

Crystal Engineering: Design of Ternary Cocrystals Based Purely on Halogen Bonding.



A thesis submitted in the partial fulfilment of requirements for the BS-MS
dual degree program (2015-2020)

Submitted by

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CERTIFICATE

This is to certify that this dissertation entitled “**Crystal Engineering: Design of Ternary Cocrystals Based Purely on Halogen Bond**” towards the partial fulfilment of the BS-MS dual degree programme at the Indian Institute of Science Education and Research (IISER), Pune represents work carried out by **Harsh Jain** at Indian Institute of Science (IISc), Bangalore” under the supervision of “**Prof. Gautam R. Desiraju**, Honorary Professor, Solid State and Structural Chemistry Unit, IISc Bangalore during the academic year 2019-2020.



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DECLARATION

I hereby declare that the matter embodied in the thesis entitled “**Crystal Engineering: Design of Ternary Cocrystals Based Purely on Halogen Bond**” are the results of the work carried out by me at the Department of Solid State and Structural Chemistry Unit, IISc Bangalore, under the supervision of **Prof. Gautam R. Desiraju** and the same has not been submitted elsewhere for any other degree.



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List of Abbreviations

SCXRD	Single Crystal X-Ray Diffraction
CSD	Cambridge Structural Database
NMR	Nuclear Magnetic Resonance
IEIB	4-iodo-1-iodoethynylbenzene
Na ₂ SO ₄	Sodium Sulphate
TFDIB	1,4-diiodotetrafluorobenzene
DMPYZ	2,6-dimethylpyrazine
TRMPYZ	2,3,5-trimethylpyrazine
MMPYZ	2-methylpyrazine
PANSHYD	p-anisaldehyde
PHNPRD	4-phenylpyridine
DMQXN	2,3-dimethylquinoxaline
TMP	2,3,5,6-tetramethylpyrazine
THF	tetrahydrofuran
CH ₃ NO ₂	nitromethane
MeOH	methanol
MeCN	acetonitrile
EtOAc	Ethyl acetate

ABSTRACT

Crystal engineering is the synthesis of crystals with predefined and targeted properties using non-covalent interactions. Halogen bond being one of the interactions is the bond between a halogen atom (Lewis acid) and a neutral or negatively charged Lewis bases. Different components are brought together and crystallized in solid state to form multicomponent crystals. The importance of halogen bonded cocrystals comes from the ability to control function and structure of solids using the moderate strengths of halogen bonds. To find design strategies for the formation of purely halogen based ternary cocrystals, some cocrystals formed by 1,4-diiidotetrafluorobenzene with different organic bases characterised using SC-XRD are reported. 4-iodo-1-iodoethynylbenzene pure crystals have been synthesized for the first time and type I and type II of halogen bonds types are noted. 1,4-diiidotetrafluorobenzene and 4-iodo-1-iodoethynylbenzene have been exploited well in the scope of getting a purely halogen based ternary cocrystal.

1. Introduction

1.1 Supramolecular Chemistry: Supramolecular chemistry has been defined as the chemistry beyond the molecules.¹ It is the chemistry of large assemblies of molecules bound by non-covalent interactions separating it well from the covalent chemistry.² The organic molecules recognize the complementarity (complementary geometrical shapes and complementary chemical functionalities) between them and tend to form supramolecules.³ The knowledge of intermolecular interactions is necessary to get well versed with the concept of supramolecular chemistry as the knowledge of covalent bond is for molecular chemistry. Some intermolecular interactions have enough strength that they tend to show their presence more regularly in the organic crystals which is an excellent example of an infinite sized supramolecule.⁴ These robust interactions in the crystals were observed by G. R. Desiraju, and he named them as supramolecular synthons.⁵ From controlling of the properties of a molecule to controlling properties of a solid (cluster of molecules) is the supramolecular picture to crystal engineering.⁶ The end goal of understanding the concepts of supramolecular chemistry is to get the noncovalent assemblies of molecules to perform the desired functions.⁴

1.2 Crystal engineering

Crystallography deals with the periodicity of atoms or molecules in a crystal. The term Crystal engineering was first given by Pepinsky in 1955.⁷ As defined by Desiraju, crystal engineering is “*the understanding of intermolecular interactions in the context of crystal packing and the utilisation of such understanding in the design of new solids with desired physical and chemical properties*”.⁸ Crystal engineering is associated with the distinguishing of molecular solids (molecular crystals, rocksalt, metal oxides) based on the intermolecular interactions and arrangement of atoms and molecules present in the structure of the solid. It has been divided into two time periods, the older crystal engineering and modern crystal engineering. Started in 1980s from the emergence of Cambridge Structural Database, modern crystal engineering mainly includes the diffraction of X-rays by crystals which helps in the determination of crystal structure and analysis of structures by computer instruments and softwares.^{9,10} It also helps in the designing of new crystal with desired properties using crystallization experiments. Being governed by different guidelines which are *Kitaigorodskii's*

*principle of close packing*¹¹, *Etter's rules*¹², *the Desiraju supramolecular synthon*⁵ and concept of *tecton* by *Wuest and Hosseini*¹³ it provides knowledge in the context of the building blocks and driving forces required for the growth of a crystal.

1.3 Supramolecular Synthons

Supramolecular synthons are those units of a crystal by the combinations of which, with the help of different intermolecular interactions, large or supermolecules (crystals) could be formed¹⁴. The concept was introduced by Desiraju in 1995.⁵ The concept of synthon helps in defining a crystal system as a network in which molecules act as nodes and interactions serve as node connections.⁶ The basic idea behind its introduction in the field was to identify them in the crystals and to retro synthesize even higher dimension crystals using these novelties.¹⁵ A crystal system can have two types of synthons, homosynthon (assemblies of similar functional groups) or a heterosynthon (different functional groups) (Figure 1). The strength of the various interactions between the molecules drives the formation of different types of synthons.

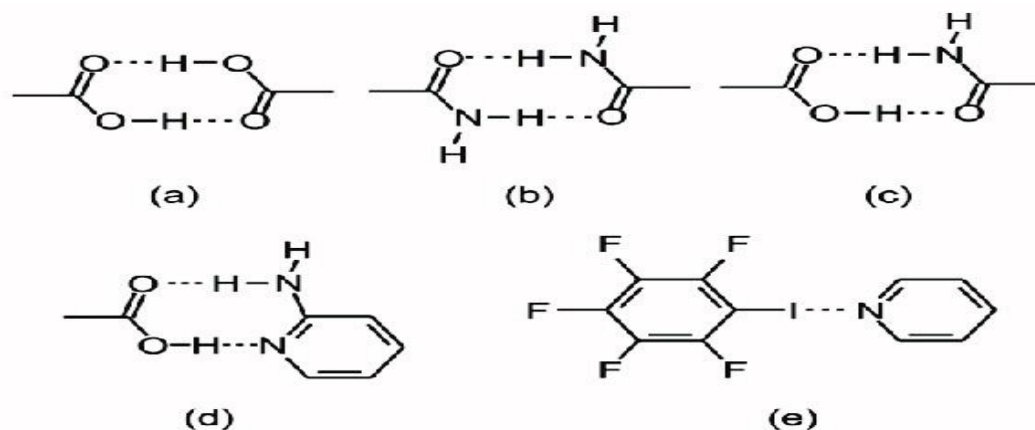


Figure 1. Examples of hydrogen bonding homosynthons (a) acid-acid and (b) amide-amide; heterosynthons (c) acid-amide and (d) acidaminopyridine. An example of a (e) halogen bonding synthon.

1.4 Cocrystals

These are the molecular solids composed of at two or more number of chemical species in an asymmetric unit.¹⁶ One the first cocrystals of 1:1 stoichiometric ratio of Quinone: hydroquinone was reported by Wöhler in 1844 (Figure 2).¹⁷ The O..H....O interactions in Quinone: hydroquinone structure were found in 1958.¹⁸ According to a group of researchers the definition states, “cocrystals are solids that are crystalline

single-phase materials composed of two or more different molecular or ionic compounds generally in stoichiometric ratio.”¹⁶ The importance of cocrystals comes from the idea to modify the properties of organic molecules in solid state changing the directions and selective reorganisations of hydrogen and halogen bonds present in the crystal.¹⁹

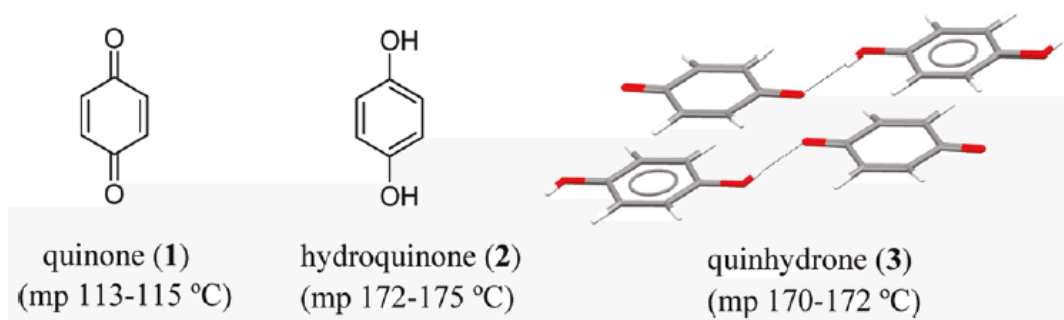


Figure 2. One of the first cocrystal structure of quinone and hydroquinone. The cocrystal is also named as quinhydrone.

2. Origin of Work

2.1 Crystal Engineering using Halogen bonds

The motive behind crystal engineering is the designing of different crystals with the desired properties using the method of retrosynthesis by the help of known crystals. As the formation of crystals depends on the strength of the interactions between the molecules, the formation of crystals by the halogen bonds being moderately strong provides much help for the formation of the desired packing in a crystal. On the other hand, comparatively stronger hydrogen bonds and various other interactions are challenging to play with due to their readiness to form tightly packed crystal structures.²⁰ They are to be designed based on the geometrical and chemical factors of the components.²¹ Metrangolo and Resnati are some noteworthy names who have been designing halogen bonded cocrystals.²² Due to its varied applications in pharmaceuticals, functional solids, biomolecular recognitions, many scientists have shown interest towards it.²³

2.2 Halogen bonds

In a covalently bonded halogen atom, the electron density on it is distributed around it highly anisotropically which enables it to act as electron donor as well as an electron

acceptor.²⁴ The non-covalent interactions in which halogens act as acceptors of electron density are termed as halogen bonds. Here a halogen atom or an electronegative atom can serve as the nucleophilic entity. A halogen bond can be described in general as R-X----Y where X is electrophilic halogen, Y is the nucleophilic donor atom and R could be carbon, nitrogen or halogen (Figure 3).^{25,26}

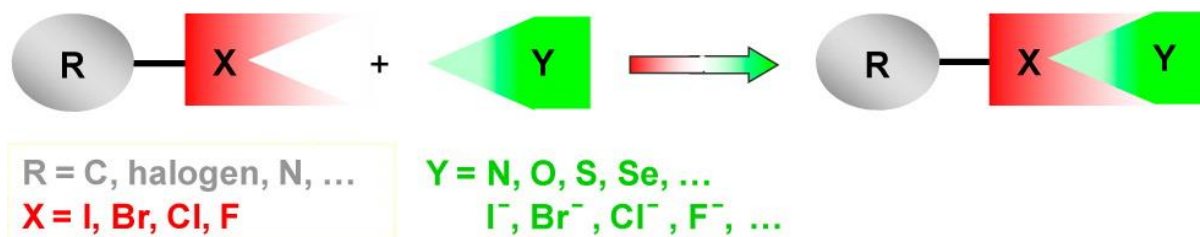


Figure 3. One of the first cocrystal structure of quinone and hydroquinone. The cocrystal is also named as quinhydrone.

Halogen bonds have been considered similar to the hydrogen bonds because of the similarity in the role of halogen in a halogen bond to the role of hydrogen in a hydrogen bond.²⁷ Halogen bond is categorised into three types (Figure 4)²⁸; (a) a conventional halogen bond between halogen and electronegative atom, (b) halogen-halogen bond due to van der Waals interaction (symmetrical), (c) halogen-halogen purely electrostatic interaction (bent).^{29,30}

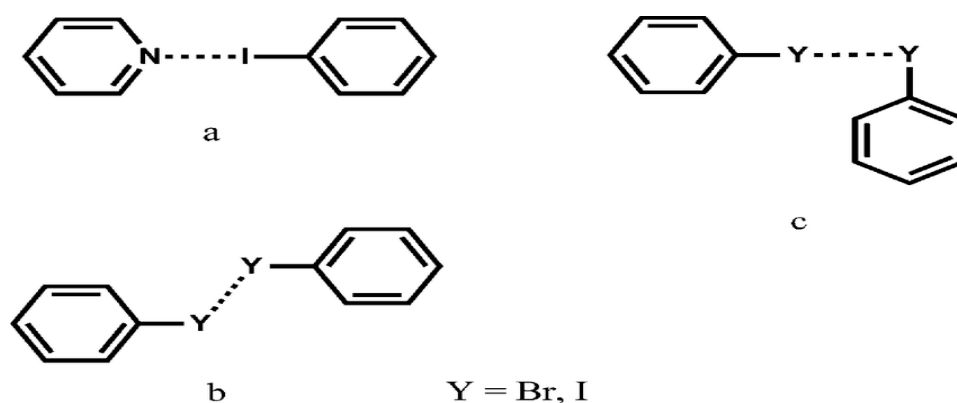


Figure 4. (a) Conventional halogen bond; (b) Type I halogen-halogen bond; (c) Type II halogen-halogen bond.

The concept of halogen bond is explained by the ‘ σ hole theory’. The presence of a closed or semi closed positive surface electrostatic potential on the outermost region along the bond axis when a halogen forms a halogen bond is named as σ hole.³¹ σ hole’s presence or absence is determined by electronegativity, polarizability and the electron-withdrawing power of atom attached to C. Its polarizability increases in the order $F < Cl < Br < I$ (Figure 5).^{26,32}

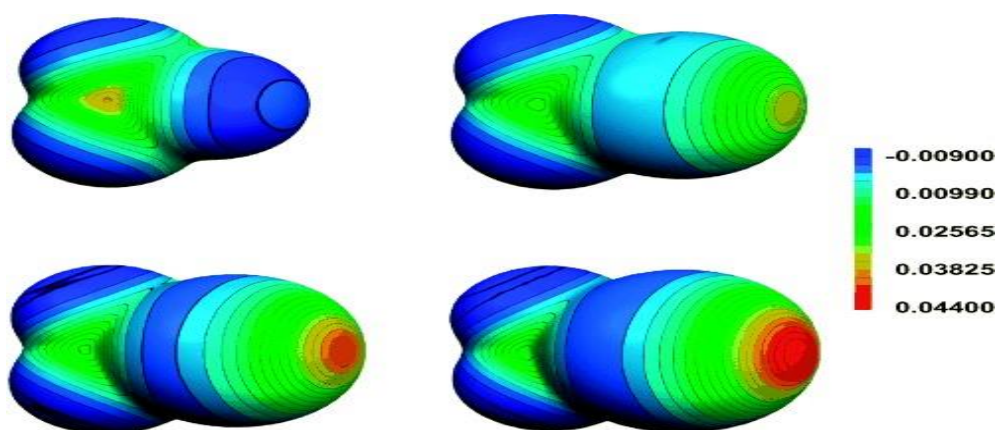


Figure 5. Increase in the positive hole on C-X (X= F, Cl, Br, I) equatorial axis with the increase in the electronegativity of the halogen atom.

2.3 Ternary cocrystal only with halogen bond- The task of formation of a ternary cocrystal only with the presence of halogen bond and no other interaction has attracted the minds of many crystallographers. This is because of the moderate strength of the halogen bond with which comes a great deal of applications. But as crystallization favours mono-component results, to design and synthesize multi-component cocrystal becomes very challenging. By optimising some of the interactions of the compounds, binary cocrystals can be isolated. But for the formation of ternary and that too with specific interactions, many additional factors come into play which are to be taken care off. This has been taken as one of the objectives of this thesis.²¹

3. MATERIALS AND METHODS

3.1 Cambridge Structural Database: The Cambridge Structural Database was started in 1965.³³ At the beginning it had only a few hundred inorganic crystals. After the recent update in August 2019, it has 1019712 structures. CSD was used for doing the research before the start of every experiment. A list was all the ternary cocrystals published was made using CSD (conquest and mercury) for the reference for

retrosynthesis. Latest versions of Conquest and Mercury were utilised for molecular representations and packing diagrams.

3.2 Synthesis

All the compounds used for the synthesis of cocrystals were purchased in the highest purity from the commercial vendors and were used without any more purification.

3.2.1 *Cocrystal synthesis*: Mechano-chemistry was used for the synthesis of multicomponent organic solids. It was carried out using the liquid assisted grinding method and crystals then obtained by slow evaporation from the solvent. Stoichiometric ratios of the compounds were ground together in a mortar with the addition of very few drops of solvent (Figure 6). The mixture obtained was dissolved in different inert solvents and left for evaporation. Quality crystals were obtained after the evaporation of the solvents.



Figure 6. Mortar-pestle 1 on the left and mortar-pestle 2 on the right. Note that the pestle of 2 is slightly smaller than that of 1.

3.2.2 Stepwise organic synthesis of 4-iodo-1-iodoethynylbenzene (IEIB)

Step 1- Synthesis of 4-iodo-1-ethynylbenzene (B): 4-iodo-1-(trimethylsilyl)ethynylbenzene (**A**) was purchased from the chemical vendors and was used as it is. In a 100 ml round bottom flask 517.8 mg of compound A and 20 mL of chloroform were added and stirred. 627 mg of potassium carbonate and 20 mL

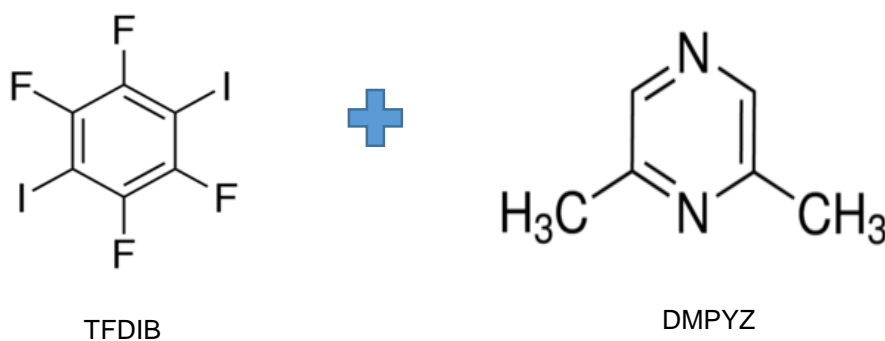
methanol were added to the stirred solution. The complete mixture was then deoxygenated and stirred for 4 hours at 25 C. 30 mL water was added, and the mixture was stirred for an extra 15 minutes. With the use of 20 mL of chloroform as an extraction solvent, the organic phase was separated, and the aqueous phase was extracted three times. The collected organic phase was dried over Na₂SO₄ and was evaporated using rotatory evaporation.

Step 2- Synthesis of 4-iodo-1-iodoethynylbenzene (IEIB)- In a 147 mg solution of **B** in 30 mL of methanol, a saturated solution of 215.7 mg iodine in methanol and 10% solution of 59 mg sodium hydroxide in water were added simultaneously. The mixture was stirred vigorously overnight. Water was added to the reaction mixture until the formation of a white precipitate. The precipitate was washed with 20 mL of water, then with 10 mL of a saturated solution of sodium bisulphite and then again with 20 mL of water. The obtained solid was dried using rotatory evaporation.³⁴

3.3 Crystallization experiments-

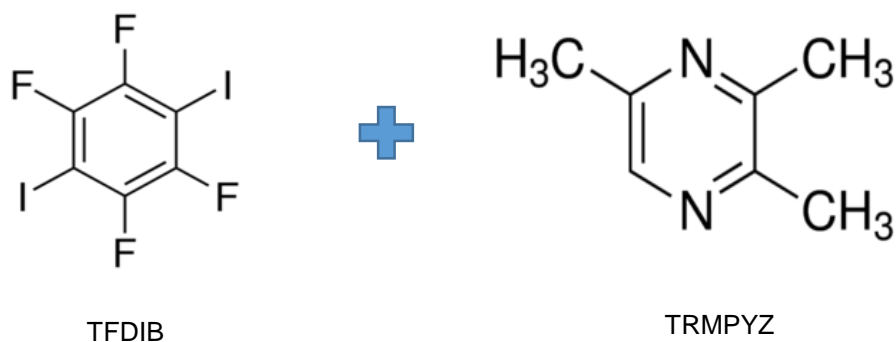
(a) 1,4-diiidotetrafluorobenzene: 2,6-dimethylpyrazine (**1**)

1,4-diiidotetrafluorobenzene and 2,6-dimethylpyrazine were taken in 1:1 molar ratio and ground in a mortar for 30 minutes along with 2-3 drops of methanol. Diffraction quality crystals were obtained from nitrobenzene at room temperature after 4-5 days.



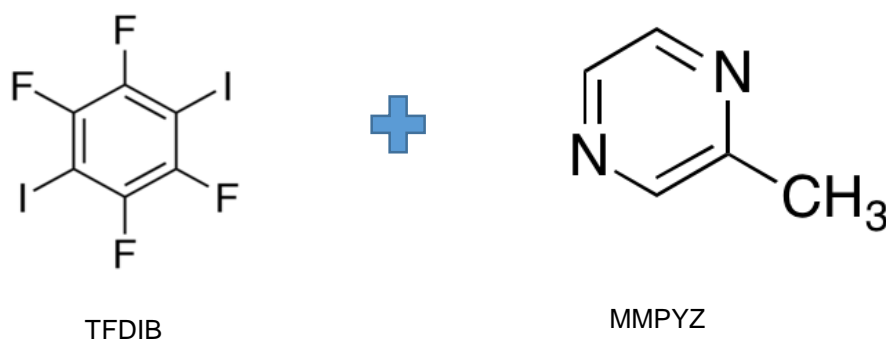
(b) 1,4-diiidotetrafluorobenzene: 2,3,5-trimethylpyrazine (**2**)

1,4-diiidotetrafluorobenzene and 2,3,5-trimethylpyrazine were taken in 1:1 molar ratio and ground in a mortar for 30 minutes along with 2-3 drops of methanol. Diffraction quality crystals were obtained from tetrahydrofuran at room temperature after 4-5 days.



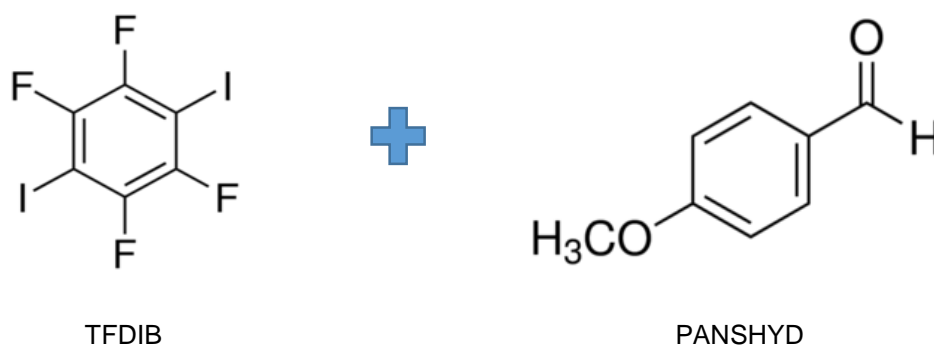
(c) *1,4-diiodotetrafluorobenzene: 2-methylpyrazine (3)*

1,4-diiodotetrafluorobenzene and 2-methylpyrazine were taken in 1:1 molar ratio and ground in a mortar for 30 minutes along with 2-3 drops of methanol. Diffraction quality crystals were obtained from tetrahydrofuran at room temperature after 4-5 days.



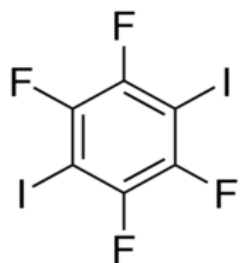
(d) *1,4-diiodotetrafluorobenzene: p-anisaldehyde (4)*

1,4-diiodotetrafluorobenzene and p-anisaldehyde were taken in 1:1 molar ratio and ground in a mortar for 30 minutes along with 2-3 drops of methanol. Diffraction quality crystals were obtained from methanol at room temperature after 4-5 days.

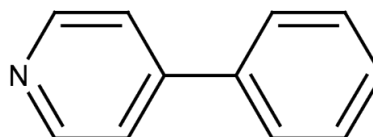


(e) *1,4-diiodotetrafluorobenzene: 4-Phenylpyridine (5)*

1,4-diiodotetrafluorobenzene and 4-Phenylpyridine were taken in 1:1 molar ratio and ground in a mortar for 30 minutes along with 2-3 drops of methanol. Diffraction quality crystals were obtained from tetrahydrofuran at room temperature after 4-5 days.



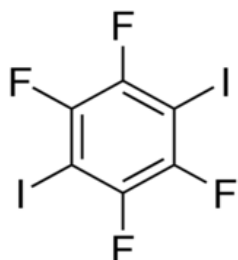
TFDIB



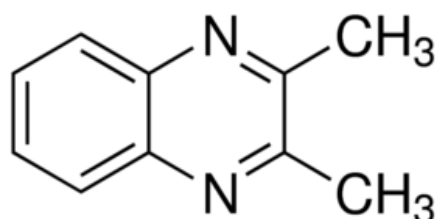
PHNPRD

(f) *1,4-diiodotetrafluorobenzene: 2,3-Dimethylquinoxaline (6)*

1,4-diiodotetrafluorobenzene and 2,3-Dimethylquinoxaline were taken in 1:1 molar ratio and ground in a mortar for 30 minutes along with 2-3 drops of methanol. Diffraction quality crystals were obtained from methanol at room temperature after 4-5 days.



TFDIB



DMQXN

3.4 Characterisation

3.4.1 *Single crystal X-ray diffraction*- The obtained crystals were then characterised by using Single Crystal X-ray Diffraction (SC-XRD) method. The crystals were put in a Rigaku Mercury375/M CCD (XtaLAB mini) diffractometer and were subjected to monochromated Mo-K α radiation at 133 K and data was collected (Figure 7). The obtained data was processed using Rigaku Crystal clear software. The structure was solved and refined using SHELX-97 using WinGXsuite. The dimensions, space groups and volume of the cell were determined. The crystal is termed as single component, binary or ternary if one, two or three chemical entities respectively are present in an asymmetric unit.



Figure 7. Rigaku Mercury375/M CCD (XtaLAB mini) diffractometer used for collecting crystal data.

3.4.2 *NMR*- The performed organic synthesis of IEIB was confirmed by matching the MNR of the obtained product with the NMR data given the publication, which was followed for the synthesis.

A list of some of the unsuccessful experiments is given below, which shows various combinations of different types of halogen containing organic molecules used for the accomplishment of the objective of the project (Table 1). All the successful experiments are listed in the results. In this list, the crystal data of some of the obtained

cocrystals corroborated the already reported crystal data with a similar set of combinations of organic molecules.

Table 1. Examples of some of the crystallization experiments performed and their results showing different halogen compounds used.

S. No.	Compound	Solvent used for crystallization	Result
1	1,4-diiodotetrafluorobenzene: tetramethylpyrazine: 4,4'-bipyridine	THF	1,4-diiodotetrafluorobenzene: tetramethylpyrazine (hexagon crystals- reported) 1,4-diiodotetrafluorobenzene: 4,4'-bipyridine (plate crystals- reported)
2	1,4-dibromobenzene: 1,4- diiodobenzene: morpholine	THF	1,4-diiodobenzene
3	tetramethylpyrazine: iodinemonochloride: 4,4'-bipyridine		Precipitate obtained
4	4,4'-bipyridine: iodinemonochloride: 1,2-Bis(4-pyridyl)ethane		Precipitate obtained
5	1,4-diiodotetrafluorobenzene: 2- Chloropyrazine: Iodopentafluorobenzene	CH ₃ NO ₂	1,4-diiodotetrafluorobenzene (reported)
6	1,4-diiodotetrafluorobenzene: morpholine: 1,4- dibromotetrafluorobenzene	MeOH	1,4-diiodotetrafluorobenzene: morpholine (reported)
7	1,4-dibromotetrafluorobenzene: morpholine: 1-Fluoro-4-iodobenzene		No crystals obtained
8	1,4-diiodotetrafluorobenzene: 2,6- dimethylpyrazine: 1-bromo-4- iodobenzene	MeCN	Poor data
9	1,4-dibromotetrafluorobenzene: 2- methylpyrazine: Iodopentafluorobenzene	MeCN	1,4-dibromotetrafluorobenzene (reported)
10	1,4-diiodobenzene: 2,3,5- trimethylpyrazine: 1-Fluoro-4- iodobenzene	MeOH	1,4-diiodobenzene (reported)

11	4-Dimethylaminopyridine: 1,4-diiidotetrafluorobenzene: 4-Aminopyridine	MeOH	4-Dimethylaminopyridine: 1,4-diiidotetrafluorobenzene (reported)
12	1,4-diiodobenzene: 1,4-diiidotetrafluorobenzene	MeCN	1,4-diiodobenzene (reported)
13	1,4-diiidotetrafluorobenzene: 4-iodoaniline: 4-chlorocinnamaldehyde	MeOH	1,4-diiidotetrafluorobenzene (reported)
14	1,4-diiidotetrafluorobenzene: 4-iodonitrobenzene	Acetone	Poor quality crystals-unmountable
15	4-iodonitrobenzene: 4-bromonitrobenzene: 1,4-dibromotetrafluorobenzene	MeOH	Poor quality crystals-unmountable
16	1,4-diiidotetrafluorobenzene: 2,6-Difluorobenzaldehyde	MeOH	1,4-diiidotetrafluorobenzene (reported)
17	1,4-diiidotetrafluorobenzene: 2,3,5-trimethylpyrazine: 4-iodo-1-iodoethynylbenzene	CH ₃ NO ₂	1,4-diiidotetrafluorobenzene: 2,3,5-trimethylpyrazine (2)
18	1,4-diiidotetrafluorobenzene: 1,4-dicyanobenzene: 4-bromobenzaldehyde	CH ₃ NO ₂	1,4-dicyanobenzene (reported)
19	1,4-dibromotetrafluorobenzene: 1,4-dicyanobenzene	THF	1,4-dicyanobenzene (reported)
20	4-iodo-1-iodoethynylbenzene: 4-phenylppyridine: 1,4-diiodobenzene	EtoAc	4-iodo-1-iodoethynylbenzene: 4-phenylppyridine (reported)

4. Results and Discussion

In the quest of solving the big problem of getting a ternary cocrystal based purely on the halogen bonding, various different binary cocrystals were obtained based on the design strategies. Some of the new binary cocrystals have shown a reasonable probability that they could be used significantly for getting a ternary cocrystal. The formation of halogen bond between a halogen and nitrogen donor and halogen and oxygen were observed successfully. The single crystal structures of new binary systems were analysed by Single Crystal Xray Diffraction (SCXRD) study.

From all the various halogen containing organic compounds and nitrogen and oxygen donating compounds used for the fulfilment of the objective of getting a ternary cocrystal based purely on the halogen bonding, different observations were made which helped in the continuation of the project. Some of the key observations are:

- The addition of iodine monochloride never gave any crystals. It always formed precipitate in the crystallization vials.
- 1,4-dibromotetrafluorobenzene also did not form crystals with any of the nitrogen donors used.
- 1,4-diiodobenzene always gave its monocomponent crystals in all the crystallization experiments performed using it.

4.1 NMR

The formation of 4-iodo-1-iodoethynylbenzene (IEIB) synthesized via organic synthesis routes was confirmed by performing NMR of the product and matching it with the already reported NMR data.³⁴ The NMR data of the products of both the steps of the synthesis are attached (Figure 8 and 9).

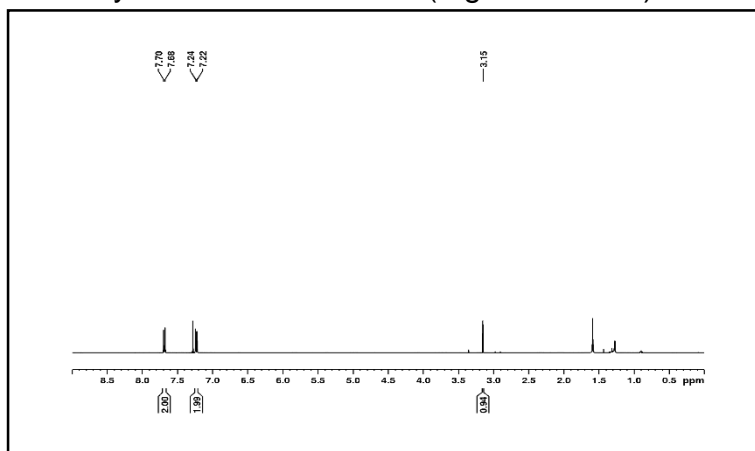


Figure 8. Recorded NMR for the step 1 product- 4-iodo-1-ethynylbenzene.

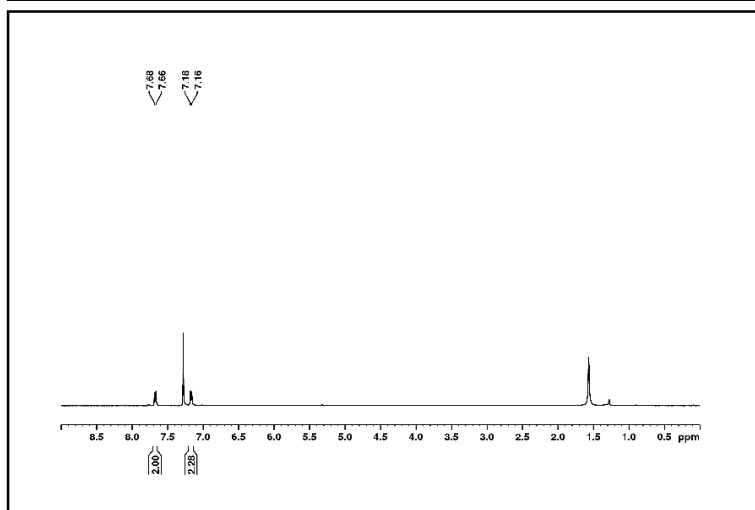


Figure 9. Recorded NMR for the step 2 final product- 4-iodo-1-iodoethynylbenzene.

4.2 The new obtained binary systems are listed.

4.2.1 *TFDIB: DMPYZ* - The single crystal structural analysis reveals that it is crystallized in triclinic P-1 space group with Z value of 2. The asymmetric unit contains one molecule of each 1,4-diiodotetrafluorobenzene (TFDIB) and 2,6-dimethylpyrazine (DMPYZ) (Figure 10(a)). It forms a 1-D chain through C-I...N interaction (3.022 \AA , $\angle 174.7^\circ$ and 2.931 \AA , $\angle 178.11^\circ$) between 1,4-diiodotetrafluorobenzene and 2,6-dimethylpyrazine molecules (Figure 10(b)). The crystallographic parameters are summarized in table 2.

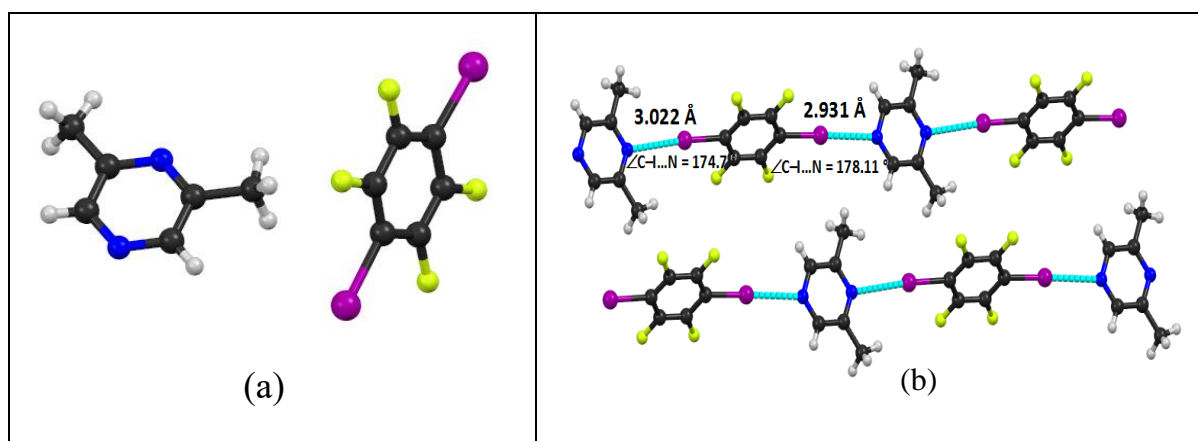


Figure 10. (a) the asymmetric unit of TFDIB and DMPYZ; (b) formation of 1-D chain through C-I...N halogen bonding between 1,4-diiodotetrafluorobenzene and 2,6-dimethylpyrazine molecules.

4.2.2 *TFDIB: TRMPYZ* – This crystal is similar to cocrystal **1**. It crystallizes in triclinic P-1 space group with Z value of 2. The asymmetric unit contains one molecule of each 1,4-diiodotetrafluorobenzene (TFDIB) and 2,3,5-trimethylpyrazine (TRMPYZ) (Figure 11(a)). In the packing it forms a 1-D chain through C-I...N interaction (3.013 \AA , $\angle 174.56^\circ$ and 2.920 \AA , $\angle 178.44^\circ$) between 1,4-diiodotetrafluorobenzene and 2,3,5-trimethylpyrazine molecules (Figure 11(b)). The crystallographic parameters are summarized in table 2.

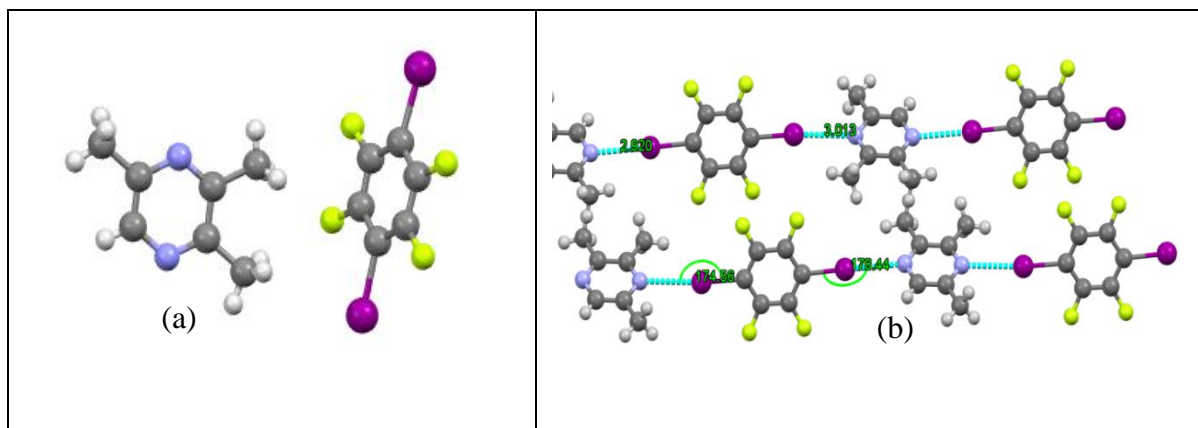


Figure 11. (a) the asymmetric unit of TFDIB and TRMPYZ; (b) formation of 1-D chain through C-I...N halogen bonding between 1,4-diiodotetrafluorobenzene and 2,3,5-trimethylpyrazine

Table 2. Crystallographic parameters for obtained crystal.

compound	DMPYZ-TFDIB (1)	TRMPYZ-TFDIB (2)
emp formula	C ₁₂ H ₈ N ₂ F ₄ I ₂	C ₁₃ H ₁₀ N ₂ F ₄ I ₂
formula weight	510.00	524.03
crystal system	triclinic	triclinic
space group	P-1	P-1
<i>a</i> / Å	7.5327(13)	7.7951(12)
<i>b</i> / Å	8.0698(14)	9.1270(13)
<i>c</i> / Å	12.434(2)	11.6962(17)
α /°	97.382(7)	96.985(7)
β /°	99.757(7)	95.846(7)
γ /°	100.220(7)	110.401(8)
<i>V</i> / Å ³	723.2(2)	764.8(2)
<i>Z</i>	2	2
<i>D_c</i> / g cm ⁻³	2.342	2.276
μ /mm ⁻¹	4.383	4.148
<i>F</i> (000)	472	488.0
θ range/°	3.3–27.5	3.1–27.5
total reflections	7441	7823
unique reflections	3304	3494
observed ref (<i>I</i> > 2 σ (<i>I</i>))	2933	2740
<i>R</i> _{int}	0.044	0.0526
goodness-of-fit (<i>F</i> ²)	1.25	0.892
<i>R</i> ₁ (<i>I</i> > 2 σ (<i>I</i>)) ^a	0.0394	0.0409
<i>wR</i> ₂ (<i>I</i> > 2 σ (<i>I</i>)) ^a	0.1182	0.1401
$\Delta\rho$ min/max/e Å ³	-2.36, 0.81	-1.74, 1.68

$$^a R_1 = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}, wR_2 = \left[\frac{\sum (w(F_o^2 - F_c^2))^2}{\sum w(F_o^2)^2} \right]^{1/2}$$

4.2.3 *TFDIB: MMPYZ* - The crystallized structure takes the space group triclinic P-1 with Z value of 1. The asymmetric unit contains one and half molecules of 1,4-diiodotetrafluorobenzene (TFDIB) and one molecule of 2-methylpyrazine (MMPYZ) (Figure 12(a)). It forms a 1-D chain through C-I...N interaction (2.808 \AA , $\angle 177.13^\circ$ and 2.909 \AA , $\angle 175.13^\circ$) between 1,4-diiodotetrafluorobenzene and 2-methylpyrazine molecules having 1 molecule of 1,4-diiodotetrafluorobenzene stacked between the chains (Figure 12(b)). The crystallographic parameters are summarized in table 3.

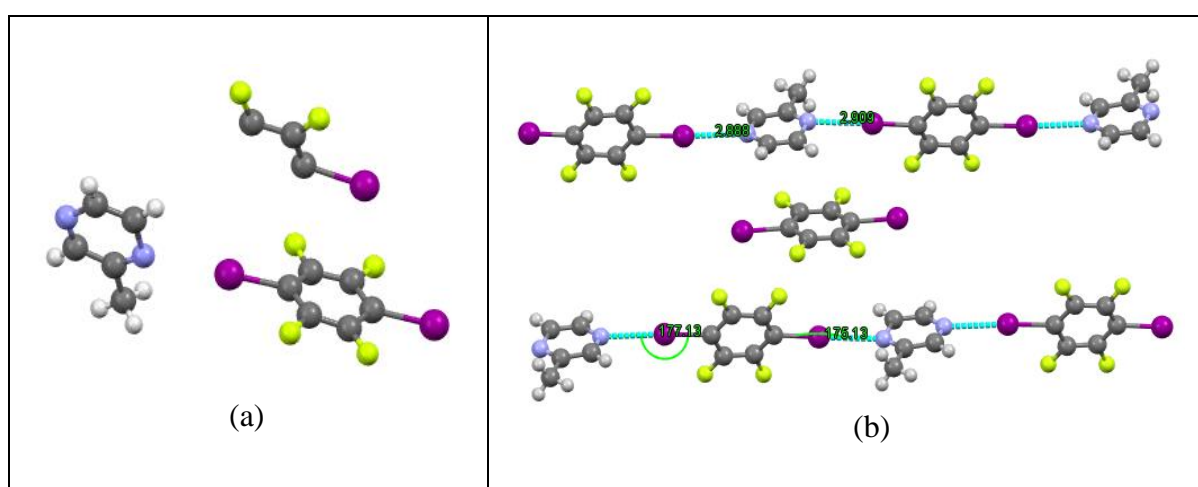


Figure 12. (a) the asymmetric unit of TFDIB and MMPYZ; (b) formation of cocystal through C-I...N halogen bonding between 1,4-diiodotetrafluorobenzene and 2-methylpyrazine molecules.

4.2.4 *TFDIB: PANSHYD* - The single crystal structural analysis reveals that it is crystallized in triclinic P-1 space group with Z value of 1. The asymmetric unit contains half symmetrical part of 1,4-diiodotetrafluorobenzene (TFDIB) and one molecule of p-anisaldehyde (PANSHYD) (Figure 13(a)). It forms ternary chains through C-I...O interaction (2.917 \AA , $\angle 174.4^\circ$) having one molecule of 1,4-diiodotetrafluorobenzene two of p-anisaldehyde molecules (Figure 13(b)). The crystallographic parameters are summarized in table 3.

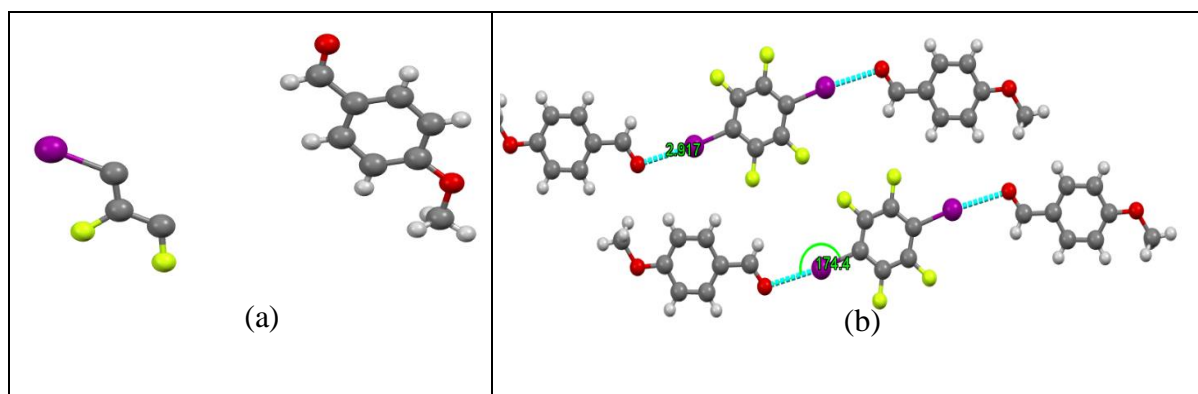


Figure 13. (a) the asymmetric unit of TFDIB and PANSHYD; (b) formation of ternary chains through C-I...O halogen bonding between 1,4-diiodotetrafluorobenzene and p-anisaldehyde molecules.

Table 3. Crystallographic parameters for obtained crystal.

compound	MMPYZ-TFDIB (3)	PANSHYD-TFDIB (4)
emp formula	C ₂₈ H ₁₂ N ₄ F ₁₂ I ₆	C ₂₂ H ₁₆ O ₄ F ₄ I ₂
formula weight	1393.82	674.15
crystal system	Triclinic	triclinic
space group	P-1	P-1
<i>a</i> / Å	5.9489(12)	8.1272(17)
<i>b</i> / Å	12.991(3)	8.2592(17)
<i>c</i> / Å	13.377(3)	9.892(2)
α /°	87.903(7)	94.114(7)
β /°	79.762(7)	104.927(7)
γ /°	89.820(6)	110.118(8)
<i>V</i> / Å ³	1016.7(4)	592.9(2)
<i>Z</i>	1	1
<i>D_c</i> / g cm ⁻³	2.276	1.888
μ /mm ⁻¹	4.663	2.708
<i>F</i> (000)	634	322
θ range/°	3.1-27.5	3.1-27.5
total reflections	10115	6240
unique reflections	4635	2715
observed ref (<i>I</i> > 2 σ (<i>I</i>))	3956	2371
<i>R</i> _{int}	0.0728	0.0570
goodness-of-fit (<i>F</i> ²)	1.25	1.086
<i>R</i> ₁ (<i>I</i> > 2 σ (<i>I</i>)) ^a	0.1298	0.0473
<i>wR</i> ₂ (<i>I</i> > 2 σ (<i>I</i>)) ^a	0.3556	0.1401
$\Delta\rho$ min/max/e Å ³	-4.54, 5.31	-1.48,0.82

$$^a R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|, wR_2 = [\sum (w(F_o^2 - F_c^2))^2 / \sum w(F_o^2)^2]^{1/2}$$

4.2.5 *TFDIB: PHNPRD* - This crystal is similar to cocrystal **4**. It crystallizes in triclinic P-1 space group with Z value of 3. The asymmetric unit contains one and half units of 1,4-diodotetrafluorobenzene (TFDIB) and three molecules of 4-phenylpyridine (PHNPRD) (Figure 14(a)). It forms ternary chains through C-I...N interaction (2.831 \AA , $\angle 175.40^\circ$) having one molecule of 1,4-diodotetrafluorobenzene two of 4-phenylpyridine molecules (Figure 14(b)). The crystallographic parameters are summarized in table 4.

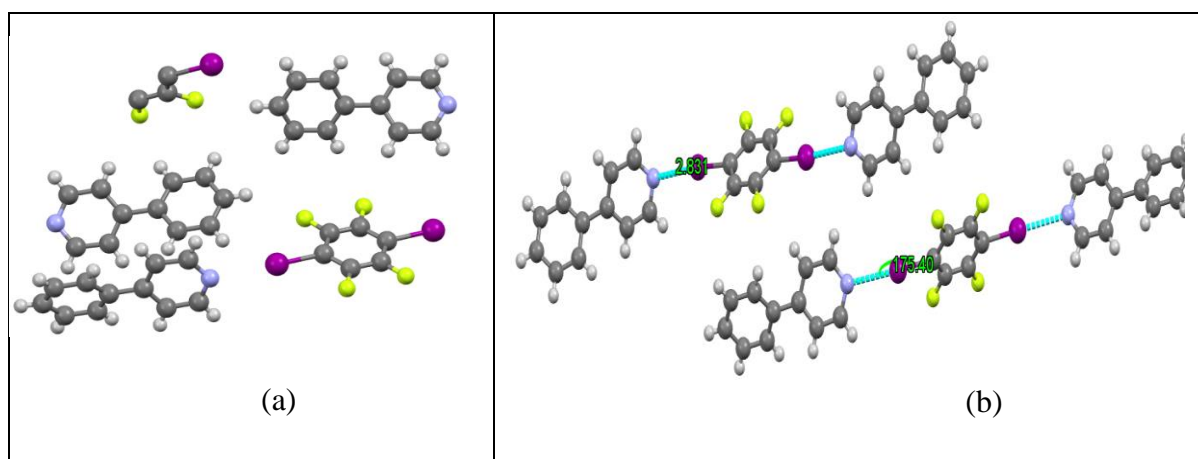


Figure 14. (a) the asymmetric unit of TFDIB and PHNPRD; (b) formation of ternary chains through C-I...N halogen bonding between 1,4-diodotetrafluorobenzene and 4-phenylpyridine molecules.

4.2.6 *TFDIB: DMQXN* - The single crystal structural analysis reveals that it is crystallized in triclinic P-1 space group with Z value of 2. The asymmetric unit contains one of each 1,4-diodotetrafluorobenzene (TFDIB) and 2,3-Dimethylquinoxaline (DMQXN) (Figure 15(a)). It also forms a 1-D chain through C-I...N interaction (3.098 \AA , $\angle 169.05^\circ$ and 3.111 \AA , $\angle 170.66^\circ$) between 1,4-diodotetrafluorobenzene and 2,3-Dimethylquinoxaline molecules (Figure 15(b)). The crystallographic parameters are summarized in table 4.

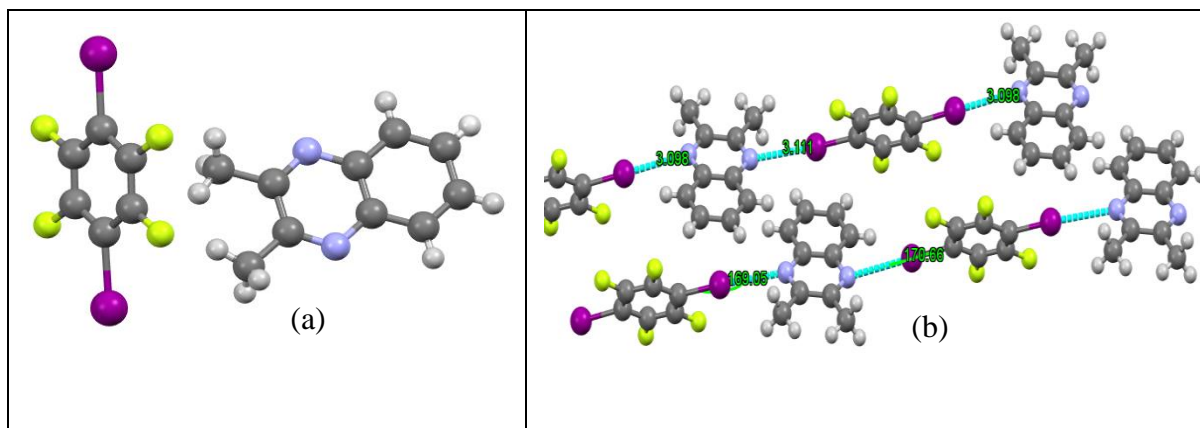


Figure 15. (a) the asymmetric unit of TFDIB and DMQXN; (b) formation of 1-D chain through C-I...N halogen bonding between 1,4-diiidotetrafluorobenzene and 2,3-Dimethylquinoxaline

Table 4. Crystallographic parameters for obtained crystal.

compound	PHNPRD-TFDIB (5)	DMQXN-TFDIB (6)
emp formula	C ₂₈ H ₁₈ N ₂ F ₄ I ₂	C ₁₆ H ₁₀ N ₂ F ₄ I ₂
formula weight	712.24	560.06
crystal system	Triclinic	triclinic
space group	P-1	P-1
<i>a</i> / Å	10.2151(11)	6.4628(15)
<i>b</i> / Å	12.5121(13)	11.042(3)
<i>c</i> / Å	16.4091(17)	11.979(3)
α /°	73.144(5)	79.101(6)
β /°	84.612(6)	84.299(6)
γ /°	78.385(5)	80.907(6)
<i>V</i> / Å ³	1964.7(4)	826.8(3)
<i>Z</i>	3	2
<i>D_c</i> / g cm ⁻³	1.806	2.250
μ /mm ⁻¹	2.449	3.845
<i>F</i> (000)	1026.0	524
θ range/°	2.9-27.5	3.2-27.5
total reflections	20614	8718
unique reflections	9005	3791
observed ref (<i>I</i> > 2 σ (<i>I</i>))	6207	3289
<i>R</i> _{int}	0.0594	0.0492
goodness-of-fit (<i>F</i> ²)	0.934	1.068
<i>R</i> ₁ (<i>I</i> > 2 σ (<i>I</i>)) ^a	0.0492	0.0400
<i>wR</i> ₂ (<i>I</i> > 2 σ (<i>I</i>)) ^a	0.1394	0.1055
$\Delta\rho$ min/max/e Å ³	-1.19, 0.87	-1.39, 1.19

$$^a R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|, wR_2 = [\sum (w(F_o^2 - F_c^2))^2 / \sum w(F_o^2)]^{1/2}$$

4.2.7 *IEIB: TMP* – This combination also forms similar cocrystals as in **1**, **2** and **6** cocrystals. It crystallizes in monoclinic P21/m space group with Z value of 2. The asymmetric unit contains half symmetric part of 4-iodo-1-iodoethynylbenzene (IEIB) and one molecule of 2,3,5,6-Tetramethylpyrazine (TMP) (Figure 16(a)). It forms a 1-D chain through C-I...N interaction (3.318 \AA , $\angle 175.81^\circ$ and 2.960 \AA , $\angle 176.91^\circ$) between 4-iodo-1-iodoethynylbenzene and 2,3,5,6-Tetramethylpyrazine molecules (Figure 16(b)). The crystallographic parameters are summarized in table 5.

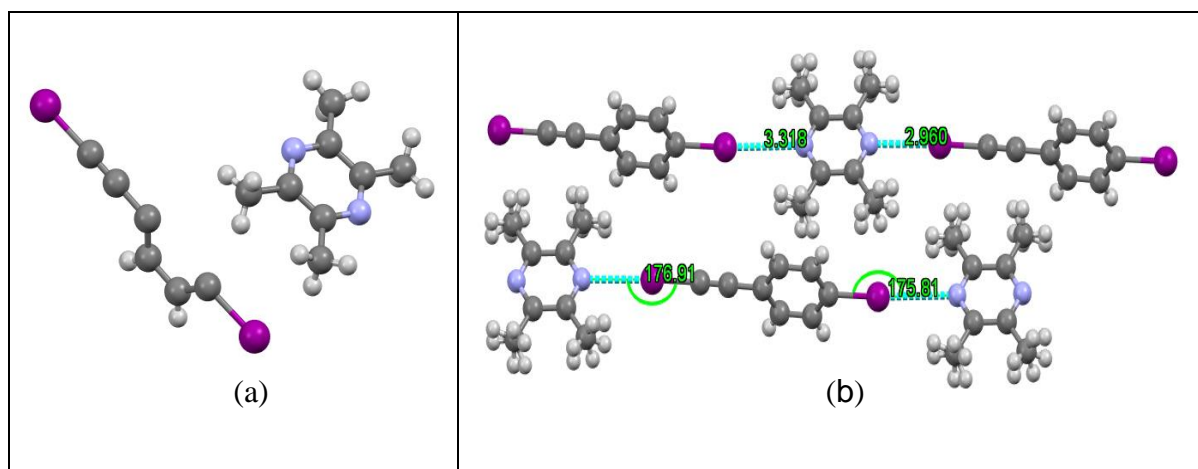


Figure 16. (a) the asymmetric unit of IEIB and TMP; (b) formation of 1-D chain through C-I...N halogen bonding between 4-iodo-1-iodoethynylbenzene and 2,3,5,6-Tetramethylpyrazine

4.2.8 *IEIB* – The mono component crystal takes the space group orthorhombic Pca21 with Z value of 4. The asymmetric unit contains one unit of 4-iodo-1-iodoethynylbenzene (IEIB) (Figure 17(a)). In the crystal it is diagonally connected with the same molecule through C-I...I interaction (3.864 \AA , $\angle 99.59^\circ$ and 3.864 \AA , $\angle 171.08^\circ$) (Figure 17(b)). The crystallographic parameters are summarized in table 5.

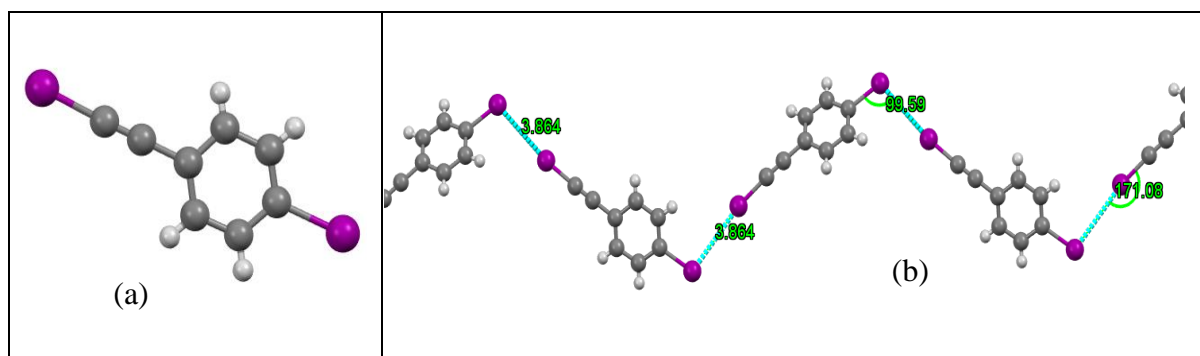


Figure 17. (a) the asymmetric unit of IEIB; (b) formation of crystal through C-I...I halogen bonding between 4-iodo-1-iodoethynylbenzene molecules.

Table 5. Crystallographic parameters for obtained crystal.

compound	IEIB-TMP (7)	IEIB (8)
emp formula	C ₁₆ H ₁₆ N ₂ I ₂	C ₈ H ₄ I ₂
formula weight	490.11	353.91
crystal system	monoclinic	orthorhombic
space group	P21/m	Pca21
<i>a</i> / Å	13.194(3)	6.116(5)
<i>b</i> / Å	7.3866(15)	7.337(6)
<i>c</i> / Å	13.297(3)	20.942(18)
α /°	90	90
β /°	140.080(10)	90
γ /°	90	90
<i>V</i> / Å ³	831.6(3)	939.7(14)
<i>Z</i>	2	4
<i>D_c</i> / g cm ⁻³	1.957	2.502
μ / mm ⁻¹	3.774	6.621
<i>F</i> (000)	464.0	632
θ range/°	3.2-27.5	3.4-27.5
total reflections	8757	4133
unique reflections	2057	2147
observed ref (<i>I</i> > 2 σ (<i>I</i>))	1866	1453
<i>R</i> _{int}	0.0603	0.0674
goodness-of-fit (<i>F</i> ²)	1.145	1.253
<i>R</i> ₁ (<i>I</i> > 2 σ (<i>I</i>)) ^a	0.0340	0.0657
<i>wR</i> ₂ (<i>I</i> > 2 σ (<i>I</i>)) ^a	0.0792	0.1055
$\Delta\rho$ min/max/e Å ³	-1.78, 1.06	-1.42, 1.43

$$^a R_1 = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}, wR_2 = \left[\frac{\sum (w(F_o^2 - F_c^2))^2}{\sum w(F_o^2)^2} \right]^{1/2}$$

- 1,4-diiidotetrafluorobenzene formed binary cocrystals with mostly all the nitrogen donors with which it was grounded, which can be noted from all the new binary cocrystals reported in the thesis.
- It can be noted from the structure of the synthesized 4-iodo-1-iodoethynylbenzene that both the iodine atoms present in the structure have different binding strengths.
- From all the experiments performed of 1,4-diiidotetrafluorobenzene with sulphur donors and oxygen donors, no bond formation of halogen with sulphur was observed, and only one case was seen where halogen formed a bond with the oxygen atom.
- The monocomponent crystal of 4-iodo-1-iodoethynylbenzene is formed through type I and type II halogen bonds having I...I (iodine- iodine) contacts. The molecules of the compound are placed orthogonally in the crystal giving supporting these contacts. The type I and type II bonds are present alternatively in the infinite chain.

5. Conclusions

All the cocrystals reported above contain the conventional type halogen bond-forming the bond between a halogen and an electronegative atom (nitrogen and oxygen here). According to the sigma hole theory, it can be noted that the sigma hole present at both the iodine's in 4-iodo-1-iodoethynylbenzene is of different strengths. This could be a very crucial form the point of view for the formation of a ternary cocrystal based purely on halogen bonding as it could accommodate two different compounds having donors of different strengths at both the iodine's in the molecule.

1,4-diiidotetrafluorobenzene forms halogen bond with most of the N-donors and some of the O-donors. This shows the high reactivity of 1,4-diiidotetrafluorobenzene which must be due to the presence of high positive electrostatic potential on the C-I axis. It gives great scope towards the formation of ternary due to readiness of bond formation.

Around 80 cocrystallization experiments were performed. It can be concluded that the formation of a ternary cocrystal is very typical as when three components are taken for cocrystallization the resultant possibilities become too many. If three components A1, A2 and A3 are taken then there is a possibility to form highly stable monocomponent; binaries of A1...A2, A2...A3 or A1...A3; solvated crystals or polymorphs of any of these. So the probability of getting an expected ternary is too less. So for the formation of a ternary cocrystal, both similarity and dissimilarity initially in the monocomponent and then the binary cocrystals is required which could become the key for the replacement of one of the components and the addition of the next component to increase the order of the crystal.

The results have been looked very carefully and work to get a ternary cocrystal only with halogen bond is continued.

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