)	5.67334(8)	11.33835(12)
α , °	90	90	90	96.996(2)	90	86.7423(9)
β , °	100.243(2)	100.897(3)	92.1764(18)	90.889(2)	94.9340(13)	77.5729(10)
γ , °	90	90	90	93.674(2)	90	69.6415(11)
Volume, Å ³	613.292(19)	631.52(4)	1246.09(4)	568.63(3)	635.147(14)	709.102(15)

Density, g/cm ³	1.843	2.023	1.763	1.792	1.834	1.854
<i>T</i> , °K	200.00(10)	220.00(10)	200.00(10)	200.00(10)	200.00(10)	200.00(10)
Crystal size, min x mid x max	0.055×0.072×0. 195	0.021×0.029×0. 089	0.02×0.02×0. 08	0.013×0.052×0. 093	0.01×0.04×0. 06	0.048×0.055×0. 071
X-ray wavelength , Å	1.54184	0.71073	1.54184	1.54184	1.54184	0.71073
μ , mm ⁻¹	20.872	5.487	18.627	20.346	18.435	16.733
Trans min / max	0.27673/1.0000 0	0.75876/1.0000 0	0.75223/1.00 000	0.554/1.00000	0.54492/1.00 000	0.474/ 0.583
θ_{min} , °	3.051	2.777	4.959	5.496	3.922	3.993
θ_{max} , °	79.624	32.632	80.279	79.581	79.886	72.114
Reflections						
collected	8298	10217	4691	14621	14339	5345
independen t	2610	4029	4691	2432	2747	5345
observed	2590	3389	4515	2336	2687	5199
<i>R</i> _{int}	0.0262	0.0262	0.0519	0.0448	0.0303	-
Threshold expression	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$
No. parameters	146	145	155	136	163	191
No. restraints	0	0	0	0	1	0
<i>R</i> ₁ (observed)	0.0262	0.0289	0.0519	0.0287	0.0222	0.0416
w <i>R</i> ₂ (all)	0.0773	0.0565	0.1375	0.0805	0.0607	0.1137
Goodness of fit (all)	1.118	0.982	1.133	1.138	1.1	1.1
ρ_{max}, ρ_{min} , e Å ⁻³	0.486, -0.486	0.697, -0.493	1.386, -0.858	0.985, -0.930	0.508, -0.643	2.684, -1.007
Completen ess to 2 θ limit	0.917	0.912	0.987	0.977	0.999	0.975

Appendix D – Additional information for Chapter 4

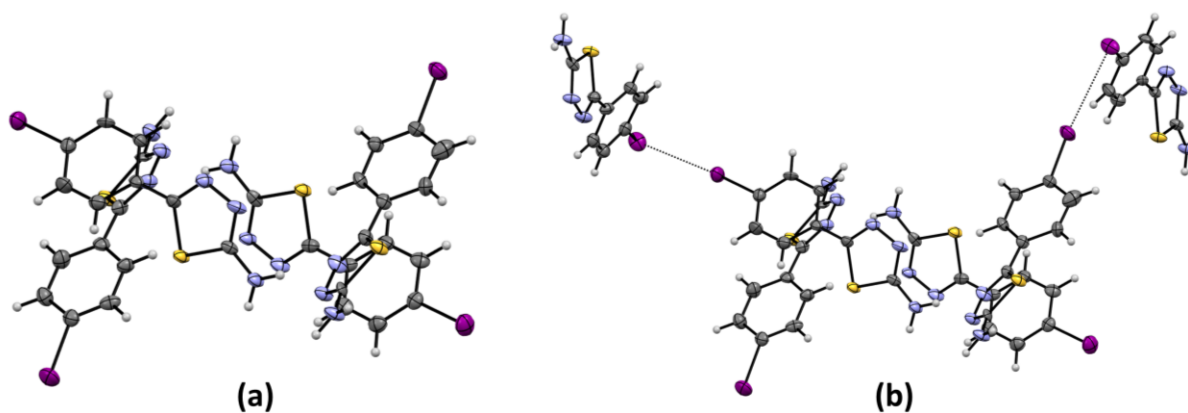


Figure D.1 T1-S-I Form I (a) asymmetric unit (b) Type II XB formation.

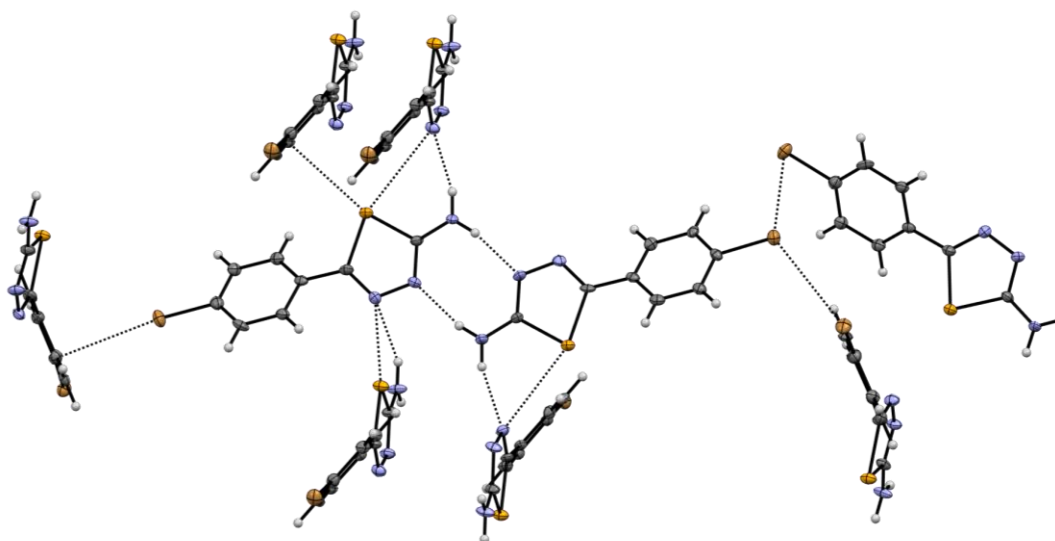


Figure D.2 T1-Se-Br halogen contact observed for the second symmetrically independent molecule in the asymmetric unit.

Appendix E – Additional information for Chapter 5

Table E.1 IE calculated without restrictions

Coformer	Cocrystal				Salt			
	T1-S-Br	T1-S-I	T1-Se-Br	T1-Se-I	T1-S-Br	T1-S-I	T1-Se-Br	T1-Se-I
35DNBA	-86.3798	-85.8449	-87.2099	-86.0539	-596.314	-595.817	-592.369	-595.402
PFBA	-82.7041	-82.5951	-82.9123	-82.0205	-577.009	-576.037	-573.061	-572.756
24DNBA	-89.0025	-88.2754	-89.644	-88.5017	-521.339	-519.336	-504.684	-500.535
4NO2	-80.4723	-79.7969	-80.6837	-80.1193	-585.173	-582.506	-581.19	-580.364
DDA	-72.4929	-71.6497	-72.5799	-72.4537	-561.602	-561.128	-559.882	-558.158
IBU	-72.3462	-71.5019	-72.5569	-71.5085	-557.431	-555.948	-555.35	-554.259

Table E.2 IE calculated with restrictions

Coformer	Cocrystal				Salt			
	T1-S-Br	T1-S-I	T1-Se-Br	T1-Se-I	T1-S-Br	T1-S-I	T1-Se-Br	T1-Se-I
35DNBA	-83.3608	-82.8279	-83.4338	-82.8387	-488.238	-486.045	-477.584	-486.096
PFBA	-80.0842	-80.2984	-80.271	-79.2519	-462.276	-461.102	-451.245	-449.362
24DNBA	-85.281	-84.2721	-85.005	-84.2572	-485.342	-482.565	-474.136	-471.046
4NO2	-79.694	-79.4091	-79.9087	-79.2454	-469.266	-467.115	-457.548	-456.322
DDA	-73.7406	-73.2787	-73.5365	-73.4337	-436.729	-435.737	-424.772	-422.55
IBU	-73.6329	-73.6612	-73.4637	-72.1769	-434.836	-432.526	-423.013	-420.935

Table E.3 Crystallographic information for the cocrystal structures

Code	4NO2/T1-S-I	4NO2/T1-Se-I	IBU/T1-S-Br	DDA/T1-S-I	35DNBA/T1-Se-Br	35DNBA/T1-S-I	35DNBA/T1-Se-I
Formula moiety	(C ₈ H ₆ IN ₃ S), (C ₇ H ₅ NO ₄)	(C ₈ H ₆ IN ₃ Se), (C ₇ H ₅ NO ₄)	(C ₈ H ₆ BrN ₃ S), (C ₁₃ H ₁₈ O ₂)	(C ₈ H ₆ IN ₃ S), (C ₆ H ₁₁ O ₃)	(C ₈ H ₆ BrN ₃ Se), (C ₇ H ₃ N ₂ O ₆)	(C ₈ H ₆ IN ₃ S), (C ₇ H ₃ N ₂ O ₆)	(C ₈ H ₆ IN ₃ Se), (C ₇ H ₃ N ₂ O ₆)
Empirical formula	C ₁₅ H ₁₁ IN ₄ O ₄ S	C ₁₅ H ₁₁ IN ₄ O ₄ Se	C ₂₁ H ₂₄ Br N ₃ O ₂ S	C ₁₄ H ₁₇ IN ₃ O ₂ S	C ₁₅ H ₁₀ Br N ₅ O ₆ S	C ₁₅ H ₁₀ IN ₅ O ₆ S	C ₁₅ H ₁₀ IN ₅ O ₆ Se
Molecular weight	470.24	517.14	462.4	418.26	515.15	515.24	562.14
Color, Habit	Colorless, Irregular	Colorless, Irregular	Colorless, Plate	Colorless, Needle	Colorless, Plate	Yellow, Irregular	Colorless, Block
Crystal system	Monoclinic	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group, Z	C 2/c, 8	Pbca, 8	Pca2 ₁ , 4	P2 ₁ /c, 4	P2 ₁ /c, 4	P2 ₁ /c, 4	P2 ₁ /c, 4
a, Å	8.55910(10)	7.56800(10)	34.4794(8)	4.82155(6)	8.15930(10)	8.1028(2)	8.2024(2)
b, Å	12.0406(2)	11.7232(2)	5.46160(10)	31.6850(4)	15.8307(2)	15.9550(3)	15.8923(4)
c, Å	32.1130(5)	37.4931(4)	11.3825(2)	10.72563(15)	13.8124(2)	13.8854(3)	13.8833(5)
α, °	90	90	90	90	90	90	90
β, °	93.8510(10)	90	90	99.8890(13)	97.856(2)	96.196(2)	96.653(3)
γ, °	90	90	90	90	90	90	90
Volume, Å ³	3301.99(8)	3326.43(8)	2143.47(7)	1614.22(4)	1767.37(4)	1784.62(7)	1797.58(9)
Density, g/cm ³	1.892	2.065	1.433	1.721	1.936	1.918	2.077
T, °K	170.00(10)	169.99(10)	170.00(10)	200.00(10)	170.00(10)	200.00(10)	200.00(10)
Crystal size, min x mid x max	0.048×0.053×0.138	0.017×0.055×0.106	0.014×0.032×0.112	0.02×0.02×0.17	0.052×0.123×0.149	0.05×0.09×0.15	0.043×0.054×0.114
X-ray wavelength, Å	1.54184	1.54184	1.54184	1.54184	1.54184	1.54184	0.71073
μ, mm ⁻¹	16.701	17.908	3.695	16.867	5.962	15.626	3.852
Trans min / max	0.75076/1.00000	0.53257/1.00000	0.72554/1.00000	0.31714/1.00000	0.74125/1.00000	0.50433/1.00000	0.74408/1.00000
θ _{min} , °	2.758	2.362	2.571	2.789	2.81	4.235	2.5
θ _{max} , °	76.974	76.772	76.364	77.704	76.515	77.795	30.053
Reflections							
collected	10293	32603	22085	35778	15721	21685	12311
independent	3334	3522	4326	3425	3722	3784	4479
observed	3275	3434	4110	3196	3555	3634	3537
R _{int}	0.0158	0.0281	0.0456	0.0443	0.029	0.0317	0.045
Threshold expression	> 2σ(I)	> 2σ(I)	> 2σ(I)	> 2σ(I)	> 2σ(I)	> 2σ(I)	> 2σ(I)
No. parameters	227	227	354	202	262	265	253

No. restraints	0	0	54	0	0	0	0
R_1 (observed)	0.0274	0.0273	0.0398	0.0644	0.1318	0.0334	0.1459
wR_2 (all)	0.0718	0.0735	0.0965	0.0652	0.133	0.0801	0.1531
Goodness of fit (all)	1.068	1.087	1.11	1.062	1.065	1.086	1.267
$\rho_{\max}, \rho_{\min}$, e $\text{\AA}^{-3}$	0.625, -0.638	0.857, -0.893	0.533, -0.511	0.515, -0.711	1.417, -1.307	1.040, -1.705	1.935, -1.284
Completeness to 2θ limit	0.951	0.995	0.997	0.998	0.997	0.993	0.85

Table E.4 Crystallographic information for the cocrystal structures

Code	PFBA/T1-S-Br	PFBA/T1-Se-Br	PFBA/T1-S-I	PFBA/T1-Se-I	24DNBA/T1-Se-I	24DNBA/T1-Se-I	24DNBA/T1-S-Br	24DNBA/T1-Se-Br
Formula moiety	(C ₈ H ₇ BrN ₃ S), (C ₇ F ₅ O ₂)	(C ₈ H ₇ BrN ₃ Se), (C ₇ F ₅ O ₂)	(C ₈ H ₇ IN ₃ S), (C ₇ F ₅ O ₂)	(C ₈ H ₇ IN ₃ Se), (C ₇ F ₅ O ₂)	(C ₈ H ₇ IN ₃ Se), (C ₇ H ₃ N ₂ O ₆), 0.5[CH ₄ O]	(C ₈ H ₇ IN ₃ S), (C ₇ H ₃ N ₂ O ₆), 0.5[CH ₄ O]	(C ₈ H ₆ BrN ₃ S), (C ₇ H ₃ N ₂ O ₆)	(C ₈ H ₆ BrN ₃ Se), (C ₇ H ₃ N ₂ O ₆)
Empirical formula	C ₁₅ H ₇ BrF ₅ N ₃ O ₂ S	C ₁₅ H ₇ BrF ₅ N ₃ O ₂ Se	C ₁₅ H ₇ F ₅ IN ₃ O ₂ S	C ₁₅ H ₇ F ₅ IN ₃ O ₂ Se	C _{15.50} H ₁₂ IN ₅ O _{6.50} Se	C _{15.50} H ₁₂ IN ₅ O _{6.50} S	C ₁₅ H ₁₀ BrN ₅ O ₆ S	C ₁₅ H ₁₀ BrN ₅ O ₆ Se
Molecular weight	468.21	515.11	515.2	562.1	578.16	531.26	468.25	515.15
Color, Habit	Yellow, Plate	Yellow, Plate	Colorless, Needle	Colorless, Irregular	Yellow, plate	Light yellow, needle	Yellow, Plate	Light yellow, plate
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group, Z	P2 ₁ 2 ₁ 2 ₁ , 4	P2 ₁ 2 ₁ 2 ₁ , 4	P2 ₁ 2 ₁ 2 ₁ , 4	P2 ₁ 2 ₁ 2 ₁ , 4	P2 _{1/n} , 4	P2 _{1/n} , 4	P2 _{1/n} , 4	P-1, 4
<i>a</i> , Å	5.86680(10)	5.82620(10)	5.89708(11)	5.85980(10)	14.5403(3)	14.6918(2)	14.5920(3)	5.00703(10)
<i>b</i> , Å	11.05580(10)	11.06750(10)	11.0951(3)	11.1679(3)	5.60804(14)	5.56154(8)	5.54229(10)	10.4368(2)
<i>c</i> , Å	25.0794(3)	25.5791(3)	25.5792(7)	25.7997(7)	23.6828(4)	23.7409(2)	23.3833(4)	17.5257(3)
α , °	90	90	90	90	90	90	90	78.9785(17)
β , °	90	90	90	90	95.8071(18)	95.9474(11)	96.9720(17)	83.2057(16)
γ , °	90	90	90	90	90	90	90	83.8671(16)
Volume, Å ³	1626.70(4)	1649.38(4)	1673.61(7)	1688.38(7)	1921.25(7)	1929.41(4)	1877.10(6)	889.30(3)
Density, g/cm ³	1.912	2.074	2.045	2.211	1.999	1.829	1.657	1.924
<i>T</i> , °K	170.00(10)	170.00(10)	200.00(10)	170.00(10)	139.99(10)	210.00(10)	139.6(7)	139.7(6)
Crystal size, min x mid x max	0.026×0.075×0.197	0.06×0.123×0.176	0.02×0.02×0.33	0.055×0.094×0.128	0.03×0.045×0.146	0.02×0.02×0.1	0.031×0.048×0.109	0.03×0.13×0.26
X-ray wavelength, Å	1.54184	1.54184	1.54184	1.54184	1.54184	1.54184	1.54184	0.71073
μ , mm ⁻¹	5.346	6.613	16.883	18.046	15.707	14.494	4.435	4.404
Trans min / max	0.67208/1.00000	0.69147/1.0000	0.78499/1.0000	0.40335/1.0000	0.45599/1.0000	0.67049/1.0000	0.92204/1.0000	0.55419/1.0000
$\theta_{\min}$, °	3.525	3.456	3.456	3.397	3.42	3.388	3.395	2.13
$\theta_{\max}$, °	77.319	77.089	77.676	76.742	77.478	80.033	77.328	33.549
Reflections								

collected	15525	14747	17195	8888	19769	17040	16378	27917
independent	3446	3471	3488	3359	4032	4127	3927	6189
observed	3397	3403	3253	3331	3701	3637	3559	5432
R_{int}	0.0326	0.0266	0.0585	0.0199	0.0359	0.0273	0.0286	0.0303
Threshold expression	$> 2\sigma(I)$	$> 2\sigma(I)$	$> 2\sigma(I)$	$> 2\sigma(I)$	$> 2\sigma(I)$	$> 2\sigma(I)$	$> 2\sigma(I)$	$> 2\sigma(I)$
No. parameters	272	253	256	249	253	253	253	319
No. restraints	0	0	0	0	0	0	0	12
R_1 (observed)	0.069	0.0749	0.03	0.0479	0.0337	0.0293	0.0931	0.0685
wR_2 (all)	0.0692	0.0753	0.0711	0.048	0.0927	0.0794	0.0952	0.0706
Goodness of fit (all)	1.057	1.083	1.075	1.06	1.116	1.109	1.086	1.027
$\rho_{\text{max}}, \rho_{\text{min}}, \rho_{\text{e}}$ $\text{\AA}^{-3}$	0.330, -0.485	0.761, -0.615	0.500, -0.503	0.472, -0.412	0.897/-0.875	0.374/-0.859	0.444, -0.613	0.794, -0.554
Completeness to 2θ limit	0.999	0.997	0.997	0.998	0.989	0.984	0.99	0.883

Appendix F – Additional information for Chapter 6

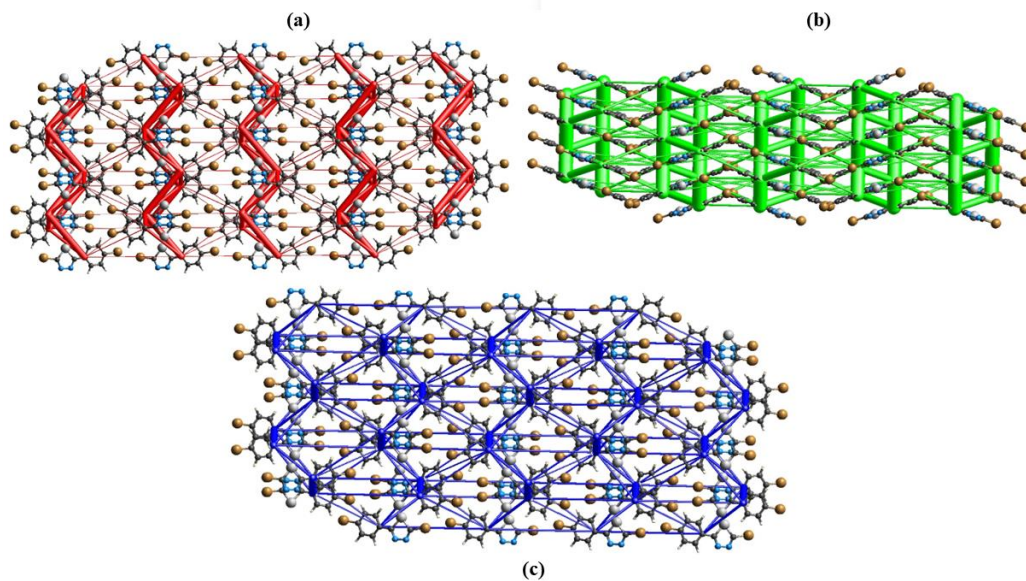


Figure F.1 Energy framework calculations showing (a) the Coulombic interactions, (b) the dispersion interactions and (c) the total inter-action energies of T2.

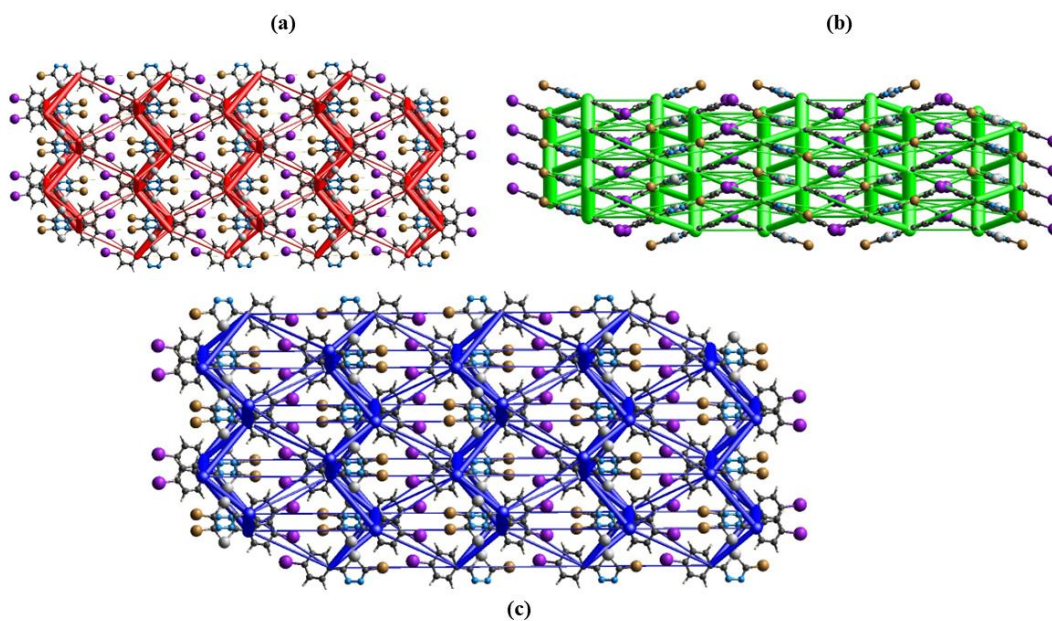


Figure F.2 Energy framework calculations showing (a) the Coulombic interactions, (b) the dispersion interactions and (c) the total interaction energies of T3.

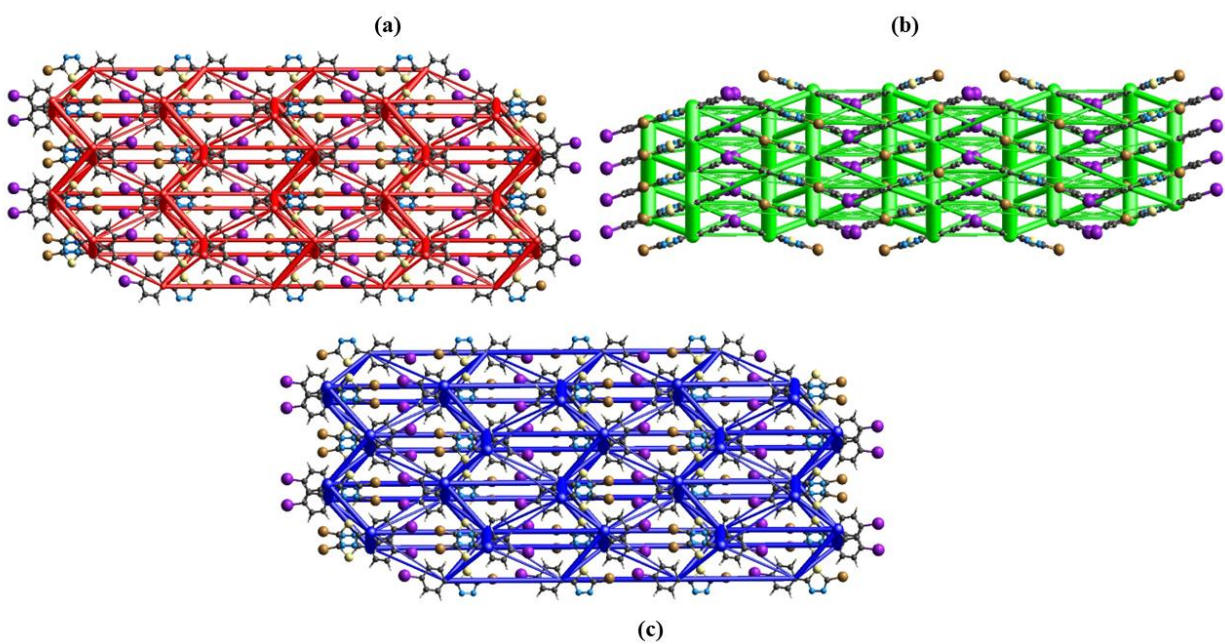


Figure F.3 Energy framework calculations showing **(a)** the Coulombic interactions, **(b)** the dispersion interactions and **(c)** the total interaction energies of **T4**.

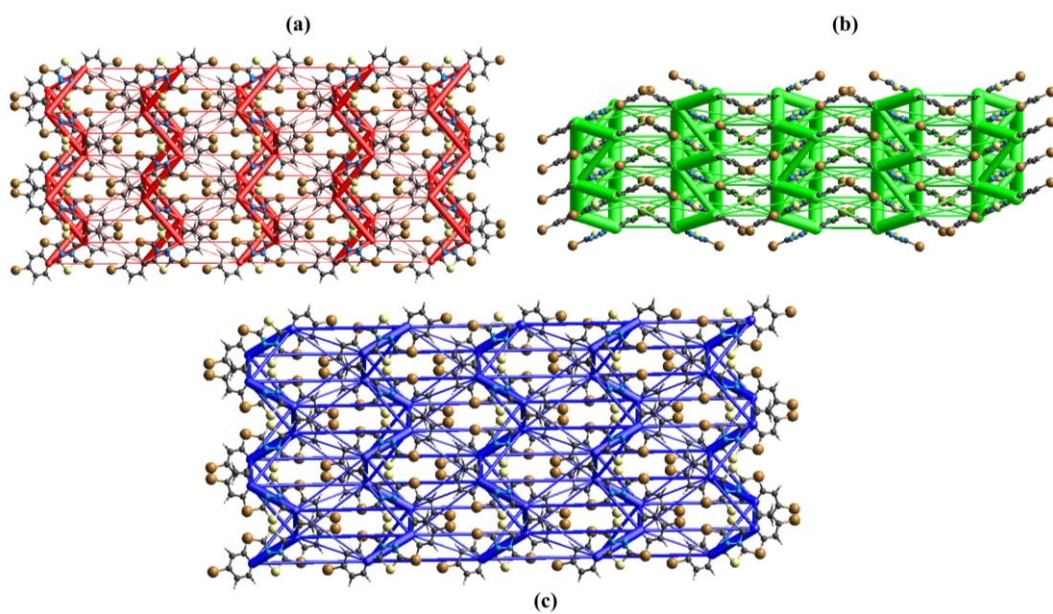


Figure F.4 Energy framework calculations showing **(a)** the Coulombic inter-actions, **(b)** the dispersion inter-actions and **(c)** the total inter-action energies of **T5**.

Table F.1 Crystallographic information for the target crystal structures

Code	T1	T2	T3	T4	T5
Formula moiety	C ₈ H ₄ I ₂ N ₂ S	C ₈ H ₄ Br ₂ N ₂ Se	C ₈ H ₄ IBrN ₂ Se	C ₈ H ₄ IBrN ₂ S	C ₈ H ₄ Br ₂ N ₂ S
Empirical formula	C ₈ H ₄ I ₂ N ₂ S	C ₈ H ₄ Br ₂ N ₂ Se	C ₈ H ₄ IBrN ₂ Se	C ₈ H ₄ IBrN ₂ S	C ₈ H ₄ Br ₂ N ₂ S
Molecular weight	413.99	366.91	413.9	367	320.01
Color, Habit	Colorless, Block	Orange, irregular	Clear light yellow, plate	Colorless, plate	Orange, irregular
Crystal system	orthorhombic	orthorhombic	orthorhombic	orthorhombic	orthorhombic
Space group, Z	Pbca, 8	Pbca, 8	Pbca, 8	Pbca, 8	Pbca, 8
<i>a</i> , Å	11.0392(2)	11.1945(5)	11.1735(4)	10.9919(2)	11.0123(5)
<i>b</i> , Å	8.1756(2)	7.1006(3)	7.1222(2)	6.99450(10)	7.3192(3)
<i>c</i> , Å	23.3673(4)	25.4725(9)	26.1875(8)	26.4076(4)	24.3068(11)
α , °	90	90	90	90	90
β , °	90	90	90	90	90
γ , °	90	90	90	90	90
Volume, Å ³	2108.95(7)	2024.74(15)	2084.00(11)	2030.29(6)	1959.14(15)
Density, g/cm ³	2.608	2.407	2.638	2.401	2.17
<i>T</i> , °K	293(2)	100.00(10)	100.00(10)	293(2)	149.99(10)
Crystal size, min x mid x max	0.027×0.054×0.065	0.02×0.02×0.02	0.06×0.1×0.3	0.012×0.039×0.048	0.011×0.024×0.039
X-ray wavelength, Å	1.54184	1.54184	0.71073	1.54184	0.71073
μ , mm ⁻¹	48.342	13.895	10.355	30.946	8.439
Trans min / max	0.209/ 0.522	0.68222/1.00000	0.33758/1.00000	0.37294/1.00000	0.776 / 0.936
θ_{min} , °	3.783	3.47	2.396	3.347	2.496
θ_{max} , °	69.06	74.839	26.019	70.701	25.349
Reflections					
collected	8336	6457	12091	7258	7401
independent	1942	1965	2055	1920	1787
observed	1753	1709	1815	1802	1463
R _{int}	0.0243	0.0368	0.0351	0.0246	0.0296
Threshold expression	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$
No. parameters	118	118	118	118	118
No. restraints	0	0	0	0	0
R ₁ (observed)	0.0262	0.0442	0.0296	0.021	0.0341
wR ₂ (all)	0.0709	0.1088	0.0697	0.0517	0.0904
Goodness of fit (all)	1.088	1.048	1.082	1.069	1.031
ρ_{max} , ρ_{min} , e Å ⁻³	1.328, -1.221	1.950, -1.464	2.003, -1.013	0.566, -0.670	1.646, - -0.462
Completeness to 2 θ limit	0.991	0.945	1	0.984	0.996

Appendix G – Additional information for Chapter 7

Table G.1 Crystallographic information for the target crystal structures

Code	SBr-Acetamide	SeBr-Acetamide Form II	SeBr-Acetamide	SeI-Acetamide	SI-Acetamide Form II	SI-Acetamide Form I
Formula moiety	C ₁₀ H ₈ Br N ₃ O S	C ₁₀ H ₈ Br N ₃ O Se	C ₁₀ H ₈ Br N ₃ O Se	C ₁₀ H ₈ I N ₃ O Se	C ₁₀ H ₈ I N ₃ O S	C ₁₀ H ₈ I N ₃ O S
Empirical formula	C ₁₀ H ₈ Br N ₃ O S	C ₁₀ H ₈ Br N ₃ O Se	C ₁₀ H ₈ Br N ₃ O Se	C ₁₀ H ₈ I N ₃ O Se	C ₁₀ H ₈ I N ₃ O S	C ₁₀ H ₈ I N ₃ O S
Molecular weight	298.16	345.06	345.06	392.05	345.15	345.15
Color, Habit	Yellow, irregular	Colorless, needle		Colorless, needle	Colorless, needle	Colorless, needle
Crystal system	monoclinic	triclinic	monoclinic	Monoclinic	Monoclinic	monoclinic
Space group, Z	P2 ₁ /c, 4	P -1, 2	P2 ₁ /c, 4	P2 ₁ /c, 4	P2 ₁ /c, 4	P2 ₁ /n, 4
a, Å	5.81020(10)	4.08280(10)	5.8978(2)	4.65263(10)	5.8328(2)	4.67470(10)
b, Å	9.00530(10)	9.4721(2)	8.9821(2)	9.4889(2)	9.0042(3)	9.41370(10)
c, Å	21.7693(4)	14.9357(2)	21.6761(7)	26.7162(6)	21.8846(7)	26.5717(3)
α, °	90	82.776(2)	90	90	90	90
β, °	93.739(2)	87.730(2)	94.950(3)	94.419(2)	93.157(3)	94.8470(10)
γ, °	90	80.824(2)	90	90	90	90
Volume, Å ³	1136.60(3)	565.57(2)	1144.00(6)	1175.98(4)	1147.63(7)	1165.14(3)
Density, g/cm ³	1.742	2.026	2.003	2.214	1.998	1.968
T, °K	210.00(10)	293(2)	293(2)	240.00(10)	240.00(10)	210.00(10)
Crystal size, min x mid x max	0.03×0.05×0.7	0.02×0.02×0.13		0.015×0.02×0.24 4	0.01×0.01×0.26	0.025×0.039×0.30 9
X-ray wavelength, Å	1.54184	1.54184	1.54184	1.54184	1.54184	1.54184
μ, mm ⁻¹	6.51	8.497		24.806	23.491	23.138
Trans min / max	0.86722/1.00000	0.61470/1.00000		0.67090/1.00000	0.69394/1.00000	0.07554/1.00000
θ _{min} , °	5.317	2.983		3.318	4.046	4.986
θ _{max} , °	77.885	79.939		79.817	79.911	77.401
Reflections collected	4049	16076		9195	3736	15707
independent	4049	2400		2503	3736	2448
observed	3802	2159		2360	3394	2388
R _{int}	-	0.0553		0.0286		0.0425
Threshold expression	> 2σ(I)	> 2σ(I)	> 2σ(I)	> 2σ(I)	> 2σ(I)	> 2σ(I)
No. parameters	147	146	146	146	147	146
No. restraints	1	0	0	0	0	0
R ₁ (observed)	0.0555	0.0439	0.0377	0.0283	0.0386	0.0287

wR ₂ (all)	0.1734	0.1271		0.0737	0.1259	0.0763
Goodness of fit (all)	1.115	1.064	1.108	1.079	1.141	1.123
$\rho_{\max}, \rho_{\min}, e \text{ \AA}^{-3}$	0.909, -1.003	0.917, -0.735		0.526	0.583, -0.846	0.692, -0.580
Completeness to 2 θ limit	0.991	0.972		-0.764	0.922	0.99

Table G.2 Crystallographic information for the target crystal structures

Code	SeI-Apropyl	SI-Apropyl	SBr-Apropyl	SeBr-Apropyl
Formula moiety	C ₁₂ H ₁₂ I N ₃ O Se	C ₁₂ H ₁₂ I N ₃ O S	C ₁₂ H ₁₂ Br N ₃ O S	C ₁₂ H ₁₂ Br N ₃ O Se
Empirical formula	C ₁₂ H ₁₂ I N ₃ O Se	C ₁₂ H ₁₂ I N ₃ O S	C ₁₂ H ₁₂ Br N ₃ O S	C ₁₂ H ₁₂ Br N ₃ O Se
Molecular weight	420.11	373.21	326.22	373.12
Color, Habit	Colorless, needle	Colorless, needle	Colorless, needle	Light yellow, needle
Crystal system	Triclinic	Triclinic	triclinic	triclinic
Space group, Z	P -1, 2	P -1, 2	P -1, 2	P -1, 2
a, Å	4.61752(8)	4.67450(10)	4.6687(3)	4.6198(2)
b, Å	9.3248(3)	9.1704(4)	9.0634(4)	9.6193(4)
c, Å	16.5101(3)	16.4222(5)	16.1882(6)	14.7798(4)
α , °	102.383(2)	104.067(3)	104.480(4)	85.356(3)
β , °	96.8677(15)	96.485(2)	97.036(4)	86.234(3)
γ , °	95.6111(18)	94.450(3)	93.612(4)	89.053(3)
Volume, Å ³	683.75(3)	674.45(4)	655.10(5)	653.19(4)
Density, g/cm ³	2.041	1.838	1.654	1.897
T, °K	200.00(10)	200.00(10)	200.00(10)	200.00(10)
Crystal size, min x mid x max	0.01×0.01×0.2	0.017×0.027×0.212	0.016×0.024×0.133	0.02×0.03×0.12
X-ray wavelength, Å	1.54184	1.54184	1.54184	1.54184
μ , mm ⁻¹	21.385	20.04	5.703	7.413
Trans min / max	0.55724/1.00000	0.87150/1.00000	0.59708/1.00000	0.81168/1.00000
$\theta_{\min}$, °	2.769	2.8	5.064	3.006
$\theta_{\max}$, °	80.853	77.802	79.532	79.774
Reflections				
collected	14833	7228	8275	7530
independent	2938	7228	2757	2748
observed	2728	6846	2418	2437
R _{int}	0.04		0.0418	0.0355
Threshold expression	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$
No. parameters	164	165	164	164
No. restraints	0	0	0	0
R ₁ (observed)	0.0333	0.045	0.0524	0.0351
wR ₂ (all)	0.0897	0.1364	0.1398	0.1007
Goodness of fit (all)	1.091	1.038	1.062	1.083
$\rho_{\max}, \rho_{\min}, e \text{ \AA}^{-3}$	0.591, -1.205	0.932, -1.035	0.939, -1.174	0.648, -0.738
Completeness to 2 θ limit	0.982	0.968	0.972	0.965

Table G.3 Crystallographic information for the target crystal structures

Code	SeBr-ApentyI	SeI-ApentyI	SI-ApentyI 608b	SBr-ApentyI
Formula moiety	C ₁₄ H ₁₆ Br N ₃ O Se	C ₁₄ H ₁₆ I N ₃ O Se	C ₁₄ H ₁₆ I N ₃ O S	C ₁₄ H ₁₆ Br N ₃ O S
Empirical formula	C ₁₄ H ₁₆ Br N ₃ O Se	C ₁₄ H ₁₆ I N ₃ O Se	C ₁₄ H ₁₆ I N ₃ O S	C ₁₄ H ₁₆ Br N ₃ O S
Molecular weight	401.17	448.16	401.26	354.27
Color, Habit	Yellow, plate	Light yellow, needle	Colorless, plate	Colorless, plate
Crystal system	triclinic	Triclinic	triclinic	triclinic
Space group, Z	P -1, 2	P -1, 2	P -1, 4	P -1, 6
<i>a</i> , Å	5.05623(13)	4.96134(18)	8.3504(3)	12.6313(3)
<i>b</i> , Å	8.3051(3)	8.6005(3)	12.6693(2)	12.8229(4)
<i>c</i> , Å	18.5299(6)	18.6434(7)	15.5993(4)	17.2043(3)
α , °	85.879(3)	85.390(3)	95.4210(16)	103.284(2)
β , °	82.627(2)	83.275(3)	90.422(3)	98.5820(17)
γ , °	82.348(2)	82.569(3)	108.460(3)	118.535(3)
Volume, Å ³	763.62(4)	781.69(5)	1557.17(8)	2270.64(11)
Density, g/cm ³	1.745	1.904	1.712	1.554
<i>T</i> , °K	209.95(10)	220.00(10)	210.00(10)	220.00(10)
Crystal size, min x mid x max	0.014×0.025×0.144	0.01×0.02×0.23	0.013×0.054×0.174	0.02×0.06×0.19
X-ray wavelength, Å	1.54184	0.71073	1.54184	0.71073
μ , mm ⁻¹	6.389	4.376	17.406	2.852
Trans min / max	0.72455/1.00000	0.52502/1.00000	0.290/1.000	0.84151/1.00000
θ_{min} , °	2.408	2.393	2.848	2.211
θ_{max} , °	79.405	33.251	80.751	30.831
Reflections				
collected	14717	8912	23690	31898
independent	3114	8912	6653	11463
observed	2511	5457	5124	7744
R _{int}	0.0463	0.067	0.0597	0.0313
Threshold expression	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$	> 2 $\sigma(I)$
No. parameters	182	183	363	574
No. restraints	0	0	13	3
R ₁ (observed)	0.0448	0.0806	0.0555	0.038
wR ₂ (all)	0.1297	0.241	0.1713	0.0911
Goodness of fit (all)	1.035	1.02	1.08	1.021
ρ_{max} , ρ_{min} , e Å ⁻³	0.881, -0.580	1.761, -1.215	1.233, -1.764	0.527, -0.316
Completeness to 2 θ limit	0.933	0.84	0.971	0.804