POLYMORPHISM AND INCLUSION PROPERTIES OF SOME BIS-HYDRAZONE COMPOUNDS OF GLYOXAL AND BUTANE-2,3-DIONE

पॉलीमॉरफिस्म एंड इन्क्लूज़न प्रॉपर्टीज ऑफ़ सम बिस-हाइड्रेज़ोन कम्पाउंड्स ऑफ़ ग्लाईओक्ज़ल एंड ब्यूटेन-2,3-डाईऑन

Thesis submitted to Jawaharlal Nehru University

for the award of the degree of

DOCTOR OF PHILOSOPHY

Vikrant Jayant

(विक्रान्त जयन्त)

Under the Supervision of

Dr. Dinabandhu Das

SCHOOL OF PHYSICAL SCIENCES

JAWAHARLAL NEHRU UNIVERSITY

NEW DELHI-110067, INDIA

JULY 2018

जवाहरलाल नेहरू विश्वविद्यालय
Jawaharlal Nehru University
भौतिक विज्ञान संस्थान
School of Physical Sciences
New Delhi -110067

नई दिल्ली -110067

July 23, 2018

Declaration

I hereby declare that the work reported in this thesis entitled "**Polymorphism and Inclusion Properties of Some Bis-hydrazone Compounds of Glyoxal and Butane-2, 3-dione**" is entirely original and has been carried out by myself at School of physical Sciences, Jawaharlal Nehru University, New Delhi under the supervision of Dr. Dinabandhu Das. I further declare that neither this thesis nor any part of it has been submitted for any degree/ diploma or any other academic award anywhere before.

Vikrant Jayant
(विक्रान्त जयन्त)

Dr. Dinabandhu Das

Thesis Supervisor
School of Physical Sciences
Jawaharlal Nehru University
New Delhi- 110067, India

Prof. Satyabrata Patnaik

Dean
School of Physical Sciences
Jawaharlal Nehru University
New Delhi- 110067, India

Dedication

मेरे आध्यात्मिक गुरू
श्री आचार्य रजनीश जी (ओशो)
को समर्पित

"अप्प दीपो भव:"
अपने दीये स्वयं बनो

"सारी शिक्षा, सारे उपदेश व्यर्थ हैं
अगर वे तुम्हें भीतर डूबने की कला नहीं सिखाते"

"Educating mind without educating the heart is no education at all"

(Aristotle)

"ओशो शरणम् गच्छामि
बुद्धम् शरणम् गच्छामि"

Acknowledgements

I am thankful to my PhD supervisor Dr. Dinabandhu Das for mentoring me academically. I sincerely thank him for introducing me into the research field of polymorphism and inclusion compounds. Without his constant encouragement, valuable suggestions and keen interest this thesis would not have converted into reality.

I would like to express my sincere gratitude to the members of doctoral committee Dr. Sobhan Sen (SPS), Dr. Pritam Mukhopadhaya (SPS), Dr. Satyendra Singh (SCNS) for their constant support and encouragement. I am very much thankful to former Dean of SPS Prof. Subhasis Ghosh and Prof. Riddhi Shah for their motivation.

I acknowledge present dean of SPS Prof. Satyabrata Patnaik for his kind help. I would like to express my gratitude to all the faculty members in SPS.

I express my sincere thanks to Dr. Nidhi Goel for her assistance. I thank to my labmates Ashutosh Srivastava, Bhavna Dwivedi, Lalita Negi and Sunil Kumar for their kind help.

I am grateful to School of Physical Sciences, Jawaharlal Nehru University, New Delhi for infrastructural facilities, University Grants Commission, India and JNU for Fellowship. I thank all the non-teaching staff members in SPS for conducing proper environment during my research work. I also wish to acknowledge technical staff in AIRF, Dr. Ajay for NMR, Mr. Saroj Kumar Jha and Mr. Plabon Borah for Mass spectroscopy at AIRF and for their cooperation in facilitating experiments required for my research.

I acknowledge Dr. Shahid Salam for compiling my thesis. I would like to acknowledge Dr. Sachin, Dr. Nibedita, Dr. Firoz, Dr. Kiran, Dr. Him Shweta for their cordial behaviour. I thank to Dr. Deepak Asthana, Dr. Ajayakumar Anchal, Dr. Shravan, Dr. Vishwa Pal, Dr. Ashwani Kumar Tripathi, Dr. Satyendra Prakash Pal, Dr. Budhi Singh, Dr. Manoj Sani, Dr. Greesh, Dr. Abhishek, Dr. Versha Aggarwal, Dr. Jitendra Saha, Dr. Jyoti Shukla, Dr. Avesh Kumar, Dr. Kalyanashis Mandal, Dr. Vishal Maurya Dr. Shudir Keshri and Dr. Ambuja for spending quality tea time and sharing their knowledge and experiences about research.

I am thankful to Babu Ram for helping me to bring liquid nitrogen from AIRF and for transferring into container during my experiment. I appreciate the help extended by Praveen Scientific (Shambhu Pandit) by providing chemicals and solvents in time. Sincere thanks to Santosh bhaiya and Mintiram for serving tea and snacks.

I want to express my special gratitude to my batchmates & colleagues Rajkumar (SLS, JNU), Awanish, Panchram, Neetu, Jogesh, Yogendra, Pratyay Ghosh, Neha, Harish, Renu, Imtiaz, Rohtash, Sunil kumar yadav, Pragya, Priyanka, Pankaj, Sanjeev Kumar, Kishor, Nasir Ali, Rahul Ranjan, Raju Mekala, Amodini Mishra and Jyoti Shakya.

I am thankful to my friends Alok, Ajay, Shibin Xavier, Ujjwal Labh, Kishor (SLS), Arshad, Prashant Kumar Gaurav, Vipul, Niranjan Kumar, Vikas Gupta and Sumit Chaudhary who supported and cared me whenever I got ill. I would also like to thank the SPS cricket team for creating cheerful moments in stress laden times.

Finally, my deepest gratitude goes to my family members, my father and mother for supporting me economically, to my brothers, Pradeep Kumar, Vikas Jayant and Neeraj Kumar Jayant and to my close friend Puneet Kansal for bringing joyfulness in my life.

Vikrant Jayant
(विक्रान्त जयन्त**)**

Contents

Abstract of the Thesis

This thesis entitled "**Polymorphism and Inclusion Properties of Some Bis-hydrazone Compounds of Glyoxal and Butane-2,3-dione"** consists of four chapters. Recent developments in the field of polymorphism and inclusion phenomenon primarily in organic materials have been discussed in **Chapter 1**. **Chapter 2** describes the specific inclusion properties and polymorphism of two bis-hydrazone compounds of glyoxal. **Chapter 3** deals with a very rare phenomenon of temperature dependent two reversible single crystal to single crystal polymorphic phase transformations of a bis-hydrazone compound. Finally, polymorphism and inclusion of various solvents in the crystal lattice of two new bis-hydrazone compounds of butane-2,3-dione have been explained in the **Chapter 4**.

CHAPTER 1

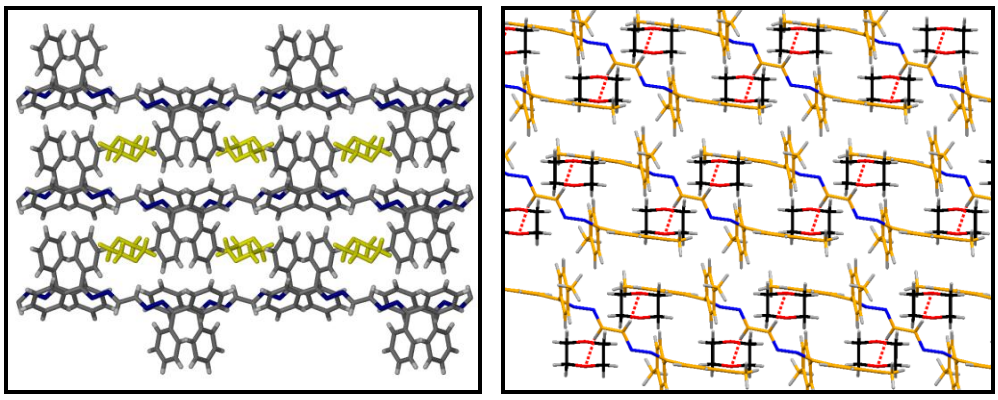
Polymorphism, widely studied phenomenon in organic solid-state chemistry, is defined by McCorne as the phenomenon of having at least two different crystal structures of same chemical compound.[1] Polymorphism is very important and essential subject to study in pharmaceutical and other specialty industry because different polymorphs have different physicochemical properties.[2]

Inclusion of solvent molecule in the crystal lattice is another fascinating area in supramolecular chemistry. This is not only important for fundamental research, but also tremendously significant in purification and separation processes.[3] Molecular recognition is the heart of this phenomenon in which host and guest molecule come closer under the influences of weak interactions and generate host-guest complex, which possesses unique properties than independent host and guest molecule.[4]

This chapter gives an overview of polymorphism and inclusion properties of organic compounds. Recent developments in these two important areas in supramolecular chemistry have been described in this chapter.

CHAPTER 2

1,4-Dioxane (DIOX) is commonly used solvent in chemistry laboratory. It has carcinogenic property that creates so many health problems even up to coma or death during excessive inhalation or overexposure.[5] Therefore, it is necessary to design host molecule, which can specifically include and separate DIOX. This chapter describes the specific inclusion of DIOX by two new bis-hydrazone compounds: ethanedial-1,2-bis(benzophenone hydrazone) (**BBHG**) and ethanedial-1,2-bis(4,4'-dimethylbenzophenone hydrazone) (**DMBHG**) derived from glyoxal. These compounds were crystallized in various solvents to prepare single crystals for the determination of structure by Single crystal X-ray Diffraction (SCXRD) or (SCD). Crystals of both the compounds grown in DIOX became opaque within 24 hours − indicating the formation of inclusion compounds of **BBHG** (**BBHG•DIOX**) and **DMBHG** (**DMBHG•DIOX**) which was indeed confirmed by the determination of crystal structure by SCD. Compound **BBHG** crystallizes with DIOX in 1 : 1 stoichiometric ratio whereas compound **DMBHG** forms the inclusion compound in 1 : 2 ratio with DIOX. None of the compounds of **BBHG** and **DMBHG** form inclusion compound in other solvents. **BBHG** and **DMBHG** also show polymorphic behavior.



(**a**) (**b**)

Figure 1. (**a**) Packing diagram of **BBHG•DIOX** viewed down the *c* axis. DIOX molecules have been shown in yellow; (**b**) Packing diagram of **DMBHG•DIOX** viewed down the *c* axis. C─H···O hydrogen bonding between DIOX and **DMBHG** molecules have been shown in red dotted line.

CHAPTER 3

Single Crystal to Single Crystal (SC-SC) transformation is very interesting phenomenon to study because simultaneous and cooperative movement of constituent atoms or molecules leads to the change of crystal structures without appreciable loss of single crystallinity. SC-SC polymorphic phase transformation induced by external stimuli is known in many organic compounds.[6] Since significant change of crystal structures is not expected in SC-SC transformation, there is possibility of this kind of transformation between isostructural polymorphs.[6b] This chapter describes a rare observation of two reversible SC-SC polymorphic phase transformations[7] of three isostructural polymorphs of a bis-hydrazone compound, **DEBH**. The reversible phase transformation has been first identified by DSC experiment and confirmed by variable temperature Single Crystal X-ray Diffraction experiment (VT-SCXRD). While, three polymorphic phases are reversibly interconvertible to each other before melting of the compound thorough SC-SC transformation, another polymorphic phase has been isolated by cooling and subsequent heating of the melt phase, generating overall four polymorphic phases.

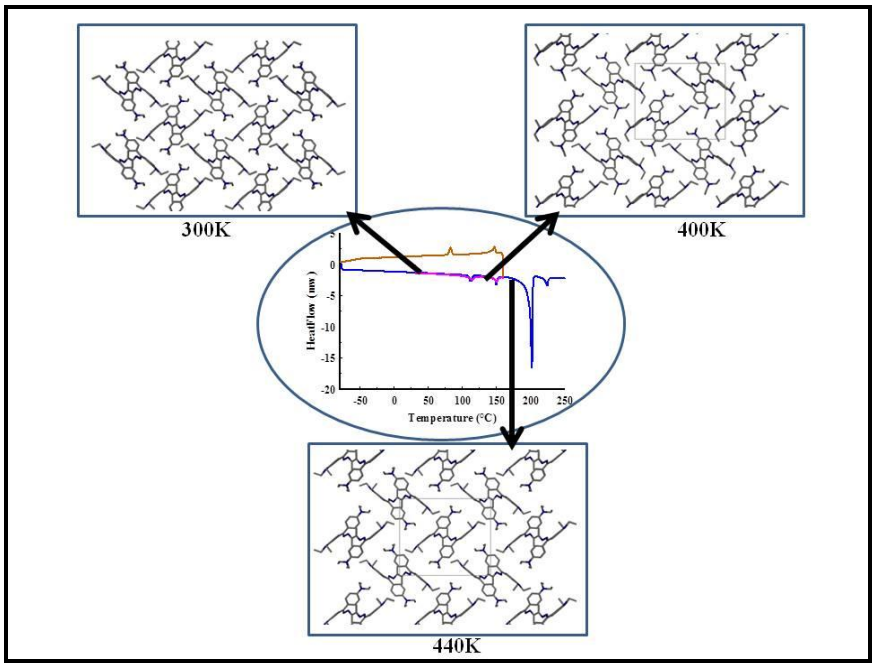


Figure 2. Packing diagram of three polymorphic phases of **DEBH** determined at different temperatures. Reversible phase transformation was observed in DSC thermogram shown in middle.

CHAPTER 4

Polymorphism and inclusion of solvent molecule in crystal lattice add complexity in designing new materials with desired properties. Yet, research in these areas remain very interesting because these assist in understanding the kinetic of crystal nucleation, molecular recognition and crystal growth.[8] Polymorphism and inclusion phenomenon are widely studied in organic materials. It has been observed that the polymorphic nature of a compound depends upon the conformational flexibility in the molecule, although crystallization conditions play very important role in the outcome of different solid forms. Similarly, there are various factors, which are responsible for inclusion of solvent molecule in crystal lattice, such as, shape and size of the substituent in the host molecule, hydrogen bonding interactions between the functional groups present the host and guest molecules. In any case, McCrone's statement "that the number of forms known for a given compound is proportional to the time and money spent in research on that compound" seems to be very provocative.[1]

Both polymorphism and inclusion properties have been observed in many organic compounds.[9] This chapter deals with the polymorphism and inclusion properties of two bis-hydrazone compounds, **DMBHB**, **DTBHB** derived from butane-2,3-dione. Although, both **DMBHB**, **DTBHB** show inclusion properties, but the tendency of inclusion of solvent of **DMBHB** is higher than **DTBHB**. This may be due the electronic effect of *N*,*N*-dimethyl substituents which increases the flexibility in the molecule. **DMBHB** includes various solvents when it was crystallized in different solvents while **DTBHB** forms only limited number of solvates. Two conformational polymorphs of each of these bis-hydrazone compounds have been isolated and characterized by X-ray diffraction and thermal analysis.

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CHAPTER-1

Polymorphism and Inclusion Phenomenon in Organic Compounds

1.1 Abstract

Polymorphism, widely studied phenomenon in organic solid-state chemistry, is defined by McCorne as the phenomenon of having at least two different crystal structures of same chemical compound. Polymorphism is very important and essential subject to study in pharmaceutical and other specialty industry because different polymorphs have different physicochemical properties.

Inclusion of solvent molecule in the crystal lattice is another fascinating area in supramolecular chemistry. This is not only important for fundamental research, but also tremendously significant in purification and separation processes. Molecular recognition is the heart of this phenomenon in which host and guest molecule come closer under the influences of weak interactions and generate host-guest complex, which possesses unique properties than independent host and guest molecule.

This chapter gives an overview of polymorphism and inclusion properties of organic compounds.

1.2 Polymorphism in General

The term Polymorphism, means **"**many forms**"** in Greek, is being used in many disciplines like linguistics, computer science, biology, genetics and crystallography. In the context of crystallography, polymorphism was first observed by Mitscherlich in 1822 in varieties of arsenate and phosphate salts, although Klaporoth first identified and described different crystal forms of calcium carbonate: calcite, vaterite and aragonite in 1788.[1] Several definitions of polymorphism available in the literature**.** According to McCrone, *"A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state*".[2] In 1969, Rosenstein and Lamy proposed a definition of polymorphism to include all the solid state forms of a material. According to Rosenstein and Lamy, *"When a substance can exist in more than one crystalline state it is said to exhibit polymorphism"*.[3] For the first time in 1983 Burger included the term '*component*' in the definition of polymorphism. He described polymorphism as, *''If the solids composed of only one component can exist in different crystal lattices"*.[4] although Bernstein doubted this definition because of the term 'crystal lattice' and also this definition excluded the phenomenon of polymorphism in in co-crystals, solvates or salts.[5] In 1987 Sharma elaborated that, *''Polymorphs means the different crystal forms, belonging to the same or different crystal systems, in which the identical units of the*

same element or the identical units of the same compound, or the identical ionic formulas or identical repeating units are packed differently".[6] Recently by Gavezzotti raised three points to define polymorphism: *''Polymorphs are a set of crystals* (i) *with identical chemical composition*; (ii) *made of molecules with same molecular connectivity, but allowing for different conformations by rotation about single bonds and* (iii) *with distinctly different three-dimensional translationally periodic symmetry operations"*.[7] In 2009 Purojit and Venugoplan has defined polymorphism as *''... the ability of a substance to exist as two or more crystalline phases that have different arrangements or conformations of the molecules in the crystal lattice"*.[8] Among the various definitions of polymorphism available in the literature, the most accepted definition given by McCrone in 1965 has passed the test of time.[2] In order to avoid the confusion of dynamic isomerism and tautomerism with polymorphism, J. Elguero proposed a new definition of polymorphism which states that "*polymorphism concerns crystal structures that are different but lead to identical liquid and vapor states with the condition that no bonds are broken or created"*.[9]

1.3 Polymorphism in Organic Compounds

Crystal polymorphism is very common phenomenon in organic and pharmaceutical compounds. Benzamide is the first organic compound studied for polymorphism. In 1832 Wohler and Liebig noticed fibrous crystals during crystallization of benzamide by slow cooling of hot aqueous solution.[10] They observed that these fibrous crystals transformed to well-shaped rhombic crystals after few moments. Wohler and Liebig described this phenomenon as phase transformation. However, crystal structure of the stable polymorph of benzamide was first determined in 1959 by Single Crystal X-ray diffraction method.[11] 173 years after the discovery of first polymorph of benzamide by Wohler and Liebig, the structure of the metastable polymorph has been determined by Davey *et al*. in 2005 by synchrotron X-ray Powder Diffraction method.[12] In the meantime, large number of organic compounds have been reported for polymorphism**.** Grant *et al*. has suggested that approximately one third of organic compounds are polymorphic.[13] Recently Matzger *et al*. have published statistical analysis of Cambridge Structural Database (**CSD**) for polymorphism in organic compounds.[14] According to their analysis 1.22% of single component organic compounds present in CSD till 2015 are polymorphic.

There are some compounds which known to be highly polymorphic. 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, commonly known as **'ROY'** due the characteristic Red, Orange and Yellow colour exhibited by the polymorphs, is highly polymorphic compound. Till date total ten polymorphs of ROY have been characterized[15] out of which crystal structure of eight polymorphs have been determined by diffraction methods.[16] Non-steroidal anti-inflammatory drug flufenamic acid (FFA) possesses at least nine polymorphs out of which crystal structure of eight polymorphs are known till date.[17] Highly explosive material triacetone-triperoxide is a hexamorphic compound and crystal structures of all the polymorphs have been characterized by single crystal X-ray diffraction experiment.[18] Recent survey shows that eleven compounds are pentamorphic in CSD.[19] In addition to that, more than fourteen compounds are tetramorphic and over hundred trimorphic compounds are present in CSD.

1.4 Classification of Polymorphism

Polymorphism is mainly divided into two classes: packing polymorphism and conformational polymorphism.[5] In addition to that polymoprphism can be classified on the basis of occurance, colour and similarity in packing. These are known as concomitant polymorphism, coloured polymorphism, synthon polymorphism, tautomeric polymorphism and isostructural polymorphism. Brief description of each of these are given below.

1.4.1 Packing Polymorphism

Packing polymorphism has been observed due to the difference in the crystal packing of same molecule in different polymorphs.[20] Generally packing polymorphism has been observed when molecules possess lack of conformational flexibility although many flexible molecules exhibit packing polymorphism.[21] Packing polymorphism is the most common phenomenon in crystal polymorphism. This can be illustrated by the following cartoon picture in (**Figure 1**) which shows different packing arrangement of same molecule in different crystal structures.

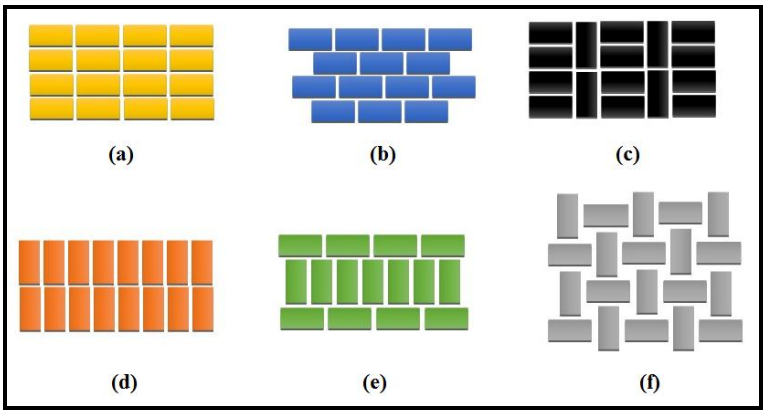


Figure 1. Representation of six different packing arrangement of same molecule in six polymorphs of a compound. Same molecule is shown in different colour in different polymorph.

Some important organic compounds which exhibit packing polymorphism shown in (**Figure 2**). The packing polymorphism not only observed in the compound of single chemical entity but also found in multi-component organic compounds.[22]

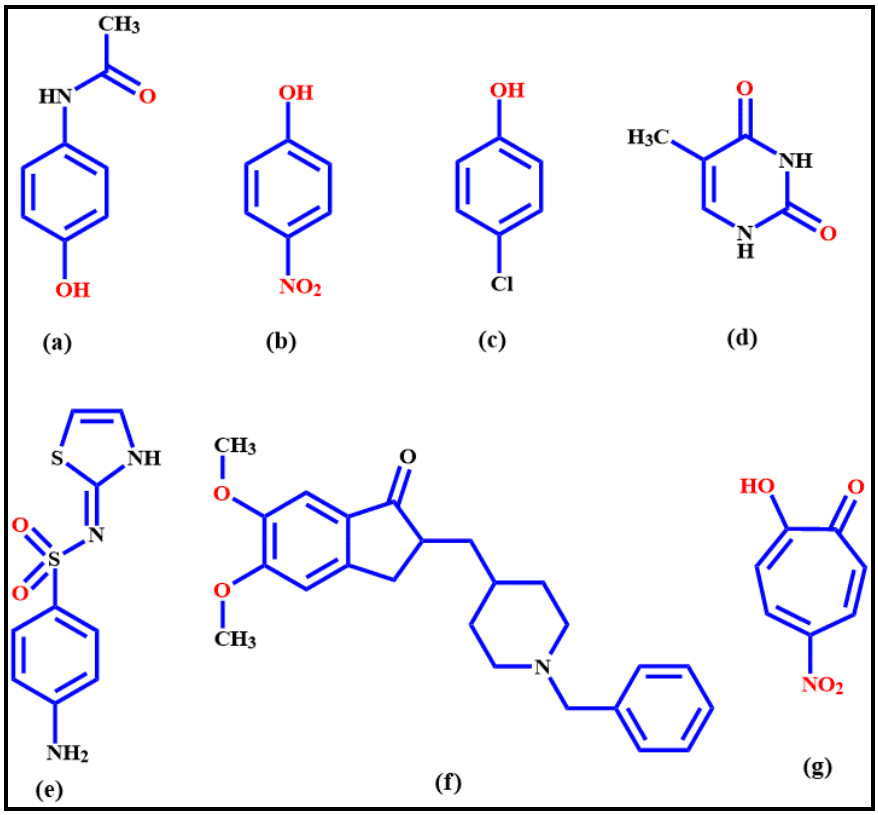
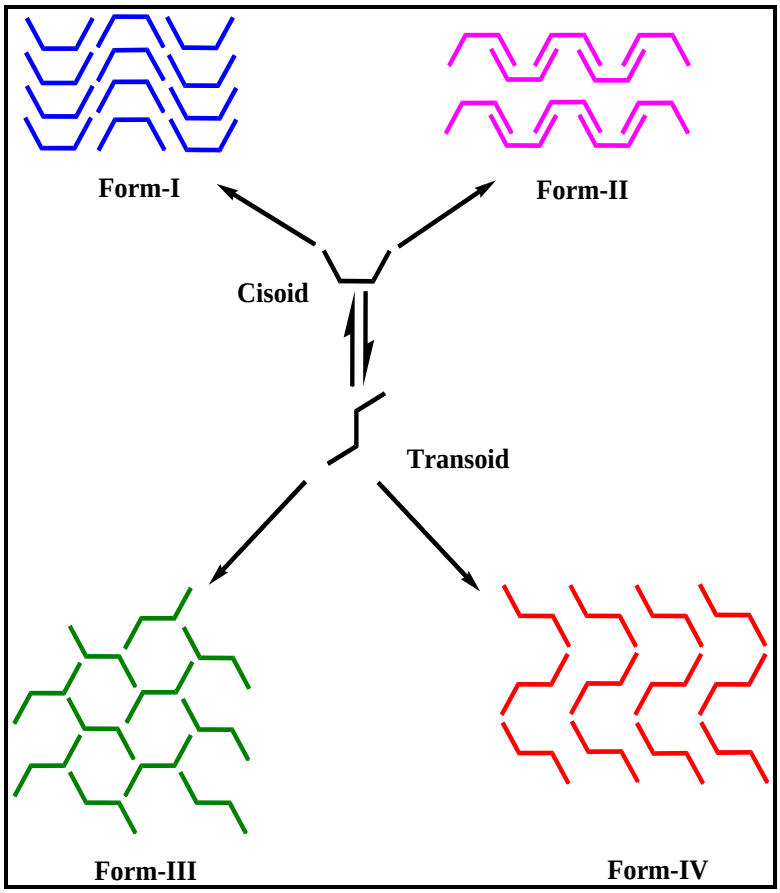


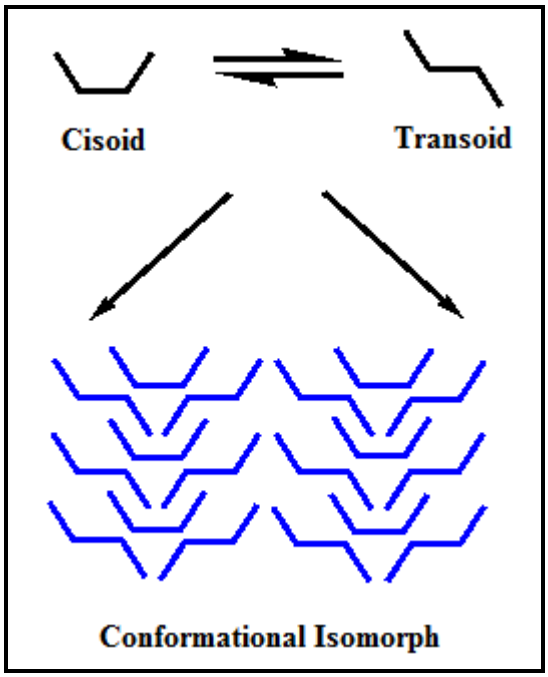
Figure 2. Molecular structures of **(a)** Paracetamol[23] **(b)** p-Nitrophenol[24] **(c)** p-Chlorophenol[25] **(d)** Thymine[26] **(e)** Sulfathiazole[27] **(f)** Donepezil[28] **(g)** 5-Nitroprolone.[29]

1.4.2 Conformational Polymorphism

Conformational polymorphism, an important sub-class of polymorphism, occurs due to the existence of different conformer of same molecule in different crystal structures of a compound.[30] Conformational flexibility in a molecule increases the chance to adopt different crystalline arrangement which leads to conformational polymorphism in many compounds (**Scheme 1.2**).[31] Conformational flexibility in a molecule arises due to torsional degrees of freedom which is a possible reason for the occurrence of conformational polymorphism. However, analyzing CSD in 2007 Bernal found that similar conformation has been observed in different polymorphs of flexible molecule[32] Therefore, conformational flexibility in a molecule does not guaranty to form conformational polymorphs. On the basis of statistical analysis of CSD, in a recent seminal review, Bernstein and Arora have elaborated quantitatively the necessary condition to define conformational polymorphism.[33] It has been mentioned that polymorphism in a conformationally flexible molecule may not always be classified as conformational polymorphism. Bernstein and Arora have pointed out that conformational change of the molecules in the different polymorphs is very much necessary to qualify as conformational polymorphism, whereas, only conformational adjustment gives rise to simple packing polymorphism.[33] Conformational change and conformational adjustment of the molecules can be demonstrated by *rmsd[r]* value of the overlaid molecules where *rmsd[r]* indicates the root-mean-square deviation between the atomic positions. Bernstein and Arora have suggested a threshold value of *rmsd[r]* above which molecules exhibit conformational change and below that value indicates conformational adjustment.[33] In some cases, co-existance of different conformers in the same crystal structure have been found.[34] This phenomenon is known as conformational isomorphous (**Scheme 1.3**).



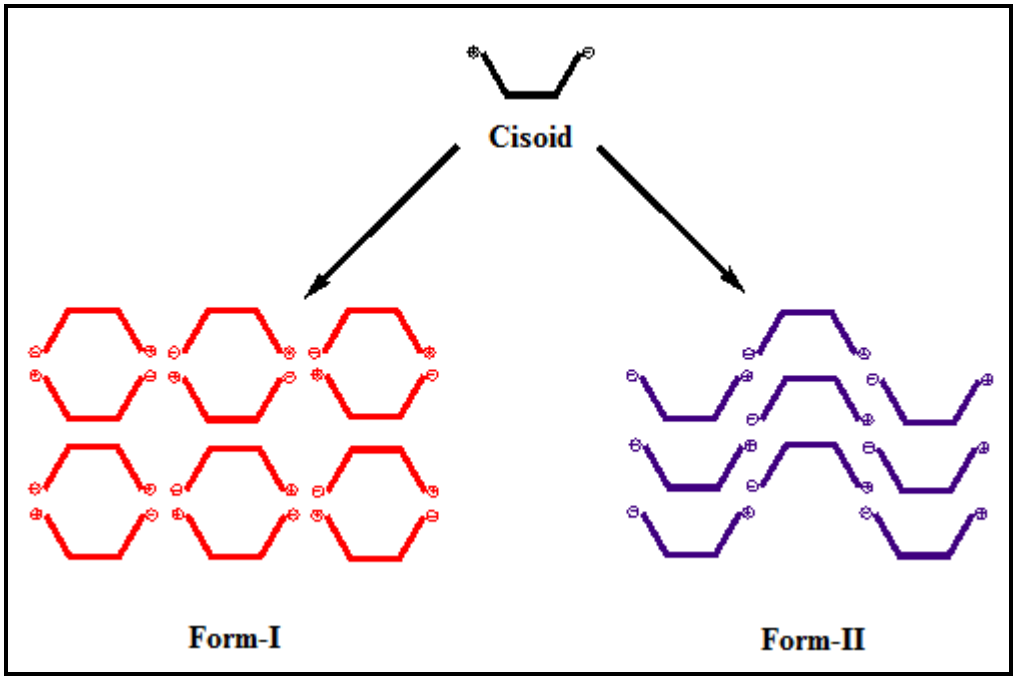
Scheme 1.2 Flexible molecules adopt different crystalline arrangements (**Form-I – Form-IV**).[31]



Scheme 1.3 General representation of conformational isomorphs.[31]

1.4.3 Synthon Polymorphism

Concept of synthon was first coined by Nobel laureate E. J. Corey in 1967 to explain the retro-synthetic process.[35] In 1995 Desiraju introduced the term "supramolecular synthon" which he defined as "*…structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions*".[36] Crystal structure of any molecule is the resultant various intermolecular interactions like van der Waals, coulombic, hydrogen bonding. Many weak interactions like C─H···O hydrogen bonding, π···π, X···X (**X** = halogen), and C─H···π interactions can play significant role for the arrangement of molecueles in the crystal structure. Supramolecular synthon is very useful concept for the analysis of these intermolecular interactions in the crystal structre. In the context of polymorphism, when a molecule forms at least two different crystal structures on the basis of intermolecular interactions, the phenomenon is known as synthon polymorphism[37] as illustrated in (**Scheme 1.4**).



Scheme 1.4 General representation of synthon polymorphs.

1.4.4 Concomitant Polymorphism

Although polymorphism is classified mainly into two main groups: packing polymoprism and conformational polymorphism, there is another important observation of this phenomenon where two or more polymorphs have been observed simultaneously

in the same crystallization apparatus at same crystallization condition. This phenomenon is known as concomitant polymorphism.[38] Since crystalliztion is governed by thermodynamic and parameters, simultaneously appearance of two or more polymorphs occurs due to the competition between these two factors. Bernstein *et al*. have rationalized qualitatively the occurance of concomitant polymorphs considering the almost equal rate of nucleation of the polymorphs.[38] Concomitant polymorphism is a hurdle to control the growth of specific polymorph which is desired in speciality industry. The first instance of concomitant polymorphism was observed by Wöhler and Liebig in the year 1832 during crystallization of benzamide.[10] Concomitant polymorphism has been observed in large number of compounds.[39] Concomitant polymorphism has been found also in macromoelcules.[40] Concomitantly polymorphs can be distinguished from each other by colour and/or morphology (**Figure 3**). Therefore, microscopic analysis is very important at initial stage of characterization of concomitant polymorphs.

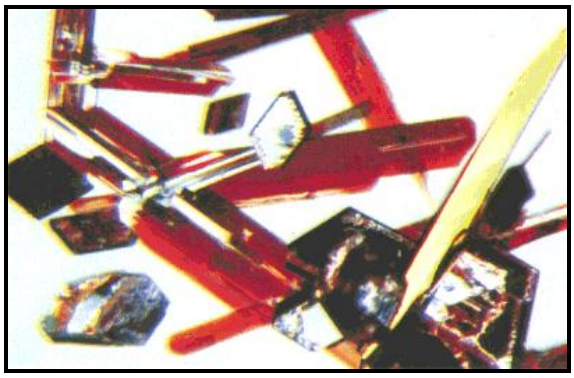


Figure 3. Three polymorphs of cyanine/oxonol dyes formed concomitantly.[38]

1.4.5 Coloured Polymorphism

There are few examples of polymorphism where the polymorphs are distinguished by colour of the individual polymorph.[41] This type of polymorphism is called coloured polymorphism. The first example of this phenomenon was reported by Hantzsch in 1908.[42] At that time the phenomenon was described as chromoisomersim and later it was termed as crystallochromy by Klebe *et al*.[43] One of the most interesting example of coloured polymorphism in recent time has been observed in case of a highly polymorphic compound 5-methyl-2-[(2-nitrophenyl) amino]-3-thiophenecarbonitrile or commonly known as ROY due to Red, Orange and Yellow colour of the polymorphs shown in (**Figure 4**).[15] Similarly, 5-Methyl-2-[(4-methyl-2-nitrophenyl)amino]-3-

thiophenecarbonitrile molecule generates four coloured polymorphic crystals, red (R), dark red (DR), light red (LR), and orange (O).[44]

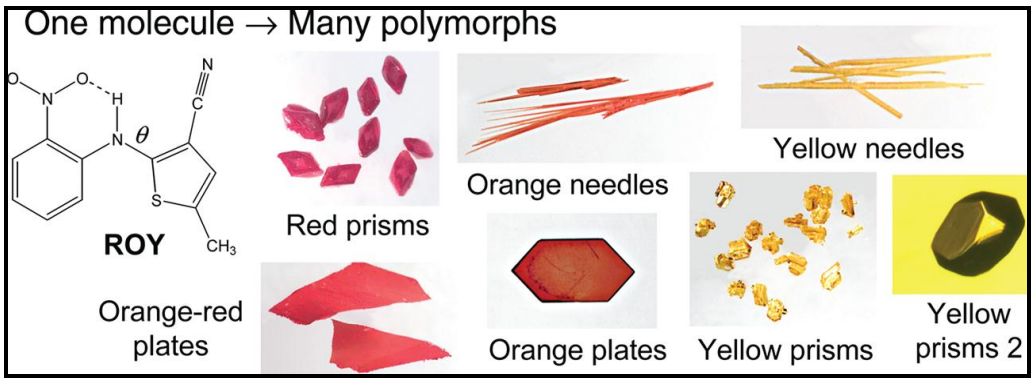


Figure 4. Coloured polymorphism in 5-Methyl-2-[(4-methyl-2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY)**.**[15]

1.4.6 Isostructural Polymorphism

Polymorphism is defined by the appearance of at least two different crystal structure of same molecule.[2] On the other hand, isotructurality describes how much similarity is there between two or more crystal structures of same or different molecule.[45] According to IUCr, two crystals are said to be isostructural if they have the same structure, but not necessarily the same cell dimensions nor the same chemical composition, and with a 'comparable' variability in the atomic coordinates to that of the cell dimensions and chemical composition.[46] Relatively new type of polymorphism, named as 'isostructural polymorphism', does not fit into the conventional definition of polymorphism since, the terms 'isostructural' and 'polymorphism' are contradictory to each other. However, ther are few instances where crystal structures of the polymorphs of some complounds are isostructural.[47]

Kálmán introduced two descriptors to explain isostructurality quantitatively between two crystal stucture: Unit-Cell similarity index denoted by **Π** and isostructurality index, $I_i(n)$.[48] These two descriptors are defined as:

$$\Pi = [(a + b + c) / (a' + b' + c')] - 1 \text{ where } (a + b + c) > (a' + b' + c')$$

$$I_i(n) = \left[1 - \sqrt{\left(\frac{\sum \Delta R_i^2}{n}\right)}\right] \text{ X } 100\%$$

Where ΔR_i values values are the differences between the orthogonalized coordinates of n identical heavy atoms in the related structures.[49] Recently Gelbrich *et al*. have

introduced 'XPac' program for quantitative description of isostructurality by calculating the similarity and dissimilarity parameters.[50]

1.4.7 Tautomeric Polymorphism

There are many definitions of polymorphim described before. The essence of all these definitions which meant polymorphism is the different arrangement of same molecule in the crystal structure. But, how much difference in the packing arrangement and how much similarity of the molecule should be there in the polymorphs? In case of tautomerism, isomers known as tautomers are rapidly interconvertible as mentioned below:

Where **X**, **Y** and **Z** are generally any of C, H, O or S and G is mostly H.[51]

Hantzsch and Herrmann termed these isomers as desmotrophs when these are stable and isolable, while if these could not be isolated isomers are called tautomers.[52] In case of tautomeric polymorphism individual tautomer appears as crystals while these are interconverted rapidly in the solution or in the melt **(**Ref. 5 pp. 2–4, 240–255 and 297–307**).** Desiraju and Bhatt have discussed tautomeric polymorphism of omeprazole based on the existence of two benzimidazole tautomers **(**5- and 6-methoxy**)** in the crystal structure with variable proportion.[53] Close analysis of the omeprazole crystals by ^{13}C and ^{15}N NMR cross polarization magic angle spinning **(**CPMAS**)** study proves the existence of only one tautomers in the solid state.[54] However, tautomeric polymorphism has been studied in many compounds, as for example**:** triclabendazole,[55] barbituric acid,[56] ranitidine,[57] sulfasalazine,[58] irbesarten,[59] 2-amino-3-hydroxy-6-phenylazopyridine,[60] 2-(2,4-dinitrobenzyl)-3- methylpyridine,[61] 4‑ Hydroxynicotinic Acid.[62]

1.5 Polymorphism Based on Stability

Stability of polymorphs is an important concern in pharmaceutical and food industries. On the basis of stability, polymorphs are classified into two groups: enantiotropic and monotropic. Lehmann first described these two classes in 1987.[63] He

defined that two polymorphs are enantiotropically related to each other when both of these can undergo a reversible phase transformation. On the other hand, if one of the polymorphs transformed to other irreversibly, the polymorphs are related monotropically.[64] In 1996 Grunenberg *et al*. explained the relationship between energy and temperature of a dimorphic system on the basis of Gibbs free energy.[65] (**Figure 5a**) shows monotropic relationship between the polymorphs A and B. On the other hand, when the polymorphs A and B are related enantiotrpically, the energy versus temperature relationship has been shown in the (**Figure 5b**). It should be noted that there is no solid to solid phase transformation before melting point in case of monotropically related polymorphs. But in case of enantiotropic polymorphism solid to solid phase transformation has been observed at the temperature T_t (**Figure 5b**) before the melting temperature of the polymorphs.

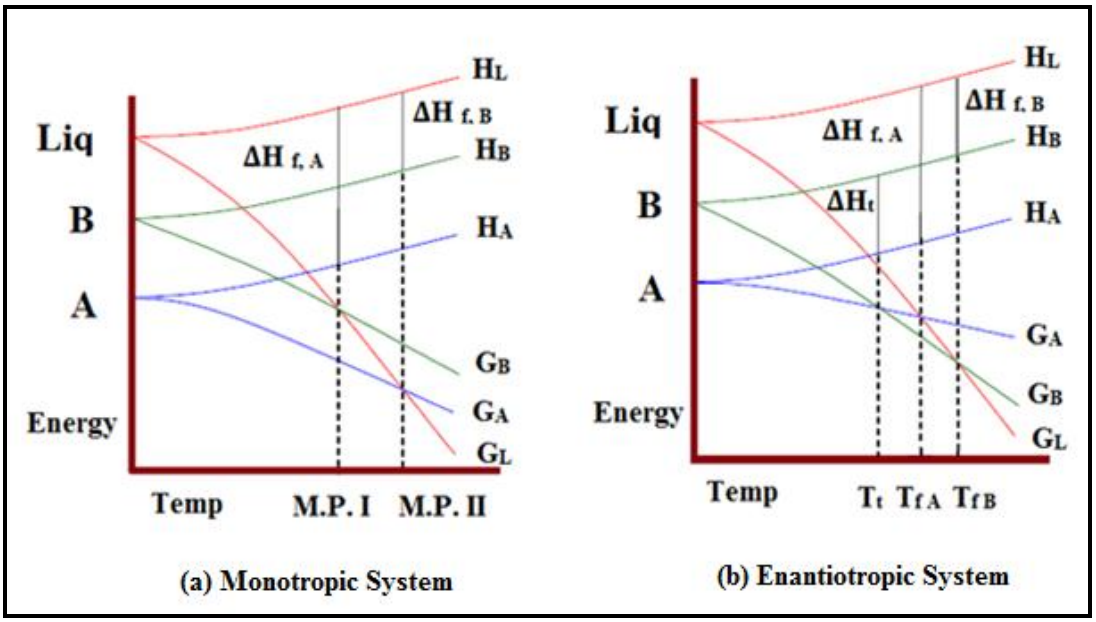


Figure 5. (a) Energy vs temperature **(**E/T**)** diagram for dimorphic monotropic system; **(b)** Energy vs temperature **(**E/T**)** diagram for dimorphic enantiotropic system.[5]

The stability of the polymorphs based on thermodynamic parameters can be predicted by some rules as described below:

1.5.1 Heat-of-Transition Rule

When two polymorphs are enantiotropically related, an endothermic phase transition is observed at a particular temperature ($T_{f,B}$) and the transition temperature (T_t in **Figure 5b**) lies below this experimental transition temperature ($T_{f,B}$). In case of

monotropic pair of polymorphs there is no transition temperature observed and experimental phase transition temperature is exothermic in nature. Burger and Ramberger observed that this rule is valid in almost all the cases although there are some exceptions.[66]

1.5.2 Heat-of-Fusion Rule

If higher melting polymorph has lower heat of fusion the polymorphs are enantiotropically related otherwise the polymorphs are monotropic. However, Grunenberg mentioned that "*the heat-of-fusion rule is suspended if the enthalpy curves for the liquid and the solid modifications diverge widely and the melting points of the solid forms are not close together. Even if the form with the higher melting point has the higher heat of fusion, the system may still be enantiotropic. In practice this can occur when the melting points of the two forms differ by more than about 30°C. To avoid such problems, this can be corrected by substitution of the enthalpy of fusion through the entropy of fusion. Thus, two other rules are preferred. The entropy-of-fusion rule and the heat-capacity rule*".[65]

1.5.3 Entropy-of-Fusion Rule

Since at melting point, difference of Gibbs free energy between solid and liquid is zero, entropy of fusion can be calculated from the following equiation:

$$\Delta S = \frac{\Delta H}{T}$$

Where ΔS is entropy of fusion, ΔH is enthalpy of fusion and T is melting temperature.

Entropy-of-fusion rule says that in case of enantiotropic polymorphism, polymorph with higher melting temperature has lower entropy of fusion. Whereas monotropic polymorph will have higher melting temperature as well as higher entropy of fusion.[67]

1.5.4 Heat-Capacity Rule

For a pair of enantiotropic polymorphs higher melting polymorph will have higher heat capacity than another. Otherwise the system is monotropic.[65]

1.5.5 Density Rule

Thermodynamically most stable compound will have highest density. On the other hand, highest density material must have most favourable packing of molecules in the crystal so that they encounter strongest intermolecular interactions. This also echos Kitaigorodskii's close packing principle.[68] In the context of polymorphism density rule implies that the two polymorphs are monotropically related if the higher melting polymorph shows the higher density, otherwise, they are related enantiotropically. This rule is applicable only for non-hydrogen bonded solids. There are some exceptions of this rule as discussed by Burger and Ramberger.[69]

1.5.6 Infrared Rule

Burger and Ramberger proposed 'infrared' rule for strong hydrogen bonded system.[69a] This rule states that the polymorph with higher bond stretching frequency may be assumed to have higher entropy. The assumption is that the bond stretching vibrations are weakly coupled to the rest of the molecules which is true for O–H and N–H stretching vibration and NH_2 symmetric stretching. Bernstein mentioned that "The successful application of infra red rule requires detailed information of the nature of the hydrogen bonds in the solid state".[5]

1.6 Importance of Polymorphism

Polymorphism is one of the most extensively studied subject in solid state chemistry since the discovery of this pehnomenon by Mitscherlich in 1822.[1a] The tremendous interest of this subject is not only due to the importance in basic research, polymorphism is extremely important in pharmaceutical and other speciality industry.[15-70] Due to difference in the crystal structure, polymorphs have different physiochemical properties such as melting point**,** density, colour, morphology, solubility, stability, bioavailability, compressibility, and hygroscopicity, dissolution rate, optical and electrical properties, compatibility and tensile strength or hardness. Therefore, it is very important to study polymorphism of compounds before formulation of compound as drug or any other product to be marketed. Importance of polymorphism can be illustrated by the case of Ritonavir which is a protease inhibitor for Human Immunodeficiency Virus (HIV) responsible for AIDS.[71] Only polymorph (**Form-I**) of ritonavir was known when it was marketed for the first time in 1996. In mid-1998 a new polymorph (**Form-II**) was discovered from the several batch of

capsules. Solubility, hence the dossolution rate of **Form-II** of ritonavir is less than that of **Form-I**. **Form-II** is also thermodynamically more stable than **Form-I**. Therefore, Pharma Company Abbott had to withdraw the original capsule from the market. Polymorphism also has significant impact on food product such ice-cream, chocolate, margarine because melting point is very important property of these materials.[72]

1.7 Single Crystal to Single Crystal Polymorphic Phase Transformation

Single-Crystal to Single-Crystal (**SC-SC**) phase transformation is a fascinating area of research where structural transformation occurs without losing single crystallinity of the material with the application of external stimuli like pressure, light, temperature etc.[73] It is very surprising that during phase transformation process the movement of the molecules does not affect the single crystallinity of the material under study, although in most of the cases crystalline material loses single crystallinity due to internal strain for molecular movement in the lattice.[74] SC-SC phase transformation is not so common phenomenon in organic materials because in most of the cases the phase transition leads to loss of single crystal mosaicity although few examples of SC-SC transformation of organic and inorganic matrials have been reported.

Since polymorphs of a compound are formed due to slight difference in intermolecular interactions polymorphic phase transformation via Single-Crystal to Single-Crystal process is very challenging although few instances are known. Barbour and co-workers have reported reversible polymorphic phase transformation of trans-9,10-Dihydroxy-9,10-bis(4-methoxyphenyl)-9,10-dihydroanthracene due to three-dimensional shift of the molecules relative to one another.[75] A Reversible SC-SC Phase transformation of 3-(2-Bromo-4-(1-methylethyl)phenyl)-1,1-dimethyl urea induced by thermal energy has been reported by Kariuki and Gamal El-Hiti.[76] Similar transformation has been observed in Chiral Salicylidenephenylethylamine.[77] Pressure induced SC-SC polymorphic phase transformation of piracetam has been reported by Pulham and co-workers.[78] Guru Row et. al have noticed SC-SC phase transformation in a carvacrol derivative induced by partial rotation of isopropyl group present in the molecule.[79] Generally packing of molecules in the crystal structures of intial and transformed phases are almost similar in case of SC-SC polymorphic phase transformation. Because drastic change in packing can lead to the loss of single crystallinity. But SC-SC polymorphic phase transformation lead to the large differences in packing observed in the polymorphs of 4,6-*O*-Benzylidene-α-D-galactosyl azide.[80]

1.8 Inclusion Phenomenon in Organic Compounds

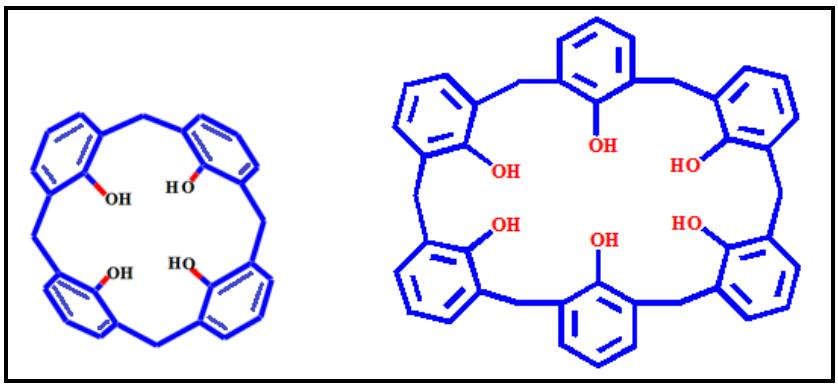
Host-guest compounds have contributed significantly in supramolecular chemistry which has been evolved strongly after accidental discovery of crown ether by Pedderson in 1967.[81] Inclusion compounds are class of host-guest compounds in which host molecule can accommodate guest molecule into the cavity or voids formed by the host molecule.[82] The interactions between the host and guest molecules in the inclusion compounds varies form ion-dipole, dipole-dipole, hydrogen bonding and van der Waals interactions.[83] Although inclusion compounds were first observed by Mylius in 1886,[84] the term "inclusion compounds," was first used by Schlenk in 1949.[85] Depending on the type of the host molecule, Barrer classified inclusion compounds into three categories: (**a**) host compounds which are stable both in the presence and in the absence of the guest molecule; (**b**) those in which the amount of guest may be changed but which have a critical concentration of guest molecules, below which the host structure becomes metastable and recrystallizes and (**c**) those in which the host framework continuously readjusts itself as the content of guest molecules fluctuates.[86] However, based on the nature of host molecules, inclusion compounds are broardly classified into two groups: cavitates and clathrates.[82] Cavitates are those inclusion compounds where the host molecule has intrinsic cavity.[87]

1.8.1 Cavitands

Cavitands are macrocyclic compounds which possess intrinsic cavities. The term 'cavitand' was originally introduced by Donald J. Cram for the first time in 1982.[88] Cavitands are mostly rigid and preorganised. Different topologies have been observed in cavitands depending upon the shape of cavity such as concave, bowl-shaped or fully encapsulating molecular surface. Depending upon the size and shape of the cavity, guest molecules bind with cavitands via ion-dipole, hydrogen bonding, dipole-dipole, and van der Waals ineractions. Properties of cavitands includes high binding affinities,[89] catalytic efficiencies,[90] and special signalling abilities.[91] Examples of some highly studied cavitands are calix[n]arene, crown ether, cryptand, spherand, resorcinarene, cyclotriveratrylenes, cucurbituril, cyclodextrin and more recently pillarene.

Calix[n]arenes are very popular macrocyclic compounds produced by the condensation reactions of n number of *p*-substituted phenols with formaldehyde.[92] The name 'calix' comes from the the shape of the molecule like flower vas with upper and

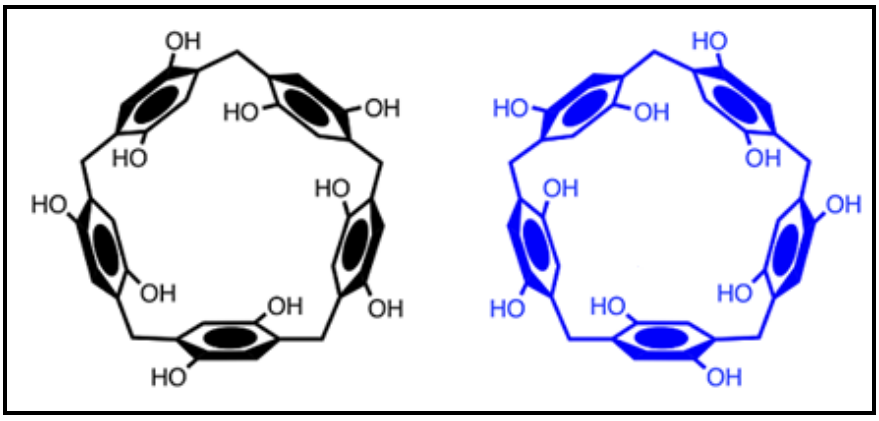
lower rims (**Figure 6**).[92a] Among all the calixarene compounds calix[4]arene is mostly studied in the context of inclusion compounds. Due to rigid conformation and suitable cavities, calix[4]arene molecule exhibit versatile host properties.[92a] Higher homologues calix[6]arene and calix[8]arene are very flexible in nature.[92a,93] Many Calixaranes have been investigated extensively for their inclusion property by various research groups.[94]



(a) **(b)**

Figure 6. Molecular structure of calix[4] and calix[6]arenes.

Relatively new in the series of macrocyclic compounds evolved as cavitands is pillar[n]arenes. In 2008 Ogoshi and co-workers first synthesized this new macrocyclic compounds which are composed of n number of hydroquinone units held together by methylene group bridging at 2-, and 5– positions.[95] Pillarenes have symmetrical pillar shaped architecture and hydroquinone rings are highly pre-organized. Due to these unique features along with π-rich cavity pillarenes are very good candidates for molecular recognition process.[96] Two conformationally different molecular structure of pillar[5]arene are shown in (**Figure 7**).

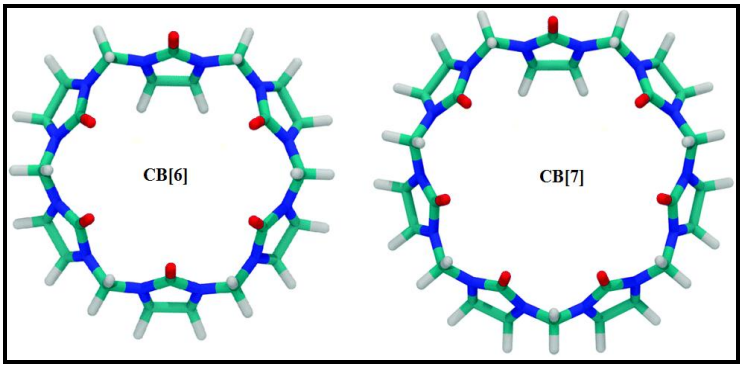


(a) **(b)**

Figure 7. Two different conformations of molecular structure of pillar[5]arene.

Pillarenes and functionalized pillarenes are potentially useful for sensing and molecular machine,[97] synthesis of nanoparticles,[98] generation artificial transmembrane channels,[99] drug delivery[100] and for gas absorption.[101]

Cucurbituril **(CB)**, pumpkin shaped macrocyclic organic cage molecules, can be synthesised by acid catalysed condensation of glycoluril and formaldehyde. Cucurbiturils are commonly represented as **CB*n***, where *n* is the number of Glycoluril units. Although Behrend first synthesized this compound in 1905.[102] Structure of cucurbituril was confirmed by Mock and co-workers in 1981.[103] CB*n* are structurally rigid and highly symmetric**.** In addition to these features, negatively charged carbonyl rims and hydrophobic cavity makes CB*n* compounds very important host**.** Host-guest chemistry of cucurbituril compounds have been studied extensively by various research groups.[104] Dipole-dipole and ion-dipole interactions are the main driving force for binding of guests by CB*n***.** CB6 have been studied for selective binding of certain guest molecuels.[105] A common SCD structure of CB[6] and CB[7] are shown in (**Figure 8**).



(**a**) (**b**)

Figure 8. The molecular structure of Cucurbiturils CB [6] and CB [7] determined by X-ray diffraction.

Cyclodextrins are cyclic oligosaccharides which are made up of glucopyranoside units attached by glycosidic bonds at C1 and C4.[106] These compounds are capable of forming inclusion complexes with other molecules due to their cone shape which contain largely hydrophobic cavity and hydrophilic surface (**Figure 9**).[107] The most common natural cyclodextrins are α, β, and γ-cyclodextrins with 6, 7, and 8 glucopyranose units respectively which shown in (**Figure 10**). Cyclodextrins are soluble in water and form a stable inclusion compounds with a wide variety of guest species in solution and as well as in the solid state. Some of these guests are alcohols, carboxylic acids, aromatic dyes, noble gases, paraffins etc. Due to hydrophobic nature

of the cavity hydrophobic molecules have greater affinity for cyclodextrin cavity. Cyclodextrins are highly used in food and flavors,[108] pharmaceutical,[109] cosmetic,[110] agriculture,[111] and chemical industries.[107a]

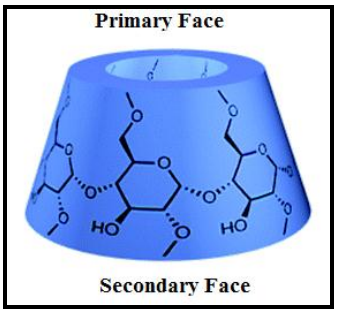


Figure 9. A **3D** Cone structure of cyclodextrin possess cavity.

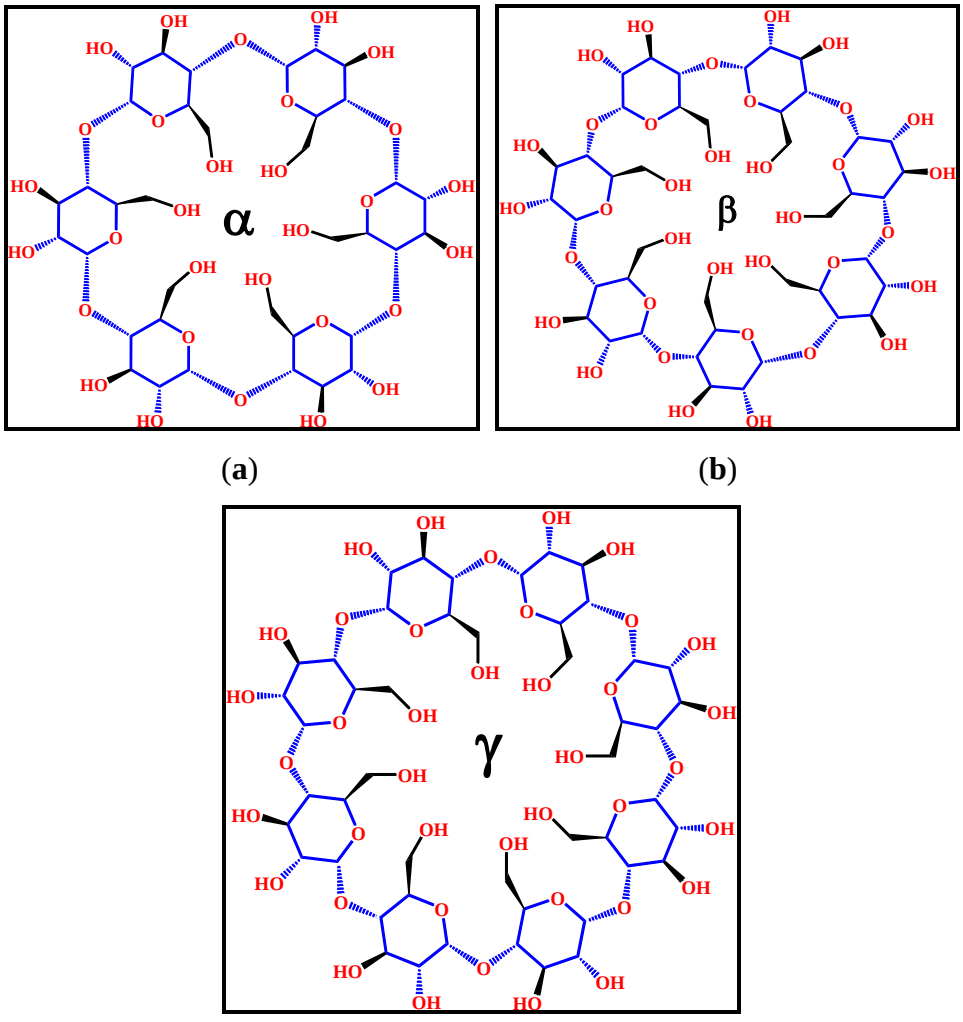


Figure 10. The **2D**-molecular structure of Cyclodextrin (**a**) **α**-Cyclodextrin (**b**) **β**-Cyclodextrin (**c**) **γ**-Cyclodextrin.

1.8.2 Clathrates

Clathrates are those inclusion compounds generated from encapsulation of guest molecules by multiple host molecules due to formation of cage or layer or channel by intermolecular intractions. The term **"**clathrate**"** derived from the Latin word **"**clathratus**"** means closed, surrounded from all sides, first introduced by H. M. Powel in 1948 with respect to the inclusion of guest molecules SO_2, Ar, Xe, HCl, HBr by β-hydroquinone.[112] According to IUPAC, clathrates are inclusion compounds in which the guest molecule entangled easily in a cage formed by the host molecule or in the lattice of host molecules.[113] On the basis of the shape of cavity formed by host molecuels through intermolecular interactions clathrates can be classified into three main groups: (**i**) Cage inclusion Compounds; (**ii**) Channel inclusion compounds and (**iii**) Layred inclusion Compounds.[114] First two catagories of inclusion compounds are stable only in presence of guest molecules.

Cage inclusion Compounds are formed when multiple host molecules through supramolecular interactions form cage network to include guest molecules. Nangia and co-workers have shown the formation of cage network in 2,4,6-tris(4-iodophenoxy)-1,3,5-triazine (I-POT) due to translation of 2D hexagonal layers, while solvent molecule traps in between the layers.[115] Recently Saha *et al*. have shown formation cage inclusion compounds by 2,4,6-Tris(4-bromophenoxy)-1,3,5-triazine (Br-POT) when it was crystallized in hexamethylbenzene (HMB) or hexafluorobenzene (HFB) separately.[116] Both the hydroxyl goups of β-hydroquinone forms cyclic hexagonal O─H···O hydrogen bonds in presence of small guest molecules such as HCl, HBr, CH_4, CH_3OH and inert gases. Guest molecules are sandwitched between two hexagonal O─H···O hydrogen bonded rings.[112] Similarly, numerous organic-host molecules have been designed such as Dianin's and related phenolic compounds,[117] hexa-host compounds[118] which formed cage inclusion compounds. Water forms number of clathrate hydrate with the formation of different cage structures.[119]

Channel inclusion compounds are very common in certain host compounds such as urea, thiourea,[120] perhydrotriphenylene (PHTP),[121] tri-o-thymotide (TOT),[122] bile acids,[123] alicyclic diols[124] and many other compounds. Urea inclusion compounds are the mostly studied for channel inclusion compounds. 1D helical channels formed by extensive hydrogen bonding between urea molecuels with the formation of honeycomb network structures. These channels are filled by guest molecules such as n-alkane, n-alkene and their derivatives.[120] Cholic acids also form channel inclusion compounds

with varieties of guest molecules such as aliphatic, ketones, fatty acids, esters, ethers, phenols, azo dyes, nitriles, alicyclic, and aromatic hydrocarbons, alcohols, peroxides, and amines.[123]

Layered inclusion compounds are formed when the guest molecules are intercalated between two layers such as, clay, graphite intercalation compound of potassium KC_8.[125] Most important feature of layered inclusion compounds is the strong interaction within the layers than that between the layers. These layerd inclusion compounds are stable after the removal of guest molecules.[126]

1.9 Selective Inclusion

Selectivity towards particular guest is the ultimate goal for desigining of host molecule.[127] There are various factors which determine the selectivity of a host towards particular guest.[128] Some of these important factors are:

(i) Size complementarity between guest and host cavity
(ii) Donor-acceptor complementarity
(iii) Solvent
(iv) Flexibility of host molecule

The formation of a host–guest complex can be explained in terms of the following equation:

$$\mathbf{H + n\bullet G \longrightarrow H\bullet n\,G}$$

Where the host molecule **H** dissolved in a liquid guest **G** and each host molecule includes/binds with **n** molecules of guest.

When the host molecule binds/includes with two different guest species, thermodynamic selectivity is defined as the ratio of the equilibrium constants K_{Guest1} & K_{Guest2} as mentioned below:

$$\text{Selctivity} = K_{Guest1} / K_{Guest2}$$

Where K_{Guest1} and K_{Guest2} are the equilibrium constant of Guest1 and Guest2 respectively.

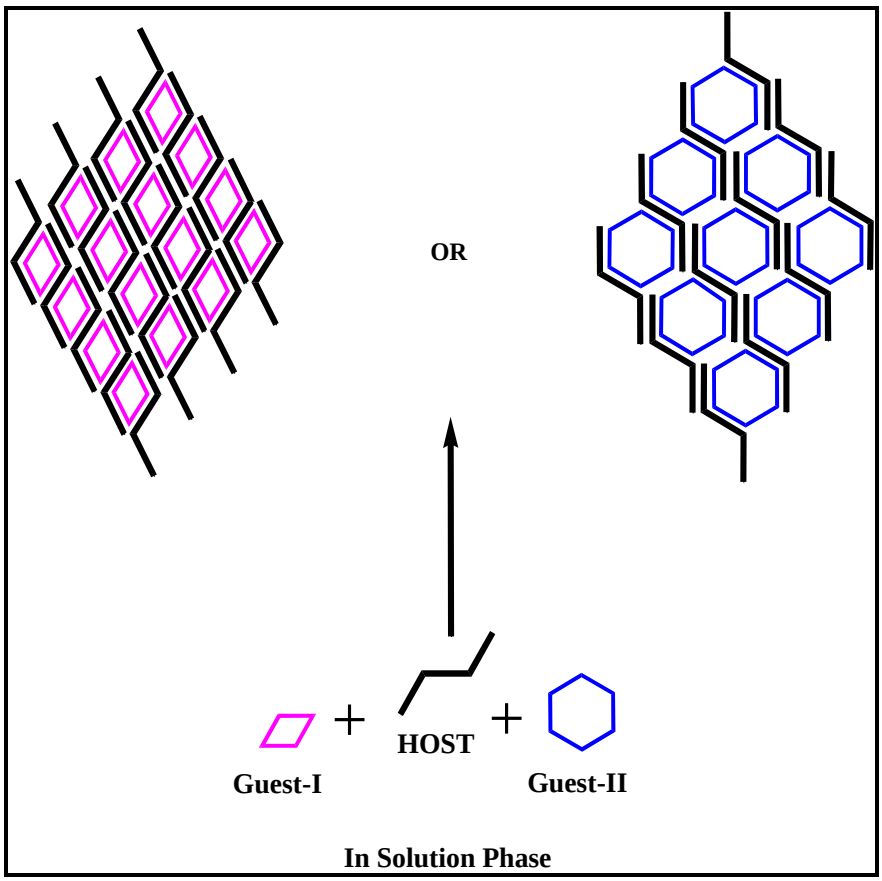
The concept of a selectivity coefficient, $K_{(A:B)}$ was first introduced by Ward[129] as mentioned below:

$$K_{(A:B)} = [K_{(B:A)}]^{-1} = Z_A \cdot X_B / Z_B \cdot X_A$$

Where A and B are two guest species.

X_A, X_B are the mole fractions of the guest species in solution such that $[X_A + X_B = 1]$

Z_A, Z_B are the mole fractions of the guest species in the crystal. This equation has been extensively used by Nassimbeni *et al*. to determine the the selectivity profile of a host for a particular guest in a mixture.[130] Selective inclusion of guest by a host compound is shown in (**Scheme 1.5**).



Scheme 1.5 Schematic representation of selective inclusion of guest by host.[123b]

Seperation of individual compound from multicomponent mixtures can be achieved by distillation, crystallization or solvent extraction method depending upon the volatility and solubility of the compounds. But the separation of a particular compound from a mixture is extremely difficult if the components of mixture have similar physical properties such as volatility and solubility. Similarly, separation of isomers from mixtures is not easy by traditional methods as mentioned before.

Selective inclusion by host compounds can be useful at this point. This phenomenon is extensively applied in industry using inorganic zeolites.[131] Resolution of optical isomers can be achieved by selective inclusion method.[132] Numerous studies based on organic host compounds have been reported for selective inclusion property. Selective inclusion property of different host cmpounds have been extensively studied by Nassimbeni, Toda, Ward and others. The host molecule 1,1,2,2-tetraphenylethane-1,2-diol is used to separate the isomers of lutidine, methylquinoline[133] and picoline.[134] Similarly, 1, 1-bis (4-hydroxy-phenyl)cyclohexane host molecule has been used to separate the isomers of phenylenediamine,[135] cresol,[136] benzenediol[136] as well as picoline.[137] Nassimbeni *et al*. have studied selectivity of 1,1,2,2-tetraphenylethane-1,2-diol host towards THF, DMA and DMF.[138] Detail study of selectivities of bulky host compounds of 9, 9'-bianthryl and 9, 9'-spirofluorene have been reviewed by E. Weber.[139] Selctive inclusion of hydroxyl compounds by 1,1'-binaphthyl-2,2'-dicarboxylic acid have been reported by Weber *et al*.[140] Miyata described selective inclusion property of cholic acid in the mixtures of various aromatic guests.[123] Recently Barton *et al*. have reported separation of xylene isomers, ethylbenzene and methyl-cyclohexanone isomers by selective inclusion property of a tetrahydroxy compound TETROL shown in (**Figure 11**).[141] Extensive study of selective inclusion by host compounds based on guanidinium moiety has been carried out by Ward and co-workers.[142]

Crown ethers, cryptands and some other macrocylic compounds are known for binding of metallic and organic cations.[143] Selectivity of these compounds towards cation depends upon vrious factors[143] among which size complementarity between cation and the host cavity is an important factor. High selectivity of 18-crown-6-ether towards K^+ is a common example where size of potassium cation exactly matches with the cavity of the crown ether shown in (**Figure 12**).

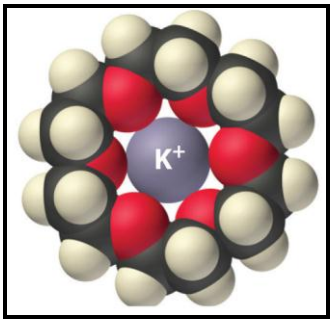


Figure 12. A cavity size of 18-crown-6 and the size of K^+ compatible to each other.

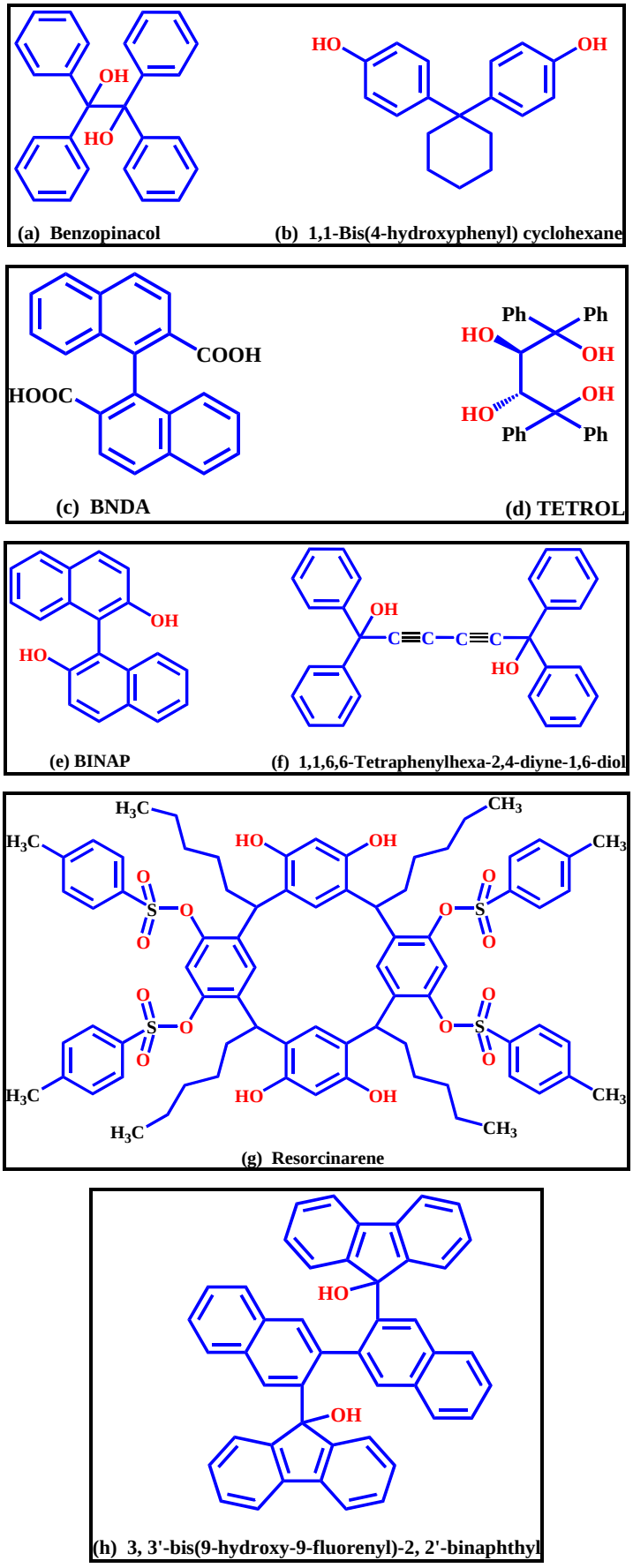
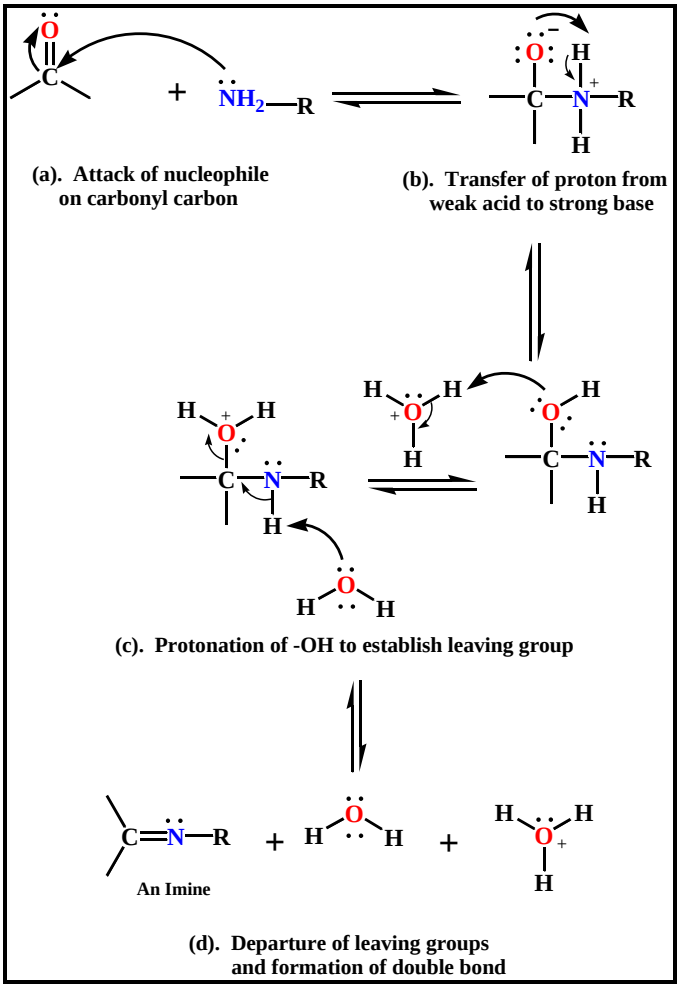


Figure 11. Molecular structure of few host molecules which studied for selectivity and inclusion properties.

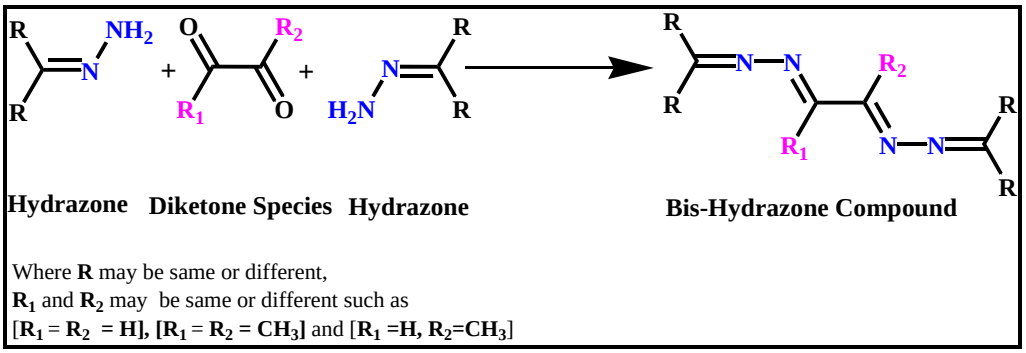
1.10 Bis-hydrazone Compounds

Hydrazones have been extensively studied and widely employed in coordination and heterocyclic chemistry.[144] A large number of hydrazone derivatives have been reported for biological activities.[145] Some hydrazone derivatives display vasodilator property,[146] anticonvulsant activity.[147] Bis-hydrazone compounds are prepared by Schiff base reaction between hydrazone and di-carbonyl compounds. Due to presence of extended conjugation bis-hydrazone compounds appear in yellow or orange colour.

Hydrazone compounds are prepared by Schiff base reaction between aldehyde or ketone and hydrazines as mentioned below (**Scheme 1.6**).[148] Although, chemistry of hydrazone compounds have been widely studied, bis-hydrazone compounds are not explored yet. Recently Abdel-Aziz *et al*. have reported antimicrobial activities of a bis-hydrazone compounds.[149] Coordiantion compounds of few bis-hydrazones compounds show luminescent properties[150] and vapochromic behaviour.[151] Therefore, it is necessary to study new bis-hydrazone compounds synthetically as well as structurally. General synthetic procedure of bis-hydrazone compounds is shown in (**Scheme 1.7**).



Scheme 1.6 A general representation of Schiff base mechanism which leads to the formation of Imine.



Scheme 1.7 General synthetic scheme of bis-hydrazone compounds.

1.11 Characterization of Polymorphs and Inclusion Compounds

There are number of methods to characterize polymorphs and inclusion compounds.[5,152] Preliminary analysis of materials for polymorphism and inclusion property are carried out by microscopy and thermal analysis. Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) are the most common techniques for thermal analysis. Generally structural characterization of polymorphs and inclusion compounds are done by X-ray diffraction techniques. Single Crystal X-ray Diffraction (SCXRD) provides unequivocal evidence of polymorphism and inclusion phenomenon. While SCXRD has some limitations, Powder X-ray Diffraction (PXRD) technique is useful to characterize the properties of bulk materials. IR and Raman spectroscopic methods are very useful to analyze the difference in intermolecular interactions, especially hydrogen bonding interactions in polymorphs. ^{13}C NMR spectroscopy also provides valuable information for characterization of polymorphs. I have used mostly SCXRD, PXRD, DSC and TGA during my research work.

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CHAPTER-2

1,4-Dioxane Specific Inclusion Property and Polymorphism of Two Bis-hydrazone Compounds of Glyoxal

2.1 Abstract

This chapter describes the specific inclusion of 1,4-dioxane (DIOX) by two new bis-hydrazone compounds: ethanedial-1,2-bis(benzophenone hydrazone) (**BBHG**) and ethanedial-1,2-bis(4,4'-dimethylbenzophenone hydrazone) (**DMBHG**) derived from glyoxal (**Scheme 2.1**). These compounds were crystallized in various solvents to prepare single crystals for the determination of structure by Single crystal X-ray Diffraction (SCD). Crystals of both the compounds grown in DIOX became opaque within 24 hours − indicating the formation of inclusion compounds of **BBHG** and **DMBHG**. Although these host molecules do not form inclusion compounds of any other solvents except DIOX, two polymorphs of each of **BBHG** and **DMBHG** were prepared by crystallization in various other solvents. Compound **DMBHG** exhibits concomitant polymorphism in some solvents. Inclusion compounds **BBHG•DIOX** and **DMBHG•DIOX** and polymorphs of **BBHG** and **DMBHG** were characterized by single crystal X-ray diffraction (SCD), powder X-ray diffraction (PXRD) and thermal analysis (TGA and DSC). Compound **BBHG** crystallizes with DIOX in 1 : 1 stoichiometric ratio whereas in DIOX inclusion compound of **DMBHG**, host to guest ratio is 1 : 2.

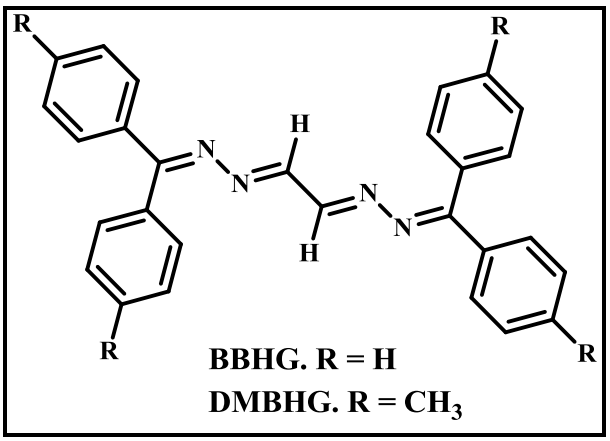
2.2 Introduction

Solvent-mediated crystallization is widely used as one of the techniques for purification of solid materials. There are two probabilities in this process of crystallization – either materials crystallized exclusively itself or the materials include the solvent molecule in the crystal lattice known as 'lattice inclusion compound'.[1-7] Inclusion of solvent molecule in the crystal lattice during solvent-mediated crystallization process is well known phenomenon in supramolecular chemistry.[1-7] The ability of inclusion of guest molecule in the crystal lattice of the host compound depends upon various structural features of the host molecule.[4-7] Preferential inclusion of particular guest molecules over the others by a host has tremendous importance in purification and separation processes.[8-11] Therefore much attention has been paid over the last few decades to the design of host molecules for selective inclusion of guest molecules.[12-17] Specific inclusion of a guest by host molecule makes the purification and separation of that guest more accurate and easy. Specific inclusion behaviour of a host especially of organic host compound towards particular guest is not explored much.

1,4-Dioxane (DIOX) is widely used as solvent in chemical laboratory for reaction and crystallization. This is a highly used solvent to process some industrial products such as inks, and dyes while a little concentration is also present in many consumer products.[18] But DIOX is a probable human carcinogen.[19] Excess exposure to DIOX is reported to cause death of human beings.[20] Therefore it is important to design host molecules, which can specifically include and separate DIOX. Recently Jung *et al.* have reported a metallocyclic compound, which is highly sensitive to DIOX.[21] Selective inclusion of DIOX over other solvents by organic host compounds have been explained by some researchers.[22-25] Specific inclusion of DIOX by organic host molecules have not been reported much.[26] However, towards the formation of shape specific porous organic framework, DIOX is used by Cooper *et al*.[27]

Polymorphism, a well-recognized subject in solid state chemistry, is defined as the phenomena of the occurrence of at least two different crystal structures of same molecule.[28] It is accepted that the occurrence of polymorphism happens due to very small differences in energy between different crystal structures of the same compound.[29-32] Screening of polymorphs of a compound is very much necessary in pharmaceutical and other industries because different polymorphs have different physical and chemical properties.[33-36] Although polymorphism adds complexity to the design of supramolecular assemblies, it assists in the understanding of the kinetics of crystal nucleation, molecular recognition and crystal growth.[34-40] Preparation of polymorphs of host compound is often difficult, and therefore innovative crystallization techniques have to be used to isolate polymorphs of particular host compound.[41,42] Solvent-mediated crystallization is employed to prepare different polymorphs of host compound by judicious choice of solvent of crystallization.[43,44]

Hydrazones are known for versatile complex formation with metal ions of variable oxidation states.[45] Various hydrazones also demonstrate biological activity.[46] In our laboratory we are trying to explore the solid state properties of varieties of bis-hydrazones derived from glyoxal and other di-keto compounds. In this chapter we report specific inclusion of DIOX by two bis-hydrazone compounds, **BBHG** and **DMBHG** derived from glyoxal **(Scheme 2.1**). We have also discussed the preparation and characterization of different polymorphs of both **BBHG** and **DMBHG**.



Scheme 2.1 Molecular structure of **BBHG** and **DMBHG**.

2.3 Result and Discussion

Bright fluorescent colour bis-hydrazone compounds of glyoxal **BBHG** and **DMBHG** were prepared by a literature reported procedure.[47] These compounds were crystallized in various solvents to prepare single crystals for the determination of structure by Single Crystal X-ray Diffraction (SCD) (see **Table 2.3 and Table 2.4** for list of solvents used in crystallization). Crystals of both the compounds grown in DIOX become opaque within 24 hours after exposure to air − indicating possible formation of inclusion compounds of **BBHG** (**BBHG•DIOX**) and **DMBHG** (**DMBHG•DIOX**) which was indeed confirmed by the determination of crystal structure by SCD. Compound **BBHG** crystallizes with **DIOX** in 1 : 1 stoichiometric ratio whereas compound **DMBHG** forms the inclusion compound in 1 : 2 ratio with DIOX. Surprisingly neither **BBHG** nor **DMBHG** form inclusion compound with other solvents. This is probably due the conformational flexibility of the host molecules, which generate voids complementary to the shape of DIOX molecules. On the other hand, conformational flexibility leads to the polymorphism of **BBHG** and **DMBHG** during crystallization in various of solvents. SCD experiments of crystals of **BBHG** grown in pyridine and the mixture of *ortho*-xylene and toluene turned out to be polymorphs of **BBHG** named as **BBHG-I** and **BBHG-II** respectively. Later the polymorph **BBHG-I** was prepared in various solvents (see **Table 2.3**). Similarly two polymorphs **DMBHG-I** and **DMBHG-II** of compound **DMBHG** were prepared. Polymorph **DMBHG-I** was first prepared by crystallization of **DMBHG** in the mixture of aniline and benzene and **DMBHG-II** was made by crystallization in mesitylene. Later it was observed that **DMBHG-I** and **DMBHG-II** appear concomitantly in various solvents (see **Table 2.4**). Concomitant polymorphism is observed in various organic

molecules.[48,49] Analysis of the crystal structures of all the polymorphs of both and **BBHG** and **DMBHG** revealed that these are conformational polymorphs.[50,51] Crystallization of **BBHG** and **DMBHG** were performed also in binary mixtures of different solvents. When one of the solvent was **DIOX** in the binary mixture, concomitant formation of solvate and solvent-free crystals were observed for both **BBHG** and **DMBHG** by controlling the volume of **DIOX**. Concomitant formation of both solvate and solvent-free crystal is a rare phenomena.[52,53] When large excess of DIOX with respect to the mass of the host **BBHG** and **DMBHG** was used no solvent-free crystal was isolated which was confirmed by powder X-ray diffraction. Concomitant formation of solvate and solvent-free crystals was also recognized by colour of the crystals. Solvated crystals of **BBHG** (i.e. **BBHG•DIOX**) were orange coloured and the crystals of **DMBHG•DIOX** were intense yellow coloured. The solvated crystals **BBHG•DIOX** and **DMBHG•DIOX** turned opaque after exposure to air for 24 hours, whereas the solvent-free polymorphs of **BBHG** and **DMBHG** did not show any change in appearance after two months. The structure of the solvent-free crystals of **BBHG** and **DMBHG** were similar to that of **BBHG-I** and **DMBHG-II** respectively confirmed by PXRD (**Figure 2.1** and **Figure 2.2**). The powder patterns of desolvated **BBHG•DIOX** and **DMBHG•DIOX** were also compared to that of **BBHG-I** and **DMBHG-II**, showing the similarities between the structures (**Figure 2.1** and **Figure 2.2**).

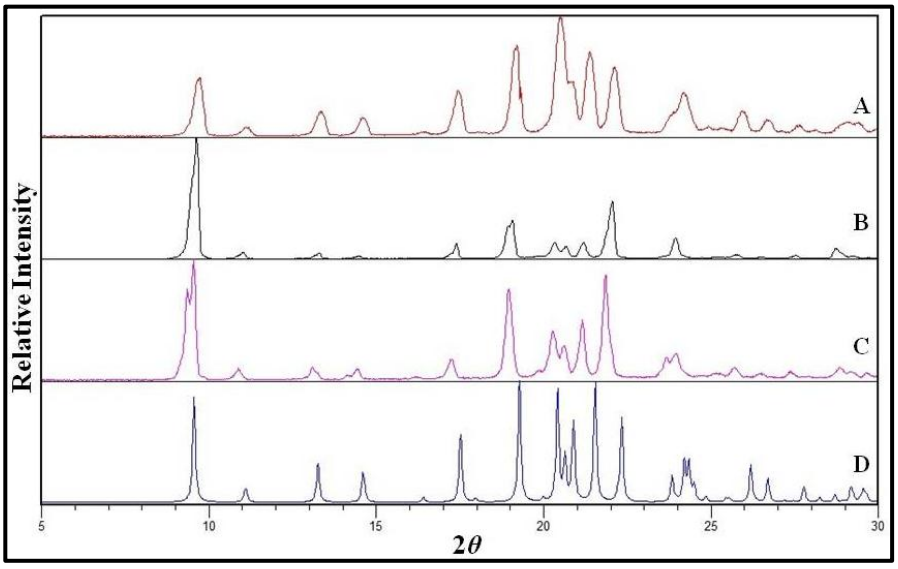


Figure 2.1 (**A**) PXRD pattern of polymorph **BBHG-I** grown in pyridine; (**B**) PXRD pattern of solvent-free crystals of **BBHG-I** grown in the mixture of DIOX and pyridine; (**C**) PXRD pattern of desolvated materials of **BBHG•DIOX**; (**D**) Simulated pattern of **BBHG-I** calculated from SCD data.

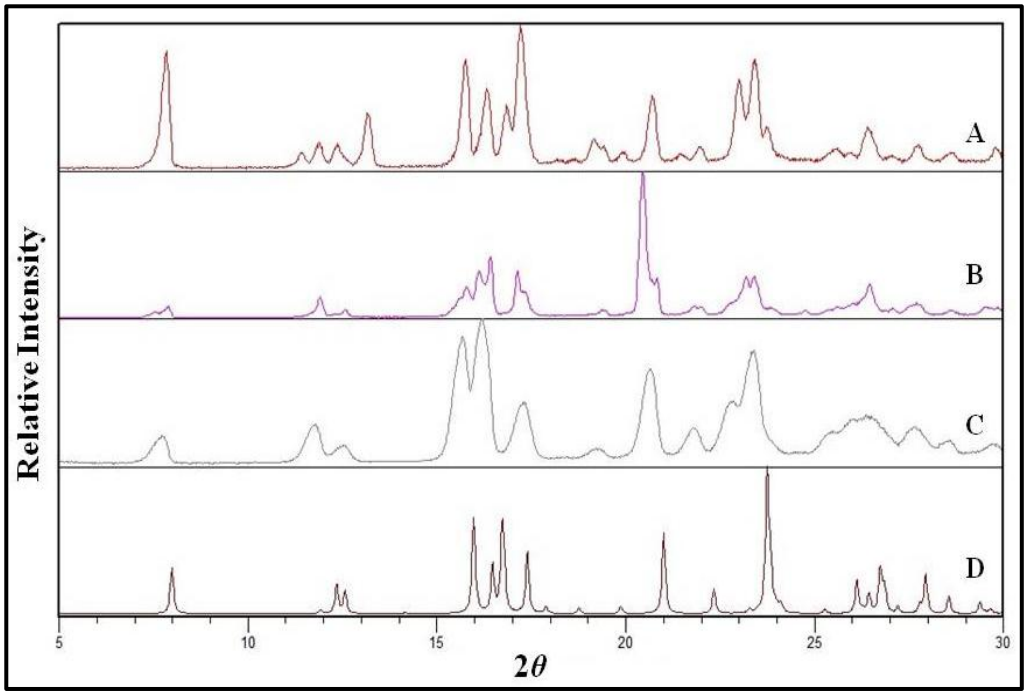
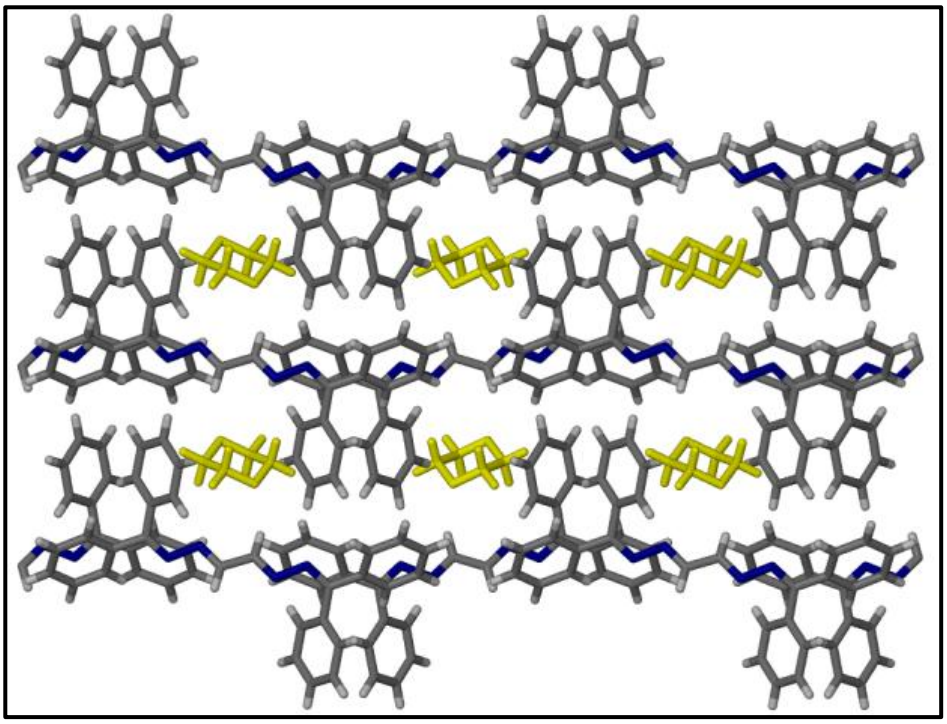


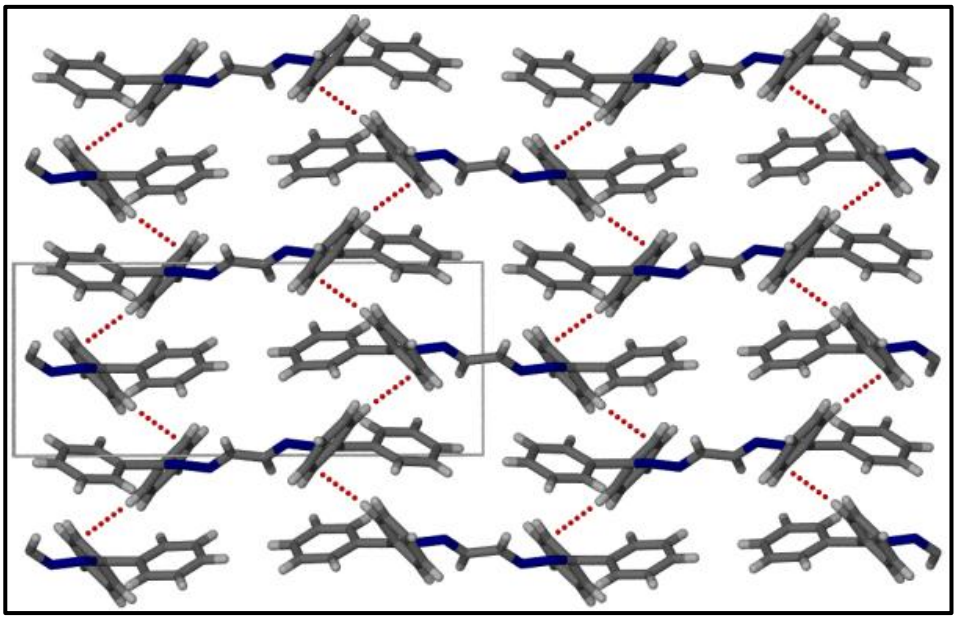
Figure 2.2 (**A**) PXRD pattern of polymorph **DMBHG-II** grown in mesitylene; (**B**) PXRD pattern of solvent-free crystals of **DMBHG-II** grown in the mixture of **DIOX** and mesitylene; (**C**) PXRD pattern of desolvated materials of **DMBHG•DIOX**; (**D**) Simulated pattern of **DMBHG-II** calculated from SCD data.

2.3.1 Crystal Structure of BBHG•DIOX

The inclusion compound of **BBHG** with DIOX crystallizes in the $P2_1/c$ space group with half molecules of both **BBHG** and DIOX in the asymmetric unit. One phenyl ring at each terminal and the conjugated unit N-N=CH-CH=N-N are linearly oriented and another phenyl ring at each terminal are pointed almost perpendicularly up and down to the conjugated spine of the molecule of **BBHG**. This conformation of the molecule facilitates the formation of channel propagation along [001] direction where DIOX molecules are located (**Figure 2.3a**). Analysis of the crystal structure viewed down *a* axis reveals that the molecules of **BBHG** are aligned parallel to *b* axis (**Figure 2.3b**). The linear arrays are held by C─H···π interactions (2.92Å, 3.809(1) Å 156º) along the *c* axis. There are no strong interactions found between host and guest molecules in this crystal structure.



(**a**)

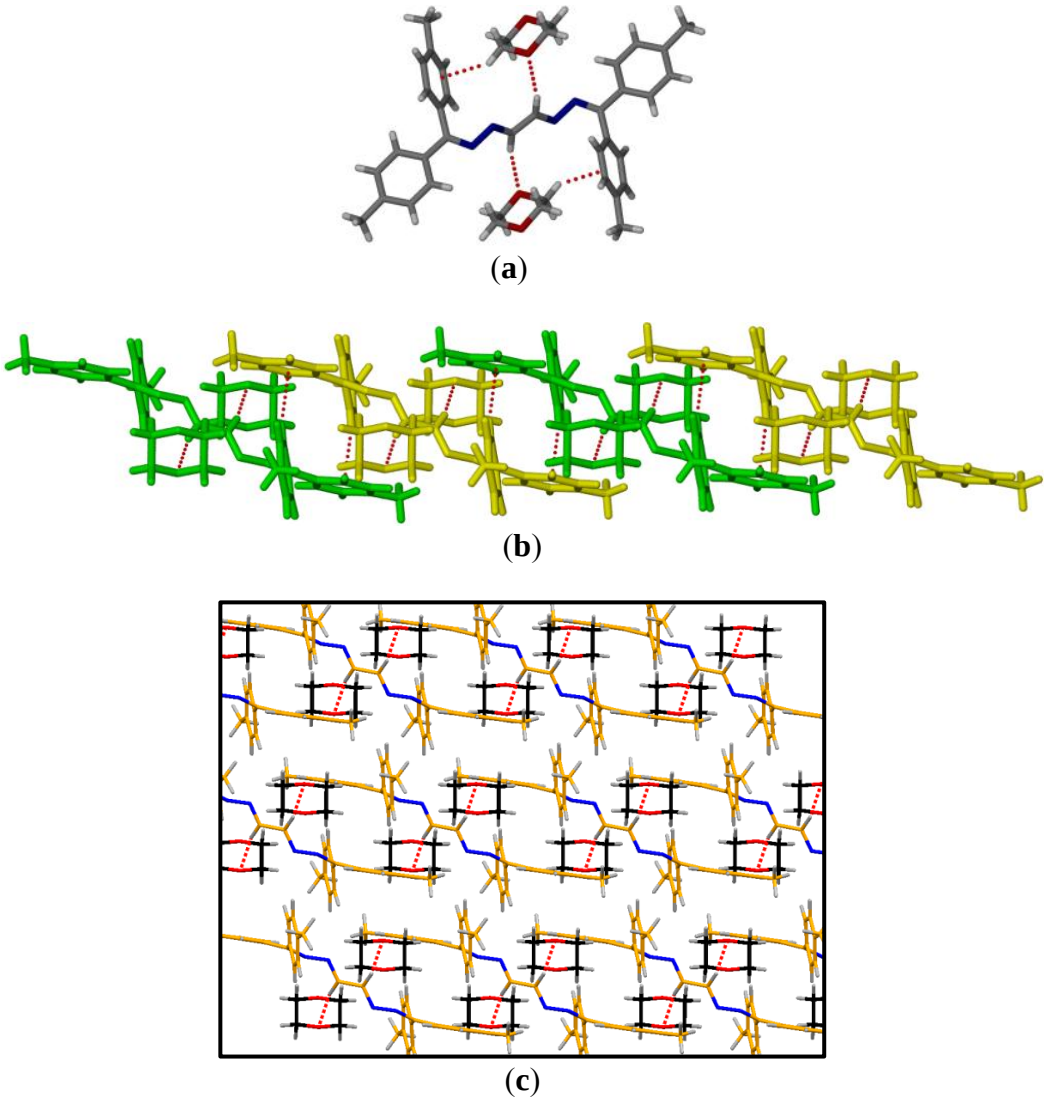


(**b**)

Figure 2.3 (**a**) Packing diagram viewed down the *c* axis showing the **DIOX** molecules residing in the channel running along the [001] direction. DIOX molecules are shown in yellow. (**b**) Packing of the host molecules are viewed down the *a* axis. C─H···π hydrogen bonds are shown in red dotted line. DIOX molecules are omitted for clarity.

2.3.2 Crystal Structure of DMBHG•DIOX

DMBHG•DIOX crystallizes in the $P\bar{1}$ space group consisting of half molecule of **DMBHG** and a full molecule of DIOX. Dihedral angle between two phenyl rings at each terminal of molecule **DMBHG** in the crystal structure is 76.42º. Each host molecule is connected to two DIOX molecules by C─H···O (2.48 Å, 3.405(2) Å, 165º) and C─H···π (2.54 Å, 3.458(2) Å, 155º) hydrogen bonds, forming a unit (**Figure 2.4a**). These units are connected with other units by C─H···π hydrogen bond (2.61 Å, 3.474(1) Å, 152º) along the [100] direction, forming 1D architecture (**Figure 2.4b**) which in turn forms parallel arrangements to form a 2D supramolecular construct (**Figure 2.4c**).



(**a**)

(**b**)

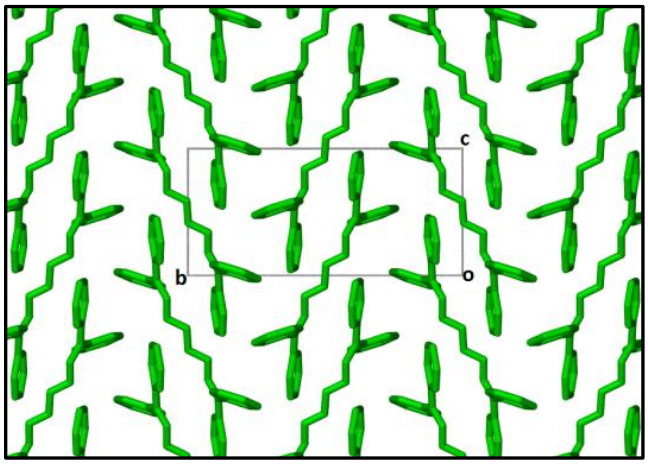
(**c**)

Figure 2.4 (**a**) Hydrogen bonded unit of one host and two guest molecules in the crystal structure of **DMBHG•DIOX**.; (**b**) 1D arrangement of host-guest units, shown in yellow and green colour, connected by C─H···π hydrogen bond along [100]; (**c**) Packing diagram viewed down the *c* axis. C─H···π hydrogen bonds are shown in red dotted line.

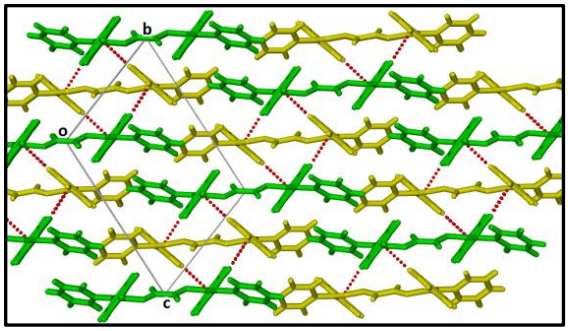
2.3.3 Crystal Structures of the Polymorphs of BBHG and DMBHG

Polymorph **BBHG-I** was obtained by crystallization of as synthesized materials of **BBHG** in varieties of solvents (**Table 2.3**). However, the polymorph **BBHG-II** was prepared by crystallization of as synthesized materials only in the mixture of *ortho*-xylene and toluene. The polymorph **BBHG-I** crystallizes in the $P2_1/c$ space group with half molecule in asymmetric unit and polymorph **BBHG-II** crystallizes in the $P\bar{1}$ space group with two half molecules in the asymmetric unit. Conformational difference between the molecules in the crystal structure of **BBHG-I** and **BBHG-II** distinguishes these polymorphs. Torsion angle of −CH=N−N=C− unit in **BBHG-I** is 130.92º whereas in **BBHG-II** it is 157.02º and 165.01º in two symmetry independent molecules (See **Table 2.6**). The dihedral angle between the planes of two phenyl rings at terminal point is 65.75º in **BBHG-I** whereas these are 72.40º and 63.25º in two symmetry independent molecules of **BBHG-II**. Molecules in **BBHG-I** are arranged in herringbone fashion viewed down *a* axis (**Figure 2.5a**). Analysis of packing of molecules in **BBHG-I** viewed down *a* axis shows that symmetry independent molecules are arranged in a row one after another (**Figure 2.5b**). These rows are connected with each other by C─H···π hydrogen bond (2.67 Å, 3.587(2) Å, 161º). Symmetry equivalent molecules are stacked along [100] direction shown in (**Figure 2.5c**).

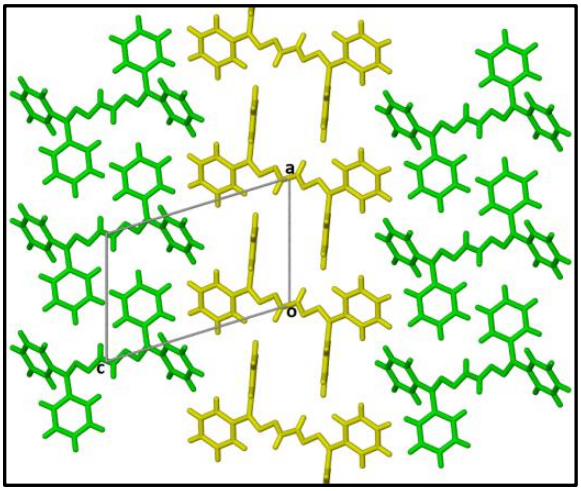
Crystal structures of polymorph **DMBHG-I** and **DMBHG-II** are solved in $C2/c$ and $P2_1/n$ space groups respectively with half molecule in asymmetric unit in both. Like **BBHG-I**, herringbone type arrangement is also observed in **DMBHG-II** (**Figure 2.6b**). These are also conformational polymorphs[51] like **BBHG-I** and **BBHG-II**.



(**a**)



(**b**)



(**c**)

Figure 2.5 (**a**) Herringbone arrangement of molecules in the polymorph **BBHG-I** viewed down the *a* axis. (**b**) Packing diagram of **BBHG-II** viewed down the *a* axis. (**c**) Stacking of symmetry equivalent molecules along [100]. Two symmetry independent molecules are shown in green and yellow. Hydrogen bonds are shown in red colour. Hydrogen atoms have been omitted for clarity.

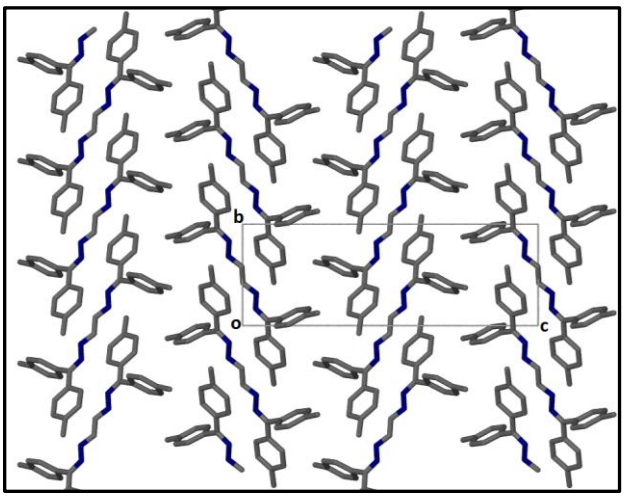
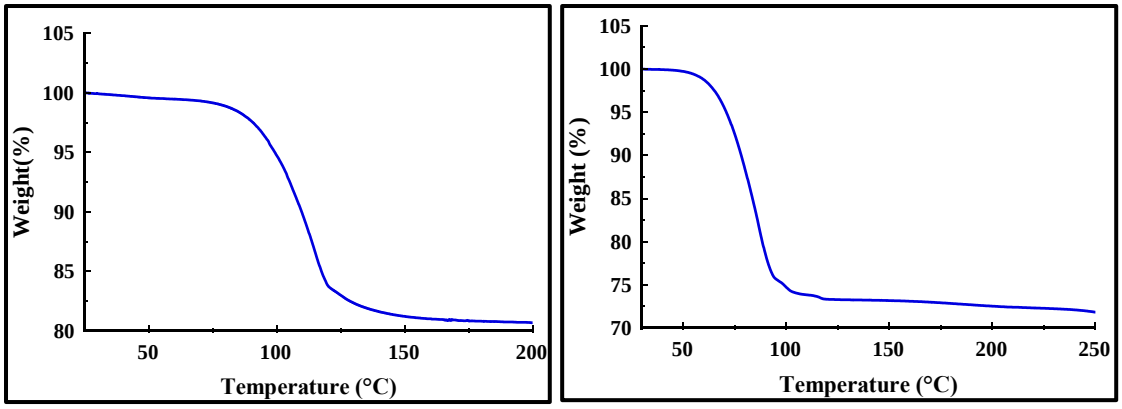


Figure 2.6 Herringbone arrangement of molecules in the crystal structure of **DMBHG-II** viewed down the *a* axis. Hydrogen atoms have been omitted for clarity.

2.4 Thermal Analysis (TA)

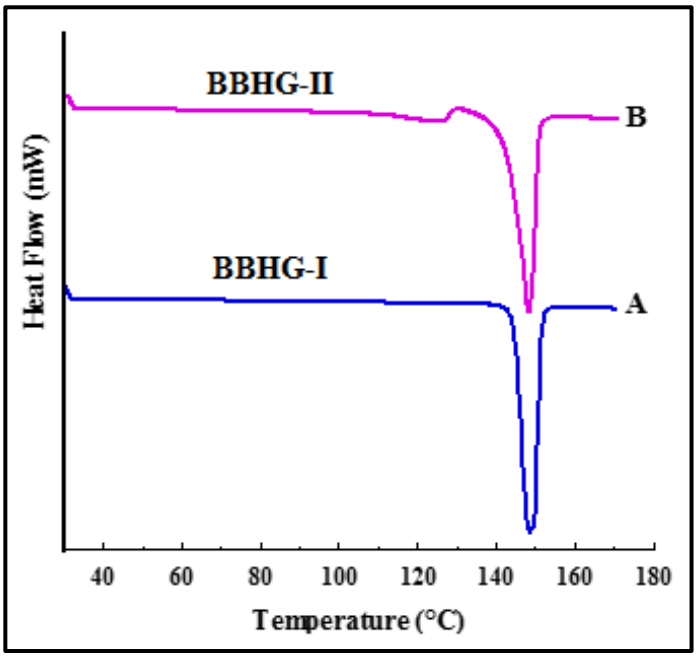
Loss of solvent in the crystal was detected by thermogravimetric analysis. TGA plot of **BBHG•DIOX** and **DMBHG•DIOX** are shown in (**Figure 2.7a**) and (**Figure 2.7b**) respectively. In case of **BBHG•DIOX**, mass loss was observed from room temperature to 120.9ºC (**Figure 2.7a**). About 17.4% mass loss was confirmed for the formation of 1 : 1 host-guest compound in **BBHG•DIOX**. In the case of **DMBHG•DIOX** solvent loss was observed from 70.4ºC to 93.8ºC (**Figure 2.7b**). 26% mass loss was observed experimentally, which confirmed the formation of inclusion compound in 1 : 2 stoichiometric ratio of host to guest.



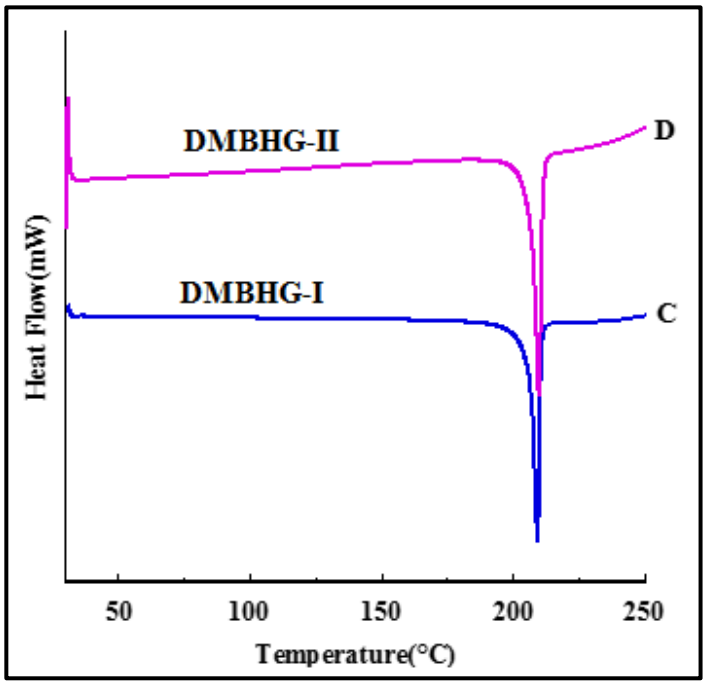
(**a**) (**b**)

Figure 2.7 TGA Thermogram of (**a**) **BBHG•DIOX** and (**b**) **DMBHG•DIOX** showing the loss of solvent.

DSC thermogram of **BBHG-I** shows only one endothermic peak at 147.7 ºC corresponding to melting. On the other hand, DSC thermogram of **BBHG-II** shows a small endothermic peak at 118 ºC followed by a melting peak at 146 ºC (**Figure 2.8a**). It suggests that the polymorph **BBHG-II** transformed to another solid phase before the melting. PXRD analysis of **BBHG-II** was done after keeping it at 125ºC for 48 hours in order to understand this solid phase transformation. The experimental PXRD pattern of **BBHG-II** after heating at 125 °C matches with the simulated pattern of **BBHG-I** shown in (**Figure 2.9**). This proves the conversion of the polymorph **BBHG-II** to **BBHG-I** before the melting and enantiotropic relation between **BBHG-I** and **BBHG-II**. It also confirms that **BBHG-I** is thermodynamically more stable than **BBHG-II**. Analysis of DSC thermogram of **DMBHG-I** and **DMBHG-II** shows there is no polymorphic phase transformation before melting at 206.6ºC and at 209.4ºC respectively (**Figure 2.8b**). Therefore, these polymorphs are monotropically related to each other.



(**a**)



(b)

Figure 2.8 (**a**) DSC thermogram of **BBHG-I** (A) and **BBHG-II** (B); (**b**) DSC thermogram of **DMBHG-I** (C) and **DMBHG-II** (D).

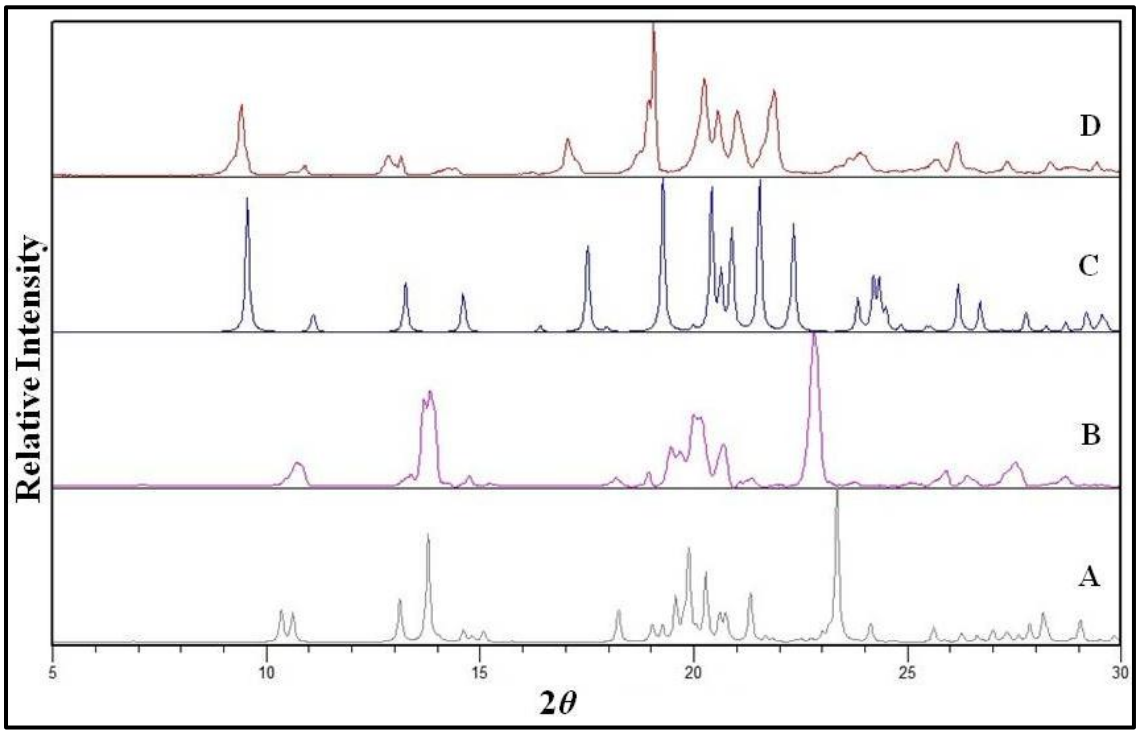


Figure 2.9 (**A**) Simulated pattern of **BBHG-II** calculated from SCD data; (**B**) Experimental PXRD pattern of **BBHG-II** before heating at 125ºC; (**C**) Simulated pattern of **BBHG-I** calculated from SCD data; (**D**) Experimental PXRD pattern of **BBHG-II** after heating the sample at 125ºC for 48 hours.

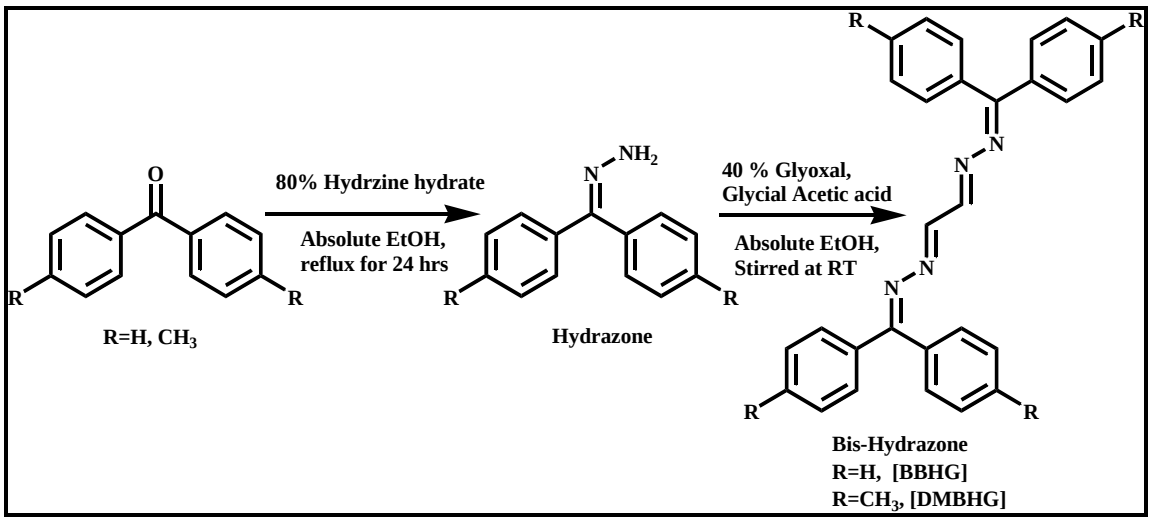
2.5 Conclusion

Solvent inclusion in a host lattice is not a new phenomenon in supramolecular chemistry, but we have reported a rare phenomenon of very specific inclusion of 1,4-dioxane by two new organic host molecules **BBHG** and **DMBHG**. Both host molecules act as DIOX sponges when these are used for crystallization in a mixture of DIOX and other solvents. This specificity arises probably due to the flexible conformation of the host molecules, which create voids complementary to the shape of only DIOX molecules. Conformational flexibility of **BBHG** and **DMBHG** also lead to the polymorphism in the outcome of crystallization of these compounds in different solvents. Concomitant polymorphism is observed in compound **DMBHG**. Currently we are engaged to design different host molecules based on bis-hydrazone to explore the selective and specific inclusion of different guest molecules.

2.6 Experimental Section

2.6.1 Synthesis of BBHG and DMBHG

The starting materials and reagents used for synthesis of compound **BBHG and DMBHG** were obtained from Alfa Aesar & Sigma-Aldrich and used without further purification. All solvents used in crystallization experiments were reagent grade. ^{1}H NMR spectra were recorded on a 500 MHz Bruker Advance III spectrometer in $CDCl_3$. The bis-hydrazone Compounds **BBHG** and **DMBHG** were synthesized after little modification of the procedure reported in literature.[47] Synthetic procedure is shown in (**Scheme 2.2**). Some characteristic features of **BBHG** and **DMBHG** are given in (**Table 2.1**) and (**Table 2.2**) respectively.



Scheme 2.2

Molecular structures were characterized by NMR spectroscopy and Mass spectrometry (MS).

NMR and MS data for compound **BBHG:**

^{1}H NMR (500 MHz, CDCl3): δ8.148 (s, 2H), δ7.245-7.676 (m, 20H).

TOF-MS (*m*/z): 415.0973(100%), 234.0213(48%).

NMR and MS data for compound **DMBHG:**

^{1}H NMR (500 MHz, CDCl3): δ8.204 (s, 2H), δ7.595 (d, 4H), δ7.167 - 7.247 (m, 12H), δ2.562 (d, 12H).

TOF-MS (*m*/z): 471.1586 (100%), 262.0493 (17%).

Table 2.1 Physical Properties of BBHG

BBHG	Physical Properties
Physical State	Powder
Colour	Yellow
Melting Point	140 °C – 150 °C
Solubility	Soluble in all organic Solvents except alcohols
Yield	84 %

Table 2.2 Physical Properties of DMBHG

DMBHG	Physical Properties
Physical State	Powder
Colour	Bright yellow
Melting Point	205 °C – 210 °C
Solubility	Soluble in all organic Solvents except alcohols
Yield	80 %

2.6.2 Crystallization of BBHG and DMBHG

Both **BBHG** and **DMBHG** were crystallized by slow evaporation method in varieties of solvents and mixture of solvents. Solvents used for crystallization and the outcome of the crystallization are shown in (**Table 2.3**) and (**Table 2.4**) for compound **BBHG** and **DMBHG** respectively.

Table 2.3 Solvents used for crystallization of compound **BBHG** and composition of crystals produced

Solvent used for crystallization of BBHG	Crystalline form obtained
DCM	**BBHG-I**
$CHCl_3$	**BBHG-I**
THF + $CHCl_3$	**BBHG-I**
Ethyl Acetate	**BBHG-I**

1,4-Dioxane	**BBHG•DIOX**
Benzene + Acetone	**BBHG-I**
Fluorobenzene + DCM	**BBHG-I**
Hexafluorobenzene + DCM	**BBHG-I**
Nitromethane + $CHCl_3$	**BBHG-I**
Toluene + $CHCl_3$	**BBHG-I**
Mesitylene + $CHCl_3$	**BBHG-I**
m-Nitrotoluene + $CHCl_3$	**BBHG-I**
Acetone	**BBHG-I**
Pyridine+ $CHCl_3$	**BBHG-I**
Acetonitrile + $CHCl_3$	**BBHG-I**
o-Xylene + $CHCl_3$	**BBHG-I**
m-Xylene + $CHCl_3$	**BBHG-I**
p-Xylene + $CHCl_3$	**BBHG-I**
MeOH + $CHCl_3$	**BBHG-I**
EtOH + $CHCl_3$	**BBHG-I**
i-PrOH + $CHCl_3$	**BBHG-I**
t-Butanol + $CHCl_3$	**BBHG-I**
Cyclohexane + DCM	**BBHG-I**
Cyclohexanone + $CHCl_3$	**BBHG-I**
Diethylether + $CHCl_3$	**BBHG-I**
DMA + $CHCl_3$	**BBHG-I**
DMF + $CHCl_3$	**BBHG-I**
DMSO + $CHCl_3$	**BBHG-I**

THF + $CHCl_3$	**BBHG-I**
Nitrobenzene + $CHCl_3$	**BBHG-I**
Anisole + $CHCl_3$	**BBHG-I**
Hexane + DCM	**BBHG-I**
Water + DCM	**BBHG-I**
o-Xylene+Toluene	**BBHG-II**

Table 2.4 Solvents used for crystallization of compound **DMBHG** and composition of crystals produced

Solvent used for crystallization of DMBHG	**Crystalline form obtained**
DCM	**DMBHG-I**
$CHCl_3$	**DMBHG-I** and **DMBHG-II** concomitantly
THF + $CHCl_3$	**DMBHG-I**
Ethyl Acetate	**DMBHG-I**
1,4-Dioxane	**DMBHG•DIOX**
Benzene + Acetone	**DMBHG-I** and **DMBHG-II** concomitantly
Fluorobenzene + DCM	**DMBHG-I** and **DMBHG-II** concomitantly
Hexafluorobenzene + DCM	**DMBHG-I** and **DMBHG-II** concomitantly
Nitromethane + $CHCl_3$	**DMBHG-I** and **DMBHG-II** concomitantly
Toluene + $CHCl_3$	**DMBHG-I**
Mesitylene + $CHCl_3$	**DMBHG-I** and **DMBHG-II** concomitantly
m-Nitrotoluene + $CHCl_3$	**DMBHG-I** and **DMBHG-II** concomitantly
Acetone	**DMBHG-I**
Pyridine+ $CHCl_3$	**DMBHG-I** and **DMBHG-II** concomitantly

Acetonitrile + $CHCl_3$	**DMBHG-I** and **DMBHG-II** concomitantly
o-Xylene + $CHCl_3$	**DMBHG-I** and **DMBHG-II** concomitantly
m-Xylene + $CHCl_3$	**DMBHG-I** and **DMBHG-II** concomitantly
p-Xylene + $CHCl_3$	**DMBHG-I** and **DMBHG-II** concomitantly
MeOH + $CHCl_3$	**DMBHG-I**
EtOH + $CHCl_3$	**DMBHG-I**
i-PrOH + $CHCl_3$	**DMBHG-II**
t-Butanol + $CHCl_3$	**DMBHG-I**
Cyclohexane + DCM	**DMBHG-I**
Cyclohexanone + $CHCl_3$	**DMBHG-I**
Diethylether + $CHCl_3$	**DMBHG-I**
DMA + $CHCl_3$	**DMBHG-I**
DMF + $CHCl_3$	**DMBHG-I**
DMSO + $CHCl_3$	**DMBHG-I**
Furan + $CHCl_3$	**DMBHG-I**
Aniline + benzene	**DMBHG-I**
Nitrobenzene + $CHCl_3$	**DMBHG-I** and **DMBHG-II** concomitantly
Anisole + $CHCl_3$	**DMBHG-I** and **DMBHG-II** concomitantly
Hexane + DCM	**DMBHG-I**
Water + DCM	**DMBHG-I**
Mesitylene	**DMBHG-II**

2.6.3 Single Crystal X-Ray Diffraction (SCXRD) Study

Single-crystal X-ray data for all the compounds in this study were collected on Bruker D8 Quest single crystal X-ray diffractometer equipped with a microfocus anode (Mo) and a PHOTON 100 CMOS detector. Suitable single crystals of inclusion compounds and polymorphs of **BBHG** and **DMBHG** for diffraction experiments were chosen under polarizable microscope. The crystals of solvates were cut and wrapped with paraton oil in order to prevent the loss of solvent. A single crystal was glued to a thin glass fiber and the temperature of the crystal was controlled using an Oxford Cryosystream 800 Plus cryostat. Diffraction data of most of the crystals described in this chapter have been collected at 100K. Data for few crystals were collected at room temperature. The data were integrated and scaled using the Bruker suite of programs.[54] The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using SHELX-2014.[55] All non-hydrogen host atoms were refined anisotropically and all hydrogen atoms were placed using calculated positions and riding models. Crystallographic data of all the structures and final refinement details are given (**Table 2.5**). Torsion angle of (C−N−N=CH) unit, dihedral angle between the planes of the terminal phenyl rings and packing indices are shown in the (**Table 2.6**).

2.6.4 Powder X-ray Diffraction (PXRD) Study

X-ray powder diffractograms were measured on Rigaku powder x-ray diffractometer, Miniflex-600 with CuK_α radiation (λ= 1.54059 Å) operating in Bragg-Brentano geometry. The crystals of the inclusion compounds were crushed gently and layered on a glass slide. In each case, data were collected at room temperature for approximately half an hour, scanning from 5º to 40º (2θ value).

2.6.5 Thermal Analysis (TA)

Differential scanning calorimetry (DSC) was performed on a Mettler Toledo DSC1 calorimeter with FRS5 DSC Sensor attached with HUBER TC100-MT chiller and STARe software V13.00. In all the cases 3 to 5 mg of sample were taken in Aluminum pan sealed with pierced lid. The samples were purged with a flow of dry nitrogen at 50 mL/min. The sample was heated at the rate of 5 °C/min from 30 to 170°C in the case of compound **BBHG** and 30 to 250°C in the case of compound **DMBHG**.

For TGA measurement Mettler Toledo TGA1 was used in combination with Minichiller MT/230 and STARe software V13.00. Before analysis, crystals taken out of mother liquor were blotted dry using filter paper and placed on alumina crucible. The samples were purged with a flow of dry nitrogen at the rate of 50mL/min. Samples were heated at the rate of 5°C/min from 30 to 200°C.

2.7 References:

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2. D. D. MacNicol, *In Inclusion Compounds*, J. L. Atwood, J. E. D. Davies, D. D. MacNicol, Eds., Academic Press: London, **1994**.
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2.8 Appendix

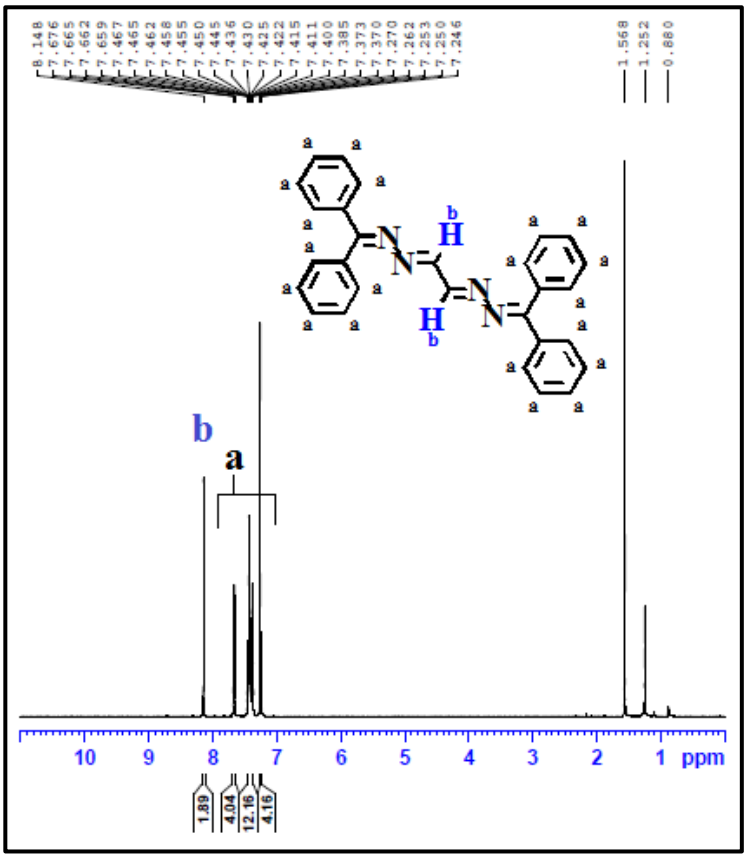


Figure 2.10 ^{1}H NMR Spectrum of **BBHG** (500 MHz, $CDCl_3$).

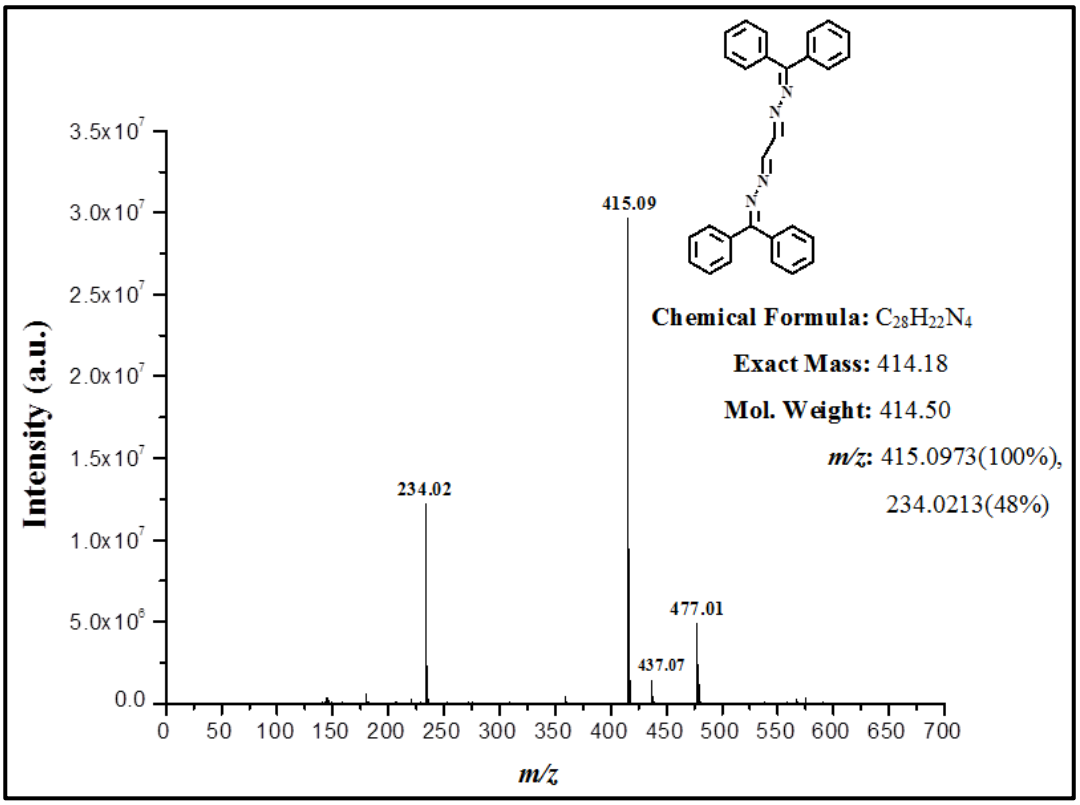


Figure 2.11 TOF Mass Spectrum of **BBHG** TOF-MS (*m/z*).

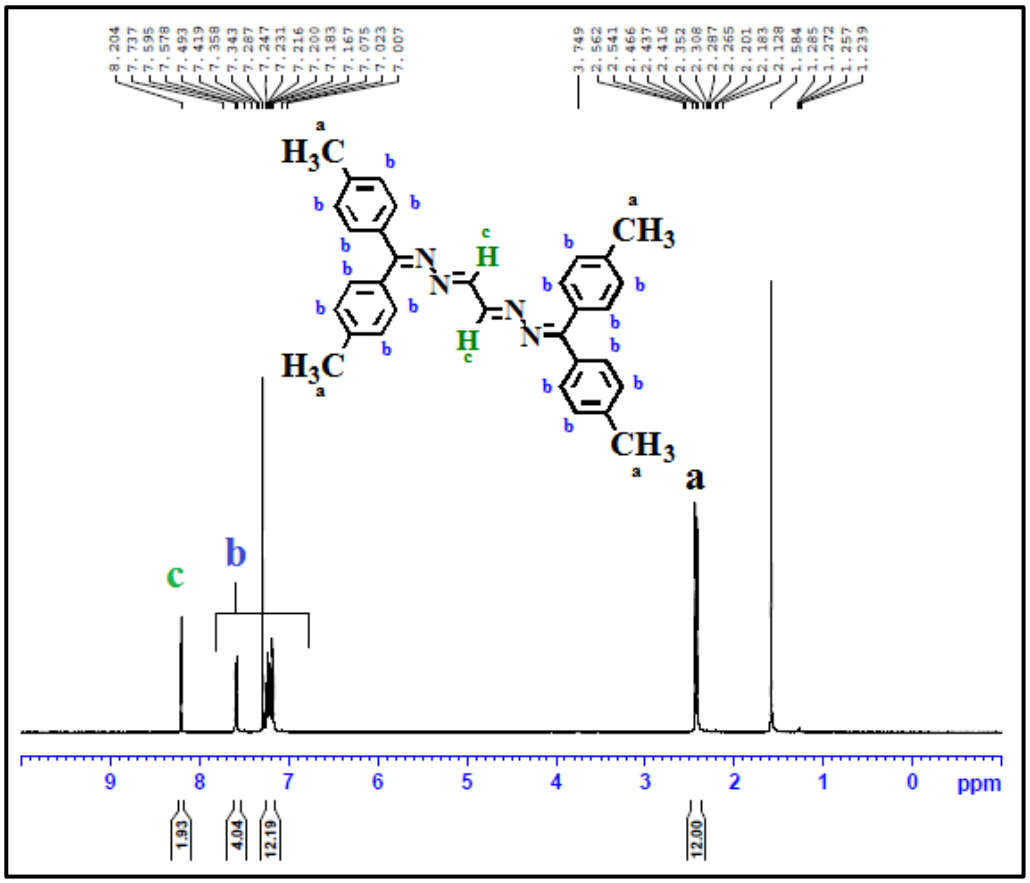


Figure 2.12 ^{1}H NMR Spectrum of **DMBHG** (500 MHz, $CDCl_3$).

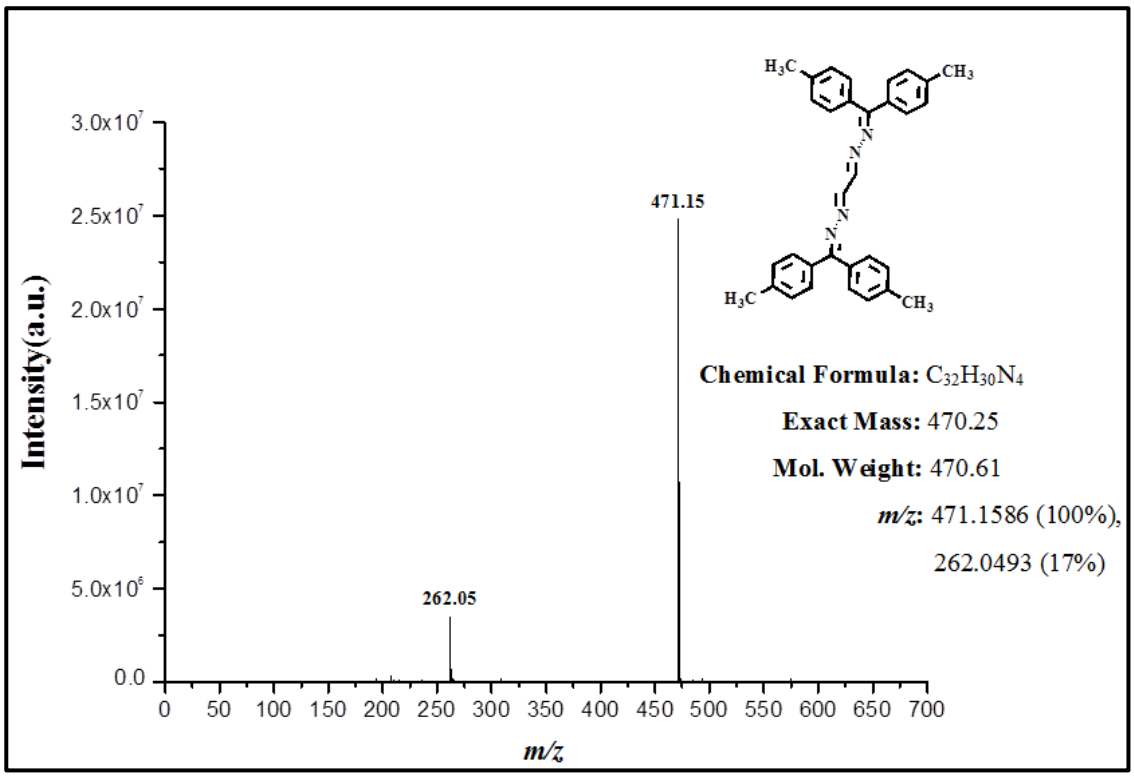


Figure 2.13 TOF Mass Spectrum of **DMBHG** TOF-MS (*m/z*).

Table 2.5 Crystal Data and Structure Refinement

Compound	**BBHG•DIOX**	**BBHG-I**	**BBHG-II**	**DMBHG•DIOX**	**DMBHG-I**	**DMBHG-II**
Moiety formula	$C_{28}H_{22}N_4$•1($C_4H_8O_2$)	$C_{28}H_{22}N_4$	$C_{28}H_{22}N_4$	$C_{32}H_{30}N_4$•2($C_4H_8O_2$)	$C_{32}H_{30}N_4$	$C_{32}H_{30}N_4$
Formula weight	502.60	414.49	414.49	646.81	470.60	470.60
Crystal system	Monoclinic	Monoclinic	Triclinic	Triclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$C2/c$	$P2_1/n$
Crystal size (mm^3)	0.50 x 0.34 x 0.17	0.38 x 0.24 x 0.20	0.47 x 0.28 x 0.15	0.24 x 0.13 x 0.10	0.41 x 0.25 x 0.11	0.49 x 0.31 x 0.15
a/Å	8.7820(8)	9.5143(4)	8.9416(5)	9.2744(5)	30.8771(13)	7.6648(4)
b/Å	19.3206(18)	15.9111(6)	9.7373(4)	9.7625(5)	5.7879(2)	7.5690(4)
c/Å	8.3676(7)	7.5626(3)	14.0714(7)	11.1020(6)	15.4347(7)	22.2053(11)
α/(deg)	90	90	107.359(2)	73.927(2)	90	90
β/(deg)	109.151(2)	103.607(1)	105.427(2)	85.040(2)	94.559(1)	94.872(2)
γ/(deg)	90	90	92.708(2)	63.074(2)	90	90
V/$Å^3$	1341.2(2)	1112.72(8)	1116.50(10)	860.30(8)	2749.7(2)	1283.58(11)
Z	2	2	2	1	4	2
D_{cal}/g cm^{-3}	1.245	1.237	1.233	1.248	1.137	1.218
T/K	100	90	100	100	299	173
μ/mm^{-1}	0.079	0.074	0.074	0.081	0.068	0.072
F_{000}	532	436	436	346	1000	500
Reflections measured	22786	13056	12396	30605	23762	23460
Unique reflections	3335	2765	5340	4270	3420	3181
Observed reflections	3043	2490	4208	3658	2531	2673
Parameters	172	145	289	219	166	223
R_{int}	0.0268	0.0343	0.0606	0.0293	0.0290	0.0323
final *R* [I >2σ(I)]	0.0384	0.0414	0.0677	0.0412	0.0504	0.0433
final *R* (all data)	0.0422	0.0460	0.0840	0.0505	0.0721	0.0543
GOF on F^2	1.019	1.020	1.024	1.015	1.039	1.055

Table 2.6 Torsion angle (−**CH**=**N**−**N**=**C**−) and dihedral angle between the planes of terminal phenyl rings:

Crystal	Torsion angle of (–CH=N–N=C–) unit	Dihedral angle	Packing Index
BBHG•DIOX	150.55º	70.58º	68.2%
BBHG-I	130.92º	65.75º	67.7%
BBHG-II	157.02º and 165.01º	72.40º and 63.25º	67.4%
DMBHG.DIOX	132.64º	76.42º	70%
DMBHG-I	150.62º	67.66º	63.3%
DMBHG-II	170.08º	88.09º	68.7%

Thermal Ellipsoid Plots:

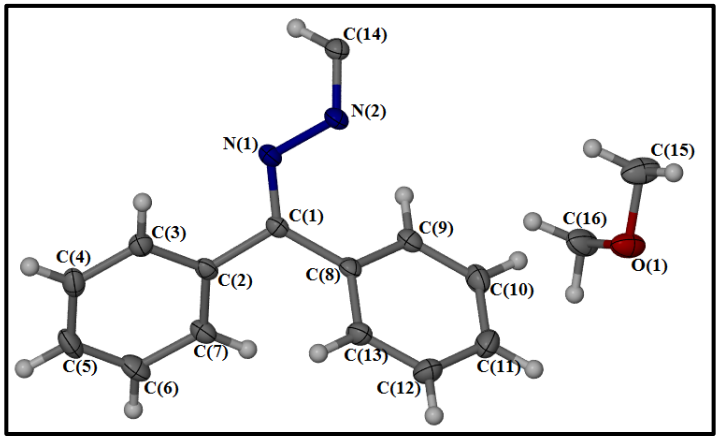


Figure 2.14 Thermal ellipsoid plot of asymmetric unit of **BBHG•DIOX**. Atoms are shown with 70% probability of thermal ellipsoids.

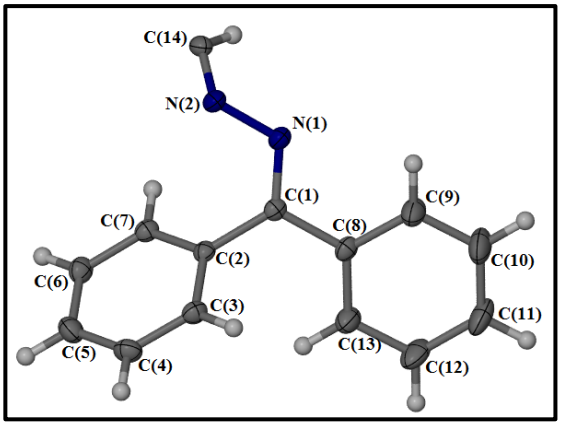


Figure 2.15 Thermal ellipsoid plot of asymmetric unit of **BBHG-I**. Atoms are shown with 70% probability of thermal ellipsoids.

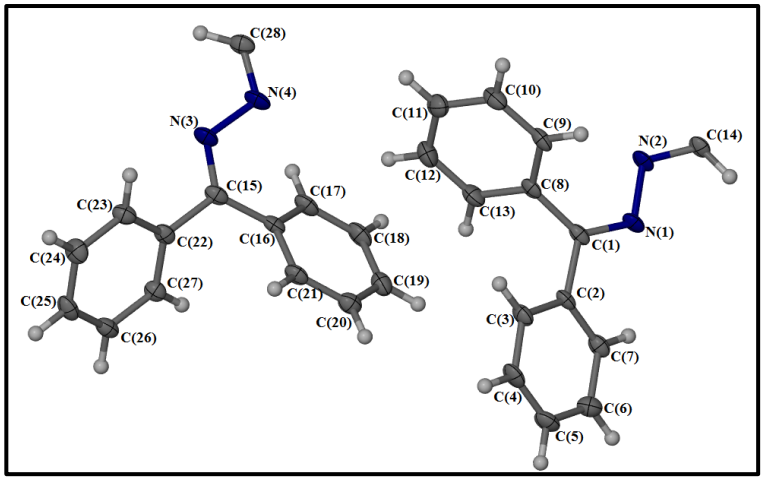


Figure 2.16 Thermal ellipsoid plot of asymmetric unit of **BBHG-II**. Atoms are shown with 70% probability of thermal ellipsoids.

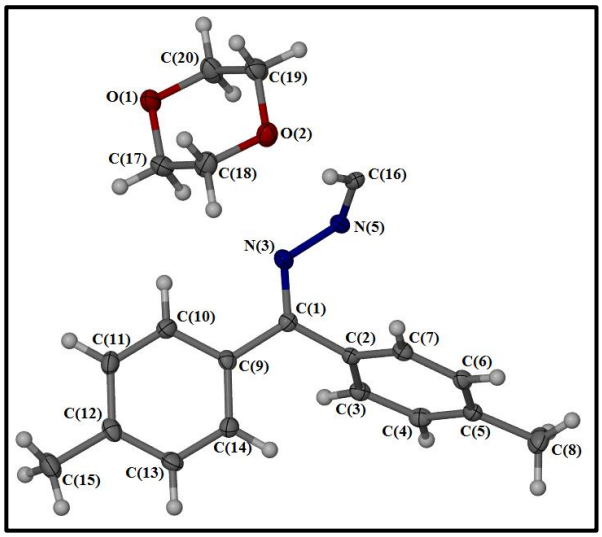


Figure 2.17 Thermal ellipsoid plot of asymmetric unit of **DMBHG•DIOX**. Atoms are shown with 70% probability of thermal ellipsoids.

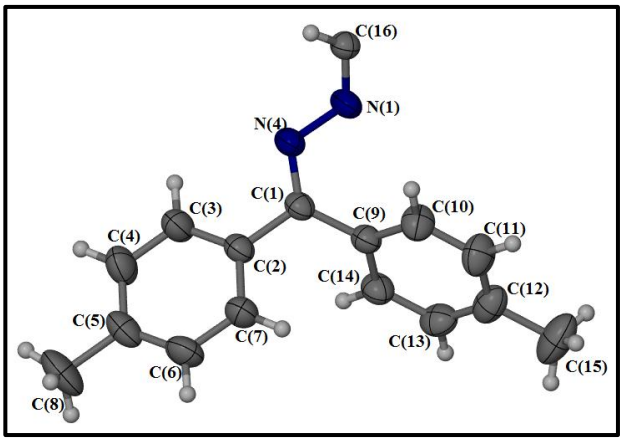


Figure 2.18 Thermal ellipsoid plot of asymmetric unit of **DMBHG-I**. Atoms are shown with 50% probability of thermal ellipsoids.

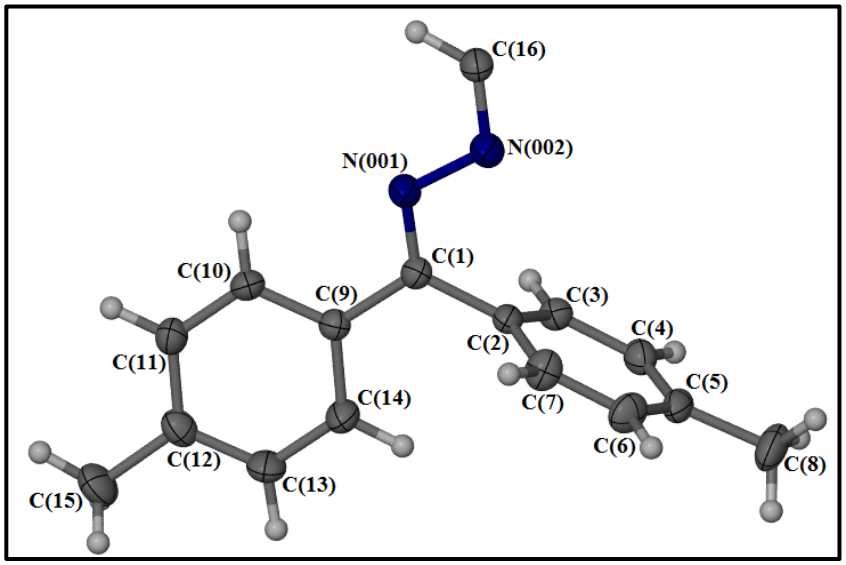


Figure 2.19 Thermal ellipsoid plot of asymmetric unit of **DMBHG-II**. Atoms are shown with 70% probability of thermal ellipsoids.

CHAPTER-3

Two Reversible Single Crystal to Single Crystal Polymorphic Phase Transformation of 2,3-Butanedione, 2,3-bis[4,4'-bis(diethylamino) benzophenone hydrazone]

3.1 Abstract

Two reversible polymorphic phase transformations of 2,3-butanedione, 2,3-bis[4,4'-bis(diethylamino)benzophenone hydrazone] (**DEBH)** have been identified in DSC experiment and confirmed by variable temperature Single Crystal and Powder X-ray Diffraction experiment. While, three polymorphic phases are reversibly interconvertible to each other through Single Crystal to Single Crystal (SC-SC) transformation before melting of the compound, another polymorphic phase has been isolated by cooling and subsequent heating of the melt phase, generating overall four polymorphic phases. Among the four phases of **DEBH**, only one phase can be prepared by solvent mediated crystallization.

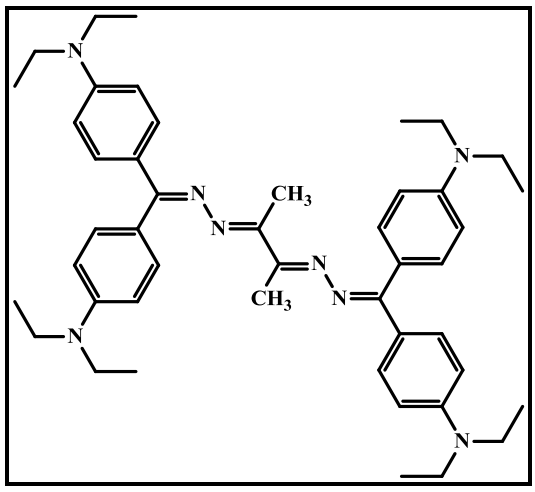
3.2 Introduction

Polymorphism has been the subject of intense research over the past decades due to its importance in pharmaceutical and other specialty industry.[1-4] Although polymorphism adds complexity in designing new materials with desired properties, research in polymorphism remain very interesting because it assists in understanding the kinetic of crystal nucleation, molecular recognition and crystal growth.[5-11] According to the most accepted definition of polymorphism, it is a phenomenon of having at least two different crystal structures of same chemical compound.[12,13] However, on this basis it is not so straight forward to define polymorphism in some instances.[14-17] Relatively new kind of polymorphism, named as 'isostructural polymorphism', does not fit into the conventional definition of polymorphism since, the terms 'isostructural' and 'polymorphism' are contradictory to each other. Nevertheless, existence of isostructural polymorphism has been reported and justified by few researchers.[18-20]

Crystallization in different solvents is the most common methods for preparation of different polymorphic phases of a compound, although many other methods are known.[21-25] In this regard, solid-to-solid phase transformation induced by external stimuli is very convenient to prepare some polymorphs.[26-28] Polymorphic phase transformation is very interesting subject to study, because this assists in understanding the kinetic and thermodynamic stability of different polymorphs of a compound.[29-31] In addition, study of polymorphic phase transformation is very much necessary in specialty chemical industry in order to recognize the storage condition of different polymorphs. Differential Scanning Calorimetry (DSC) is one of the most important

techniques for the analysis of phase transformation.[32-35] DSC can certainly indicate polymorphic phase transformation in case of enantiotropic polymorphism where the transformation occurs before melting of the compound. Reversible and irreversible nature of the transformation can also be easily verified in DSC experiment.[36]

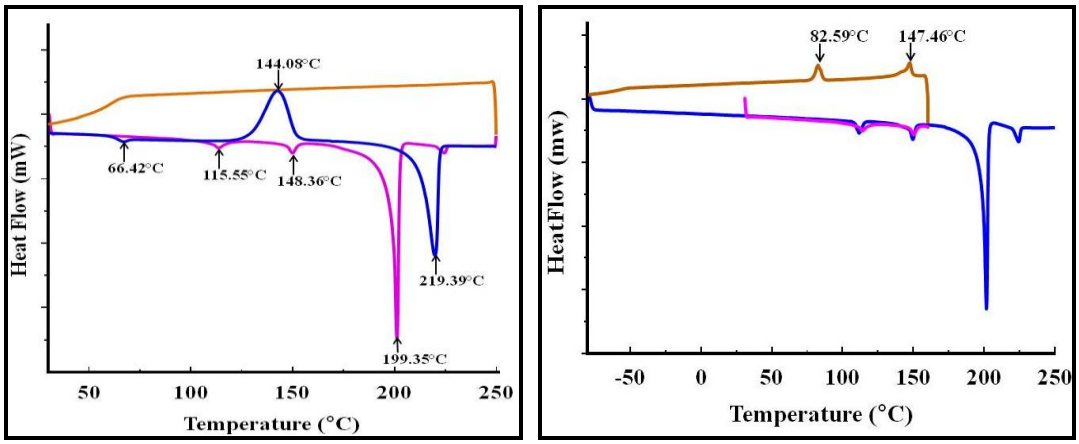
Single Crystal to Single Crystal (SC-SC) polymorphic phase transformation induced by external stimuli is known in many organic compounds.[37-41] SC-SC transformation is very interesting phenomenon to study because simultaneous and cooperative movement of constituent atoms or molecules leads to the change of crystal structures without appreciable loss of single crystallinity. Since significant change of crystal structures is not expected in SC-SC transformation, there is possibility of this kind of transformation between isostructural polymorphs. In this communication, we have reported a rare observation of two reversible SC-SC polymorphic phase transformations of three isostructural phases of a new bis-hydrazone compound, **DEBH** (**scheme 3.1)**. These phases initially were identified by DSC experiment and confirmed by variable temperature Single Crystal X-ray Diffraction experiment (SCD). Bernstein *et al*. have observed similar phase transformation in a pharmaceutical compound.[42] Among these three phases, only one phase is stable at room temperature and can be prepared by solvent mediated crystallization. Overall, four polymorphic phases of **DEBH** have been found. Thermodynamically most stable polymorph of **DEBH** has been prepared by melt crystallization and confirmed by X-ray diffraction study (PXRD and SCD).



Scheme 3.1 Molecular structure of 2,3-butanedione, 2,3-bis[4,4'-bis(diethylamino)benzophenone hydrazone], (**DEBH)**.

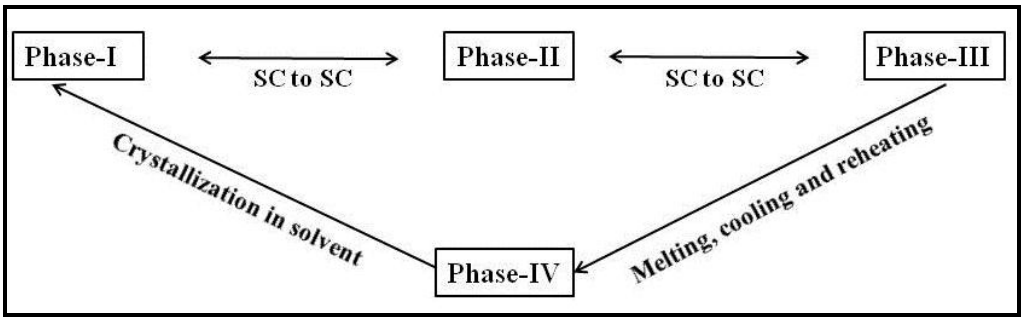
3.3 Results and Discussion

Present study is part of ongoing research on inclusion property and polymorphism of bis-hydrazone compounds in our laboratory. Recently we have reported specific inclusion property and polymorphism of two bis-hydrazone compounds.[43] Although, **DEBH** does not exhibit inclusion property, two solid to solid phase transformation have been observed in DSC thermogram recognized by two endothermic peaks at 115.55° C and 148.36° C respectively followed by melting at 199.35° C (**Figure 3.1a**). DSC study demonstrates that before melting **DEBH** has at least three polymorphic phases: **Phase-I** stable till 111° C, **Phase-II** exist from 121.4° C to 142.65° C and **Phase-III** observed till 195° C. Further analysis of DSC thermogram of as-synthesized material indicates the glassy state after cooling of melt phase [glass transition temperature (T_g) at 66.42 ° C] during reheating and subsequently crystallizing at 144° C followed by melting at 219.39 °C (**Figure 3.1a**). Hence, a new polymorph which is named as **Phase-IV** has been detected by cooling and reheating of the melt phase of **DEBH**. In another DSC experiment while heating was halted at 160° C, two exothermic peaks have been detected at peak temperature 147.46° C and 82.59° C respectively during cooling of the sample (**Figure 3.1b**). This suggests that **Phase-III,** reversibly transformed to **Phase-II** and then converted back to **Phase-I** showing some hysteresis in the reversible transformation of **Phase-II** to **Phase-I** (**Figure 3.1b**). Melting point profile indicates that **Phase-IV** is thermodynamically most stable polymorph of **DEBH**. It was observed that **Phase-IV** does not convert back to **Phase-I** after melting of **DEBH** (**Figure 3.2**). It suggests that **Phase-IV** is monotropically related to **Phase-I** while relationship of **Phase-II** and **Phase-III** is enantiotropic with **Phase-I**. Among all the four phases, only **Phase-I** can be prepared by slow evaporation of different solvents. Co-relation of polymorphic phases has been shown in (**Scheme 3.2**.)



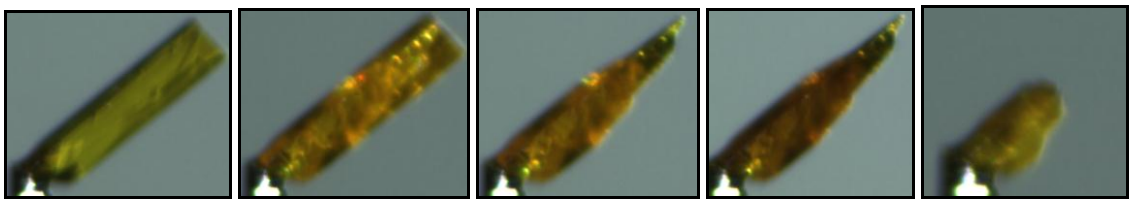
(**a**) (**b**)

Figure 3.1 DSC thermogram of as-synthesized material by heat-cool-heat method showing polymorphic phase transformation. Heating in first segment shown in magenta colour, cooling segment shown in orange colour and blue colour indicates reheating. Peak temperatures have been indicated by arrow. (**a**) Melting is shown in the first segment followed by cooling and then reheating; (**b**) DSC thermogram showing reversible polymorphic phase transformation of **Phase-I**, **Phase-II** and **Phase-III**.



Scheme 3.2 Co-relation of different Phases of **DEBH.**

Further investigations have been carried out by X-ray diffraction in order to understand the structural changes of all the phases and to rationalize the reversible phase transformations of **Phase-I**, **Phase-II** and **Phase-III** induced by temperature. Variable temperature Single Crystal X-ray Diffraction (VT-SCXRD) study has been performed on a single crystal glued to a thin glass fiber. Temperature of the data collection was decided according to the phase transformations observed in DSC experiment. Full intensity data were collected at 27°C, 127°C and 167°C. Although there was some deterioration of the single crystal due to high temperature (See **Figure 3.2** for photograph of the single crystal at different temperature), it was fair enough to collect intensity data of the same crystal at 107° C and again at 27°C reversibly by cooling the crystal. All the data were solved and structures were determined at each temperature (See **Table 3.2** for crystallographic details).



27°C (during heating) **127°C (during heating)** **167°C** **107°C (during cooling)** **27°C (during cooling)**

Figure 3.2 Photographs showing the single crystal used for X-ray diffraction study at different temperature. Snapshots are taken after finishing intensity data collection at each temperature mentioned below the photograph.

Crystal structures of **Phase-I**, determined at 27° C (during heating and cooling), were solved in $P2_1/c$ space group with half molecule present in the asymmetric unit while the crystal structures of **Phase-II**, determined at 127° C (during heating) and 107° C (during cooling), were solved in $P2_1$ space group with one molecule in asymmetric unit. Diffraction data at 167°C were solved for the structure of **Phase-III** in $P2_1/c$ space group with half molecule present in asymmetric unit. Overlay of molecules of **DEBH** show the difference in molecular conformation between **Phase-I** and **Phase-II** due to twisting of ethyl groups in *N*,*N*-diethyl substituent (**Figure 3.3**). However, no significant conformational changes of molecules have been found in the crystal structure of **Phase-I** and **Phase-III** (**Figure 3.4**). Analysis of the crystal structures reveals the crystal structures of **Phase-I**, **Phase-II** and **Phase-III** are almost isostructural. Molecules in these phases are arranged in herringbone fashion viewed down the *a* axis (**Figure 3.5**) while molecules are connected by C−H···π hydrogen bond (See **Table 3.3** for hydrogen bonding).

Reversible phase transformation of bulk material of **DEBH** was verified by variable temperature Powder X-ray diffraction experiment (VT-PXRD). Powder patterns recorded at 27° C, 127° C and 167° C while heating the sample match with the simulated pattern from SCD data of **Phase-I**, **Phase-II** and **Phase-III** respectively. Powder patterns recorded at 127° C and 27° C while cooling the sample indicates the reversible polymorphic phase transformation of **Phase-III** to **Phase-II** and then back to **Phase-I** respectively (**Figure 3.6**).

Phase-IV crystallizes in $P\bar{1}$ space group with one molecule in the asymmetric unit. Conformation of **DEBH** molecules in **Phase-IV** is different from other phases due

to change of torsion angle of (−C=N−N=C−) unit (see **Table 3.4**). Analysis of the crystal structure reveals that this conformation assists in efficient packing of the molecules which may be the reason of higher melting point of **Phase-IV (**See **Figure 3.7** for packing diagram of **Phase-IV)**.

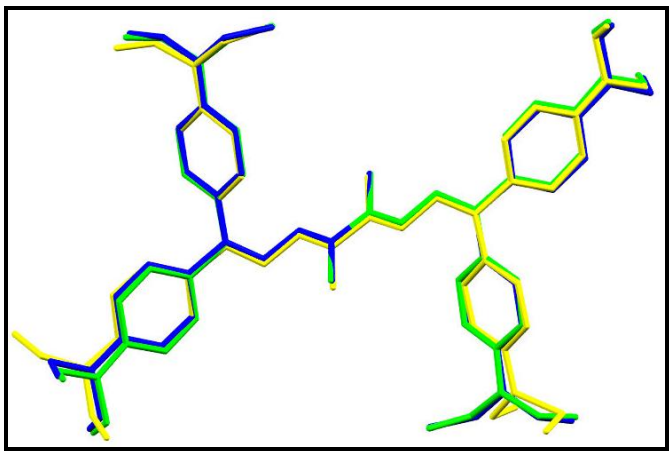


Figure 3.3 Overlay diagram of molecules in different phases showing conformational differences. Green colour for **Phase-I**, yellow colour for **Phase-II** and blue colour for **Phase-III**. Hydrogen atoms have been omitted for clarity.

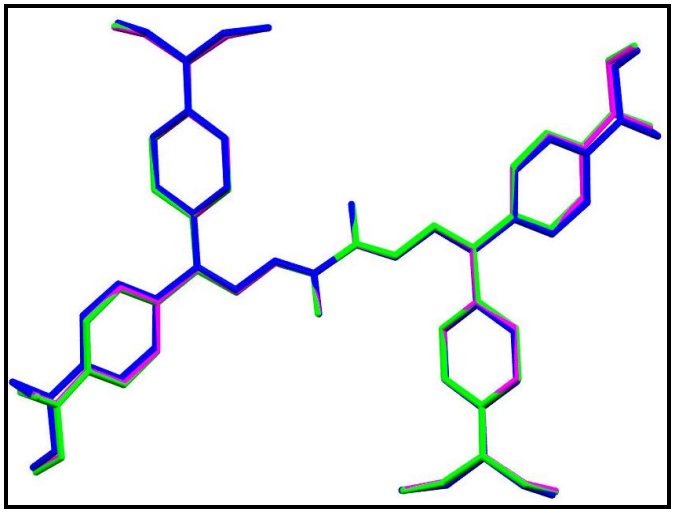
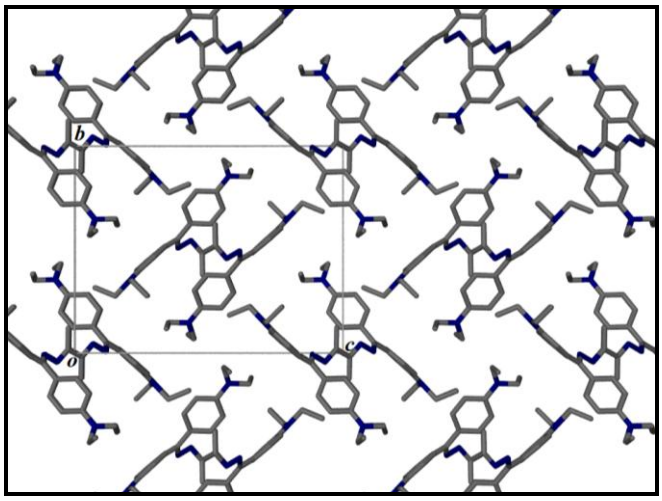
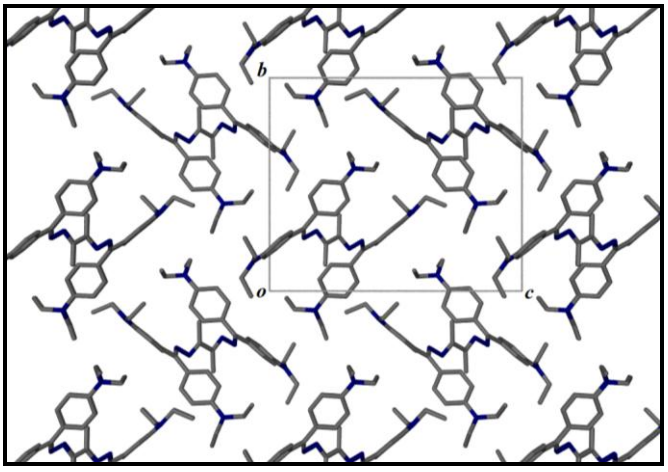


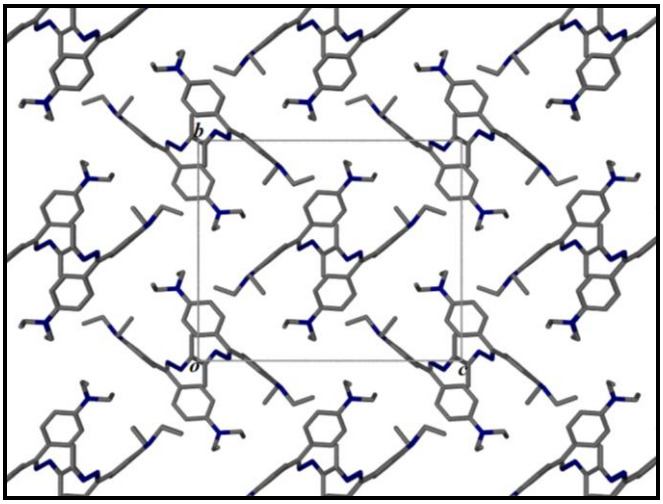
Figure 3.4 Overlay diagram of the molecules showing the conformational similarity in **Phase-I** and **Phase-III**. Green colour for **Phase-I** at 27°C initially, blue colour for **Phase-III** at 167°C and magenta colour for **Phase-I** at 27°C after cooling. Hydrogen atoms have been omitted for clarity.



(**a**)



(**b**)



(**c**)

Figure 3.5 Herringbone arrangement of the molecules in (**a**) **Phase-I**, (**b**) **Phase-II** and (**c**) **Phase-III** viewed down *a* axis. Hydrogen atoms have been omitted for clarity.

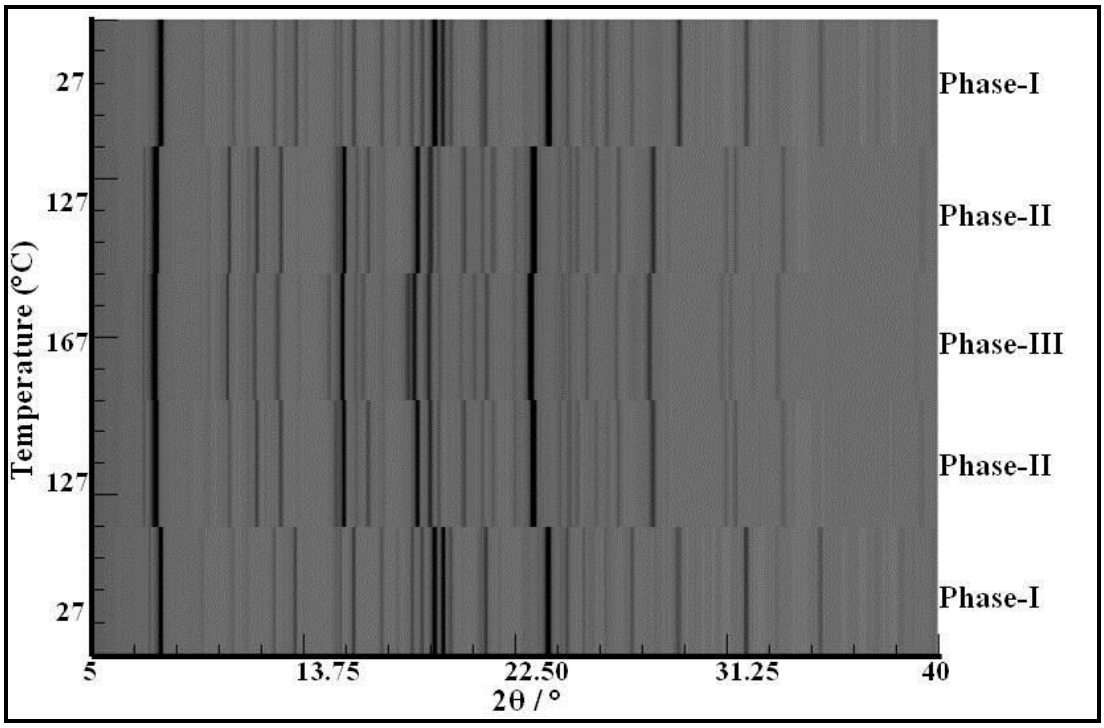


Figure 3.6 Powder X-ray Diffraction pattern (plotted using Powder3D)[44] recorded at different temperature showing reversible phase transformation. Note that the Temperature axis is not shown on a linear scale.

Reversible transformation through SC-SC process between **Phase-I**, **Phase-II** and **Phase-III** of **DEBH** can be rationalized on the basis of flexible conformation of **DEBH** molecules. Conformation of the molecules in all the phases is temperature dependent. Molecules of **DEBH** in **Phase-I** are centrosymmetric in nature. Twisting of ethyl group on *N*,*N*-diethyl substituent induced by thermal energy deviates the centre of inversion making the molecules of **DEBH** non-centrosymmetric in **Phase-II**. As the temperature increases further non-centrosymmetric **DEBH** molecules become centrosymmetric again in **Phase-III**. All these conformational changes happen without significant change of very smoothly crystal structures. When the crystal was cooled to room temperature, **DEBH** molecules back to the initial conformation.

3.4 Conclusion

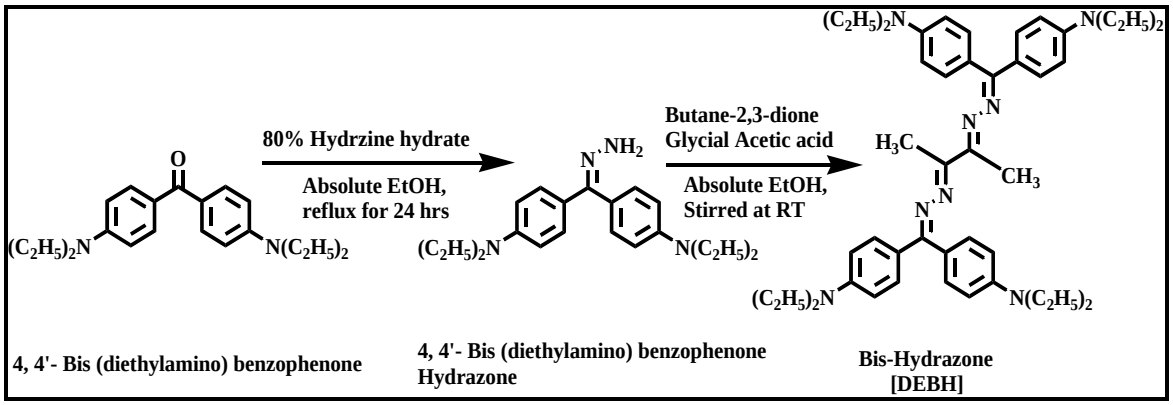
In conclusion, here I have reported a very rare phenomenon of temperature dependent two reversible Single Crystal to Single Crystal polymorphic phase transformations of a bis-hydrazone compound. Conformational flexibility of **DEBH**

molecules leads to the transition of centrosymmetric to non-centrosymmetric and again back to centrosymmetric without loss of single crystallinity with the change of temperature.

3.5 Experimental Section

3.5.1 Synthesis and Crystallization of DEBH

The starting materials and reagents used for synthesis of compound **DEBH** were obtained from Alfa Aesar & Sigma-Aldrich and used without further purification. All solvents used in crystallization experiments were reagent grade. ^{1}H NMR spectra were recorded on a 500 MHz Bruker Advance III spectrometer in $CDCl_3$. The bis-hydrazone compounds of butane-2,3-dione (**DEBH**) was synthesized after little modification of the procedure reported in literature.[45] Synthetic scheme for compound **DEBH** shown in (**Scheme 3.3**). Some characteristic features of **DEBH** are given in (**Table 3.1**).



Scheme 3.3

Molecular structure was characterized by NMR spectroscopy and Mass spectrometry (MS).

NMR and MS data for compound **DEBH:**

^{1}H NMR (500 MHz, $CDCl_3$): δ7.638 (d, 4H), δ7.202 (d, 4H), δ6.672 (d of d, 8H), δ 3.444 (multiplet, 16H), δ2.208 (s, 6H), δ1.229 (t, 24H).

TOF-MS (*m/z*): 727.4912 (100%), 364.2497 (17%).

Table 3.1 Physical Properties of DEBH

DEBH	Physical Properties
Physical State	Powder
Colour	Bright yellow
Melting Point	195 °C - 200 °C
Solubility	Soluble in all organic solvents except alcohols
Yield	73 %

DEBH was crystallized by slow evaporation method. Dissolving this compound in almost all common solvents available in our laboratory generated crystals of **Phase-I** only.

3.5.2 Differential Scanning Calorimetric (DSC) Study of DEBH

Differential scanning calorimetry was performed by heat-cool-heat method on a Mettler Toledo DSC1 calorimeter with FRS5 DSC Sensor attached with HUBER TC100-MT chiller and STARe software V14.00. About 6 mg of as-synthesized compound **DEBH** was taken in 40 μL Aluminum pan sealed with pierced lid. The sample was purged with a flow of dry nitrogen gas at 50 mL/min. DSC data were collected by heat-cool-heat method. The sample was first heated at the rate of 5 °C/min from 30 to 250 °C. In the second step, the sample was cooled at the rate of 10 °C/min from 250 °C to -80 °C. Finally, the sample was reheated from -80 °C to 250 °C at the rate of 5 °C/min. In the second experiment, sample was first heated at the rate of 5 °C/min from 30 °C to 160 °C. In the second step, the sample was cooled at the rate of 10 °C/min from 160°C to -80°C. Finally, the sample was reheated from -80°C to 250 °C at the rate of 5 °C/min.

3.5.3 Variable Temperature Single Crystal X-ray Diffraction (VT-SCXRD) Study

Single crystal X-ray structures were collected on Bruker D8 Quest single crystal X-ray diffractometer equipped with a microfocus anode (Mo) and a PHOTON 100 CMOS detector. A suitable single crystals of polymorphs of **DEBH** for diffraction experiments were chosen under polarizable microscope and the crystals were cut and wrapped with paraton oil and single crystal was glued to a thin glass fiber and the

temperature of the crystal was controlled using an Oxford Cryosystream 800 Plus cryostat. The single-crystal data were initially recorded at 27°C and then by heating the crystal successive datasets were collected at 127°C and 167°C. Reversibly by cooling the crystal the intensity data were collected at 107°C and 27°C. The data were integrated and scaled using the Bruker suite of programs.[46] The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using SHELX-2014.[47] All non-hydrogen host atoms were refined anisotropically and all hydrogen atoms were placed using calculated positions and riding models.

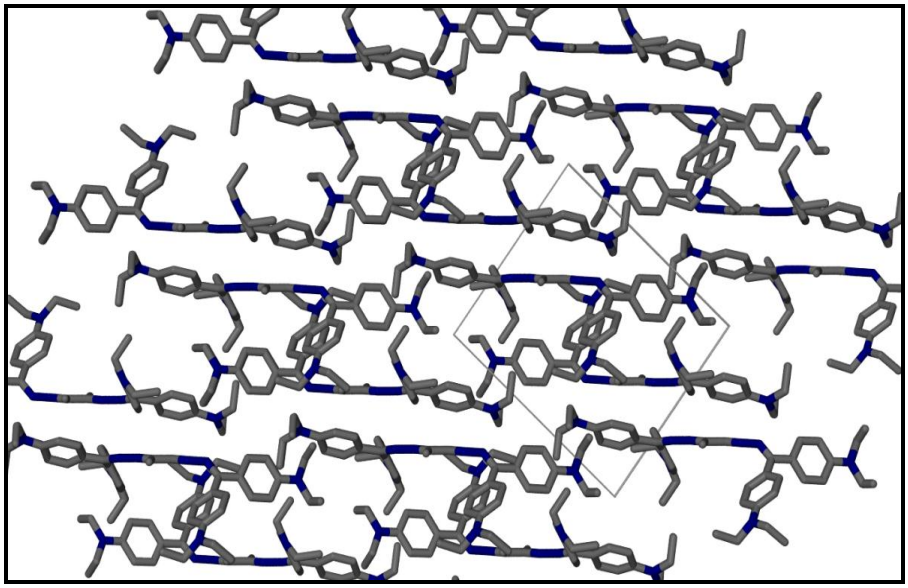


Figure 3.7 Packing diagram of **Phase-IV** viewed down *a* axis. Hydrogen atoms have been omitted for clarity.

3.5.4 Variable Temperature Powder X-ray Diffraction (VT-PXRD) Study

X-ray powder diffractograms were measured on PANalytical Empyrean X-ray diffractometer with CuK_α radiation, (λ = 1.54059 Å) operating in Bragg-Brentano geometry. Powder sample was loaded in XRK 900 chamber from Anton Paar. Initially the pattern was recorded at 27°C. Sample was heated at the rate of 10°/min and put isothermal condition for 5 minutes. Subsequently the data were recorded 127°C and 167°C by heating the sample. Similarly, the data were collected at 87 °C and 27 °C reversibly by cooling the sample at the rate of 10°/min. In each case, data were collected in the 2θ range between 5° to 40° with a step size of 0.02° and counting time 2 sec per step. Experimental PXRD patterns are shown in (**Figure 3.8–Figure 3.12**).

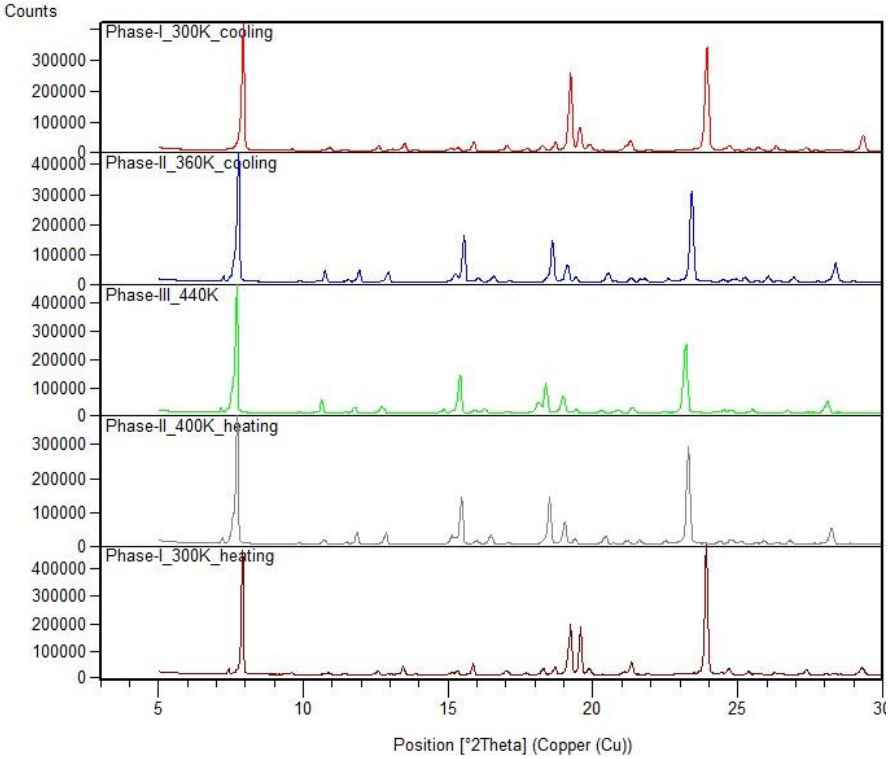


Figure 3.8 Experimental PXRD pattern of **DEBH** at different temperature during heating and cooling of the same sample.

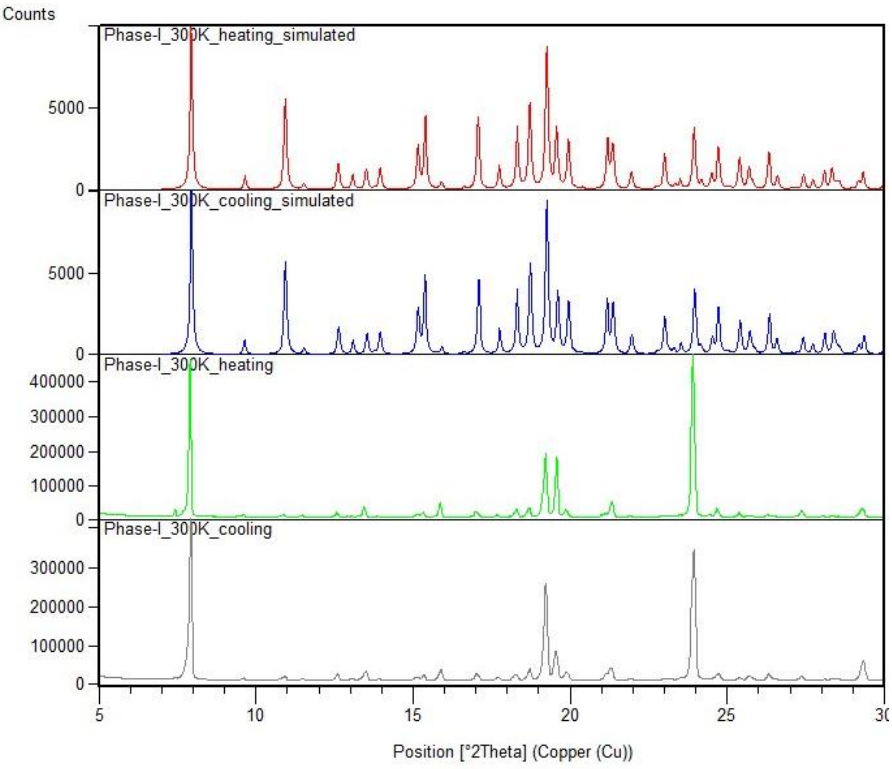


Figure 3.9 Simulated and experimental PXRD pattern of **Phase-I**.

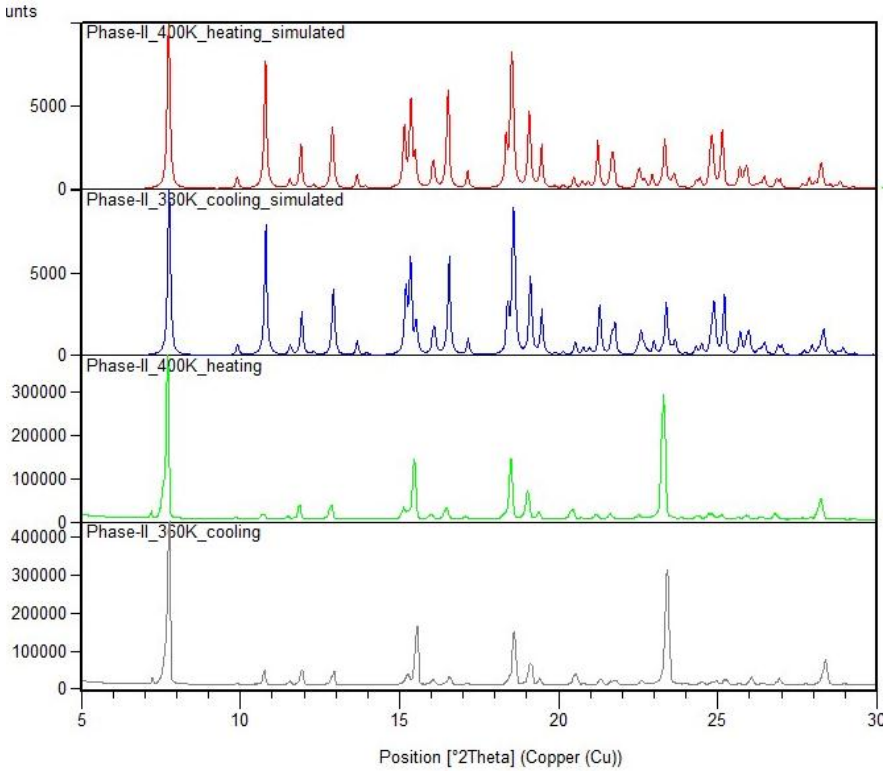


Figure 3.10 Simulated and experimental PXRD pattern of **Phase-II**.

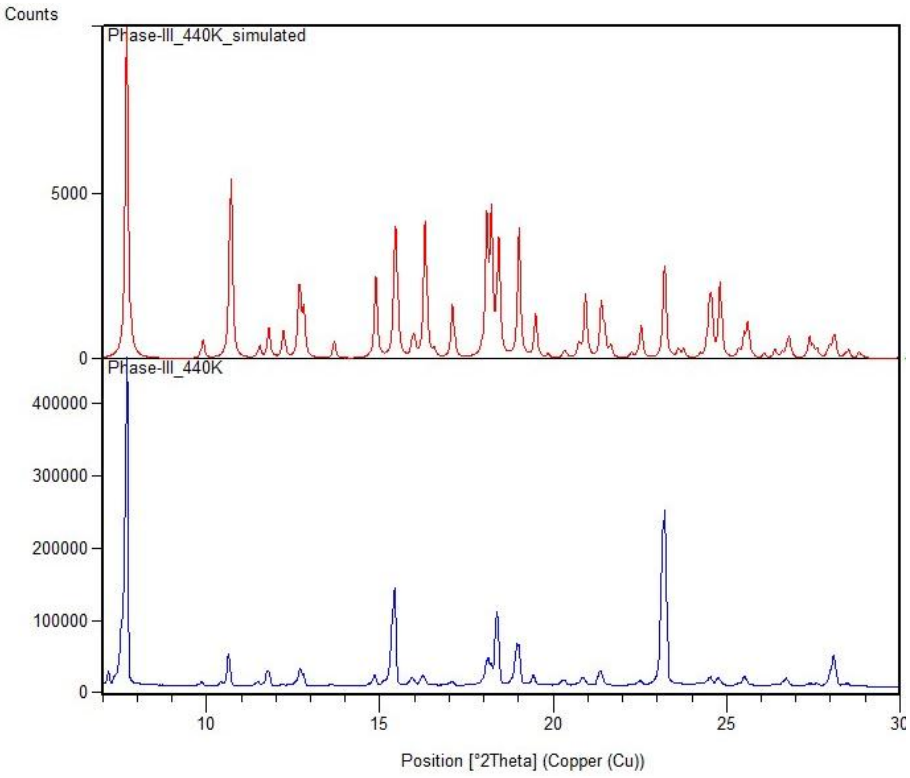


Figure 3.11 Simulated and experimental PXRD pattern of **Phase-III**.

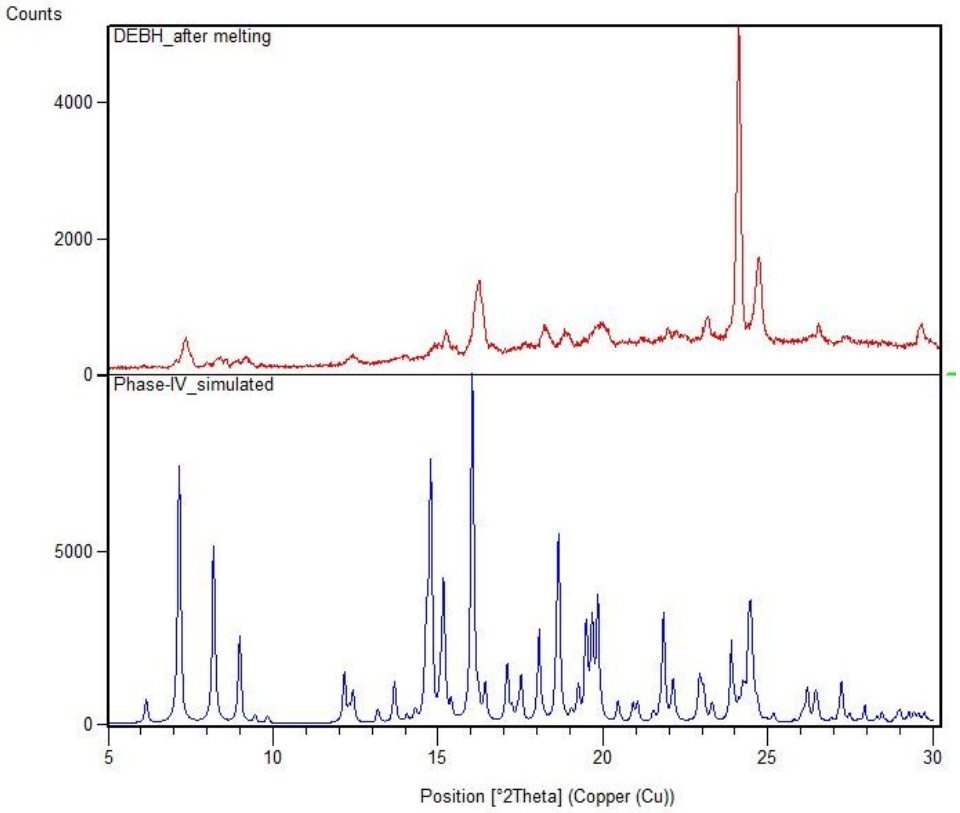


Figure 3.12 Experimental PXRD pattern of melt phase of **DEBH** and simulated pattern of **Phase-IV**.

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3.7 Appendix

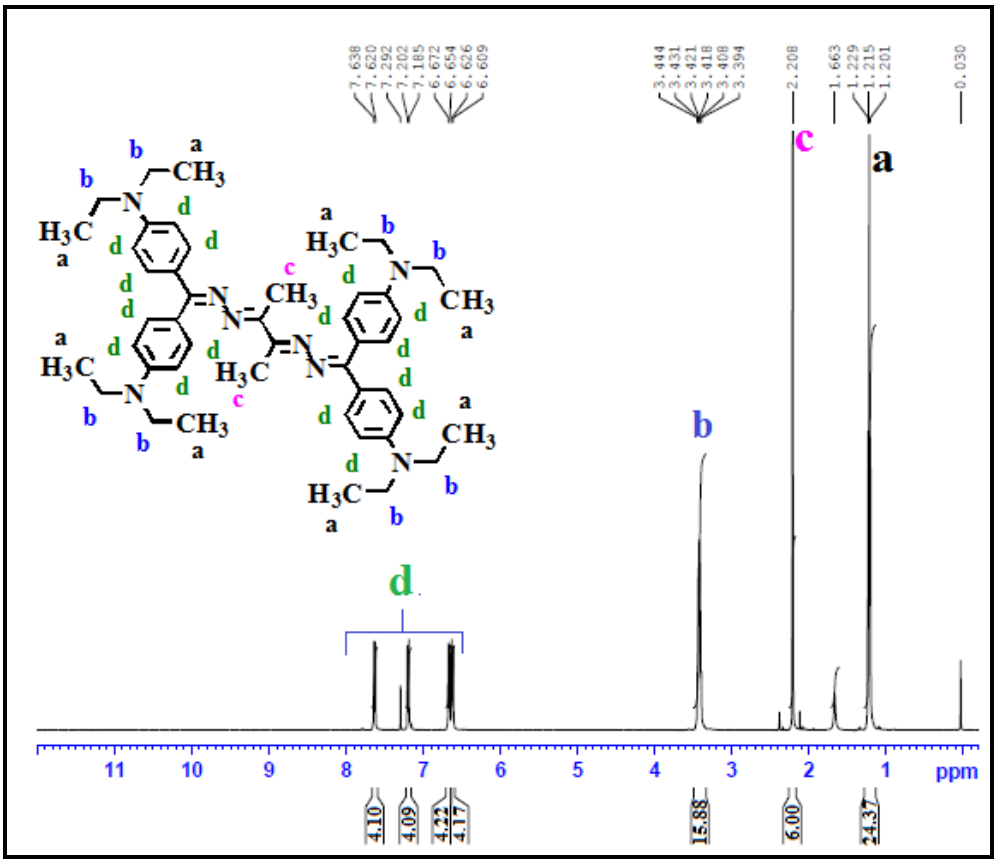


Figure 3.13 ^{1}H NMR Spectrum of **DEBH** (500 MHz, $CDCl_3$).

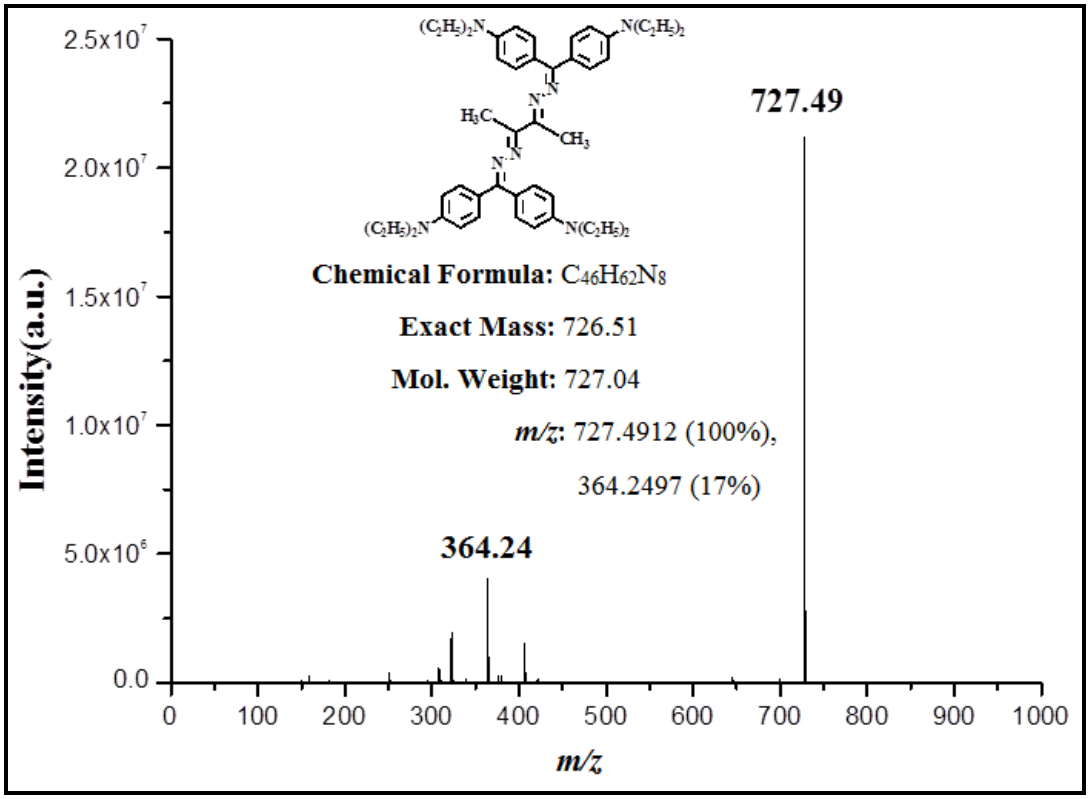


Figure 3.14 TOF Mass Spectrum of **DEBH** TOF-MS (*m/z*).

Table 3.2 Crystal Data and Structure Refinement

Polymorphic phases of **DEBH**	**Phase-I_27°C_heating**	**Phase-II_127°C _heating**	**Phase-III_167°C**	**Phase-II_107°C _cooling**	**Phase-I_27°C _cooling**	**Phase-IV**
Moiety formula	$C_{46}H_{62}N_8$	$C_{46}H_{62}N_8$	$C_{46}H_{62}N_8$	$C_{46}H_{62}N_8$	$C_{46}H_{62}N_8$	$C_{46}H_{62}N_8$
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/c$	$P2_1$	$P2_1/c$	$P2_1$	$P2_1/c$	$P\bar{1}$
Crystal size (mm^3)	0.50 x 0.14 x 0.13	0.50 x 0.14 x 0.13	0.45 x 0.14 x 0.13	0.45 x 0.14 x 0.13	0.21 x 0.11 x 0.09	0.45 x 0.17 x 0.15
a/*Å*	8.1436(4)	8.2486(6)	8.3347(13)	8.2378(11)	8.1415(9)	11.8579(6)
b/*Å*	14.0421(7)	14.8820(12)	15.000(2)	14.8453(17)	14.0127(17)	13.0119(7)
c/*Å*	18.4519(10)	17.9606(14)	18.024(3)	17.933(2)	18.476(2)	15.1255(8)
α/(*deg*)	90.000	90	90	90.000	90.000	87.445(3)
β/(*deg*)	96.365(2)	95.555(4)	97.123(5)	95.341(4)	96.319(3)	69.899(3)
γ/(*deg*)	90.000	90.000	90.000	90.000	90.000	73.212(3)
V/Å^3	2097.03(19)	2194.4(3)	2236.0(6)	2183.6(5)	2095.0(4)	2094.3(2)
Z	2	2	2	2	2	2
D_{cal}/g cm^{-3}	1.151	1.100	1.080	1.106	1.153	1.153
T/K	300	400	440	380	300	100
μ/mm^{-1}	0.069	0.066	0.065	0.066	0.069	0.069
F_{000}	788	788	788	788	788	788
Reflections measured	19295	28407	47938	42728	32133	64385
Unique reflections	5185	10346	5592	10833	5210	10547
Observed reflections	2828	3929	1951	4616	2502	6628
Parameters	250	498	250	498	250	692
R_{int}	0.0470	0.0802	0.1291	0.0953	0.1079	0.0808
final *R* [I >2σ(I)]	0.0633	0.0765	0.1163	0.0698	0.0786	0.0685
final *R* (all data)	0.1627	0.2503	0.2952	0.1350	0.1364	0.1244
GOF on F^2	1.026	0.993	1.014	0.999	1.037	1.026

Table 3.3 Details of C─H···π hydrogen bond observed in **Phase-I**, **Phase-II** and **Phase-III** at different temperature

Polymorph	**H···π (center of Ph ring) distance (Å)**	**C···π (center of Ph ring) distance (Å)**	**<C−H···π**
Phase-I_27°C_heating	2.83	3.512(3)	129º
	2.93	3.685(2)	139º
Phase-I_27°C_cooling	2.84	3.506(3)	127
	2.93	3.686(3)	139
Phase-II_127°C_heating	2.94	3.711(8)	141
	2.90	3.718(7)	144
Phase-II_107°C_cooling	2.90	3.768(6)	150
	2.95	3.716(6)	140
Phase-III_167°C	2.87	3.712(14)	148
	3.00	3.759(5)	140

Table 3.4 Torsion angle of (–C=N–N=C–) unit and dihedral angle between the planes of terminal phenyl rings in different Phases

Polymorph	**Torsion angle of (−C=N−N=C−) unit**	**Dihedral angle**
Phase-I_27°C_heating	130.37º	65.84º
Phase-I_27°C_cooling	129.76º	65.91º
Phase-II_127°C_heating	137.32º and 134.20º	60.46º and 65.41º
Phase-II_107°C_cooling	137.94º and 134.39º	59.62º and 65.10º
Phase-III_167°C	132.28º	64.42º
Phase-IV	172.12º and 137.52º	60.07º and 61.73º

Thermal Ellipsoid Plots:

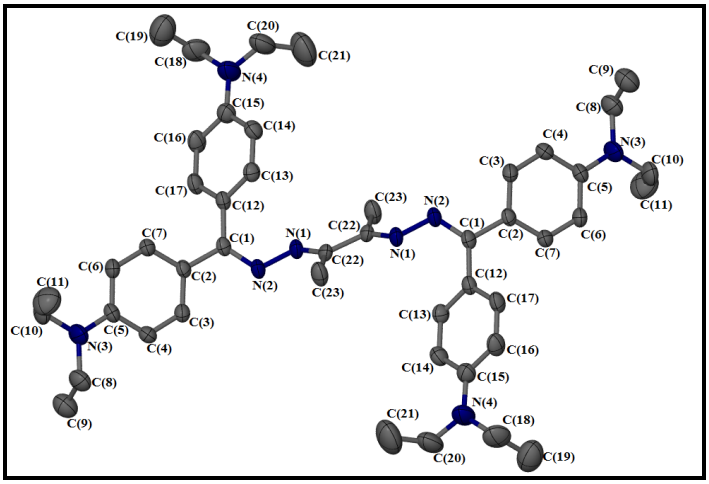


Figure 3.15 Thermal ellipsoid plot of the molecule of **Phase-I** at 27°C during heating. Atoms are shown with 50% probability of thermal ellipsoids.

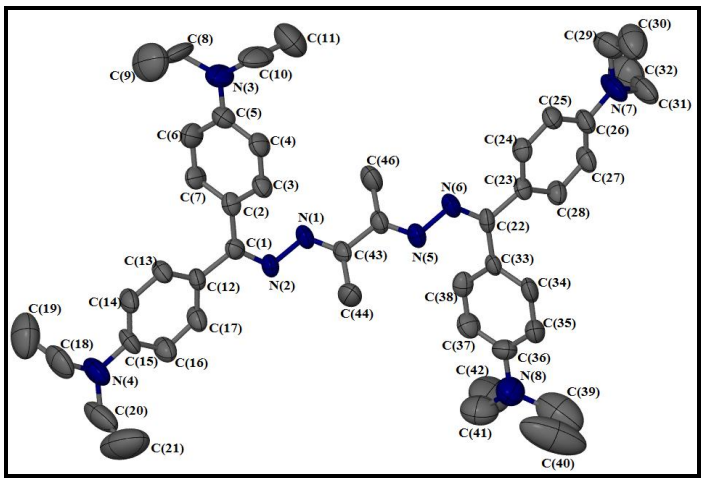


Figure 3.16 Thermal ellipsoid plot of the molecule of **Phase-II** at 127°C during heating. Atoms are shown with 50% probability of thermal ellipsoids.

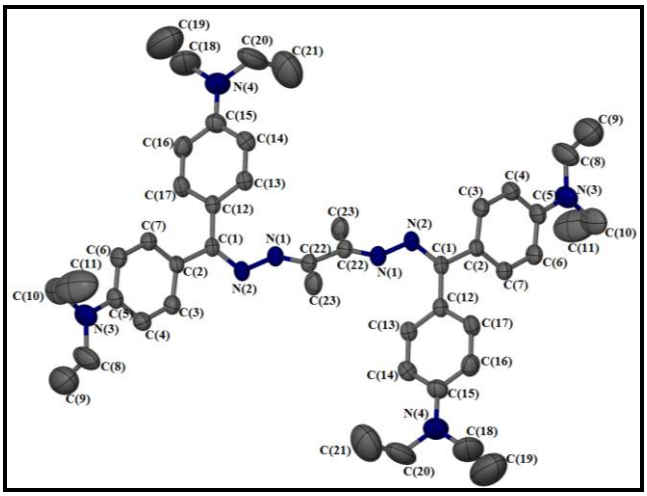


Figure 3.17 Thermal ellipsoid plot of the molecule of **Phase-III** at 167°C. Atoms are shown with 30% probability of thermal ellipsoids.

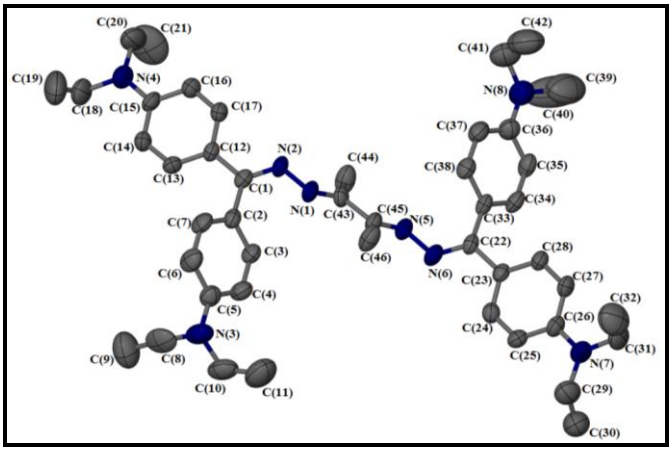


Figure 3.18 Thermal ellipsoid plot of the molecule of **Phase-II** at 107°C during cooling. Atoms are shown with 50% probability of thermal ellipsoids.

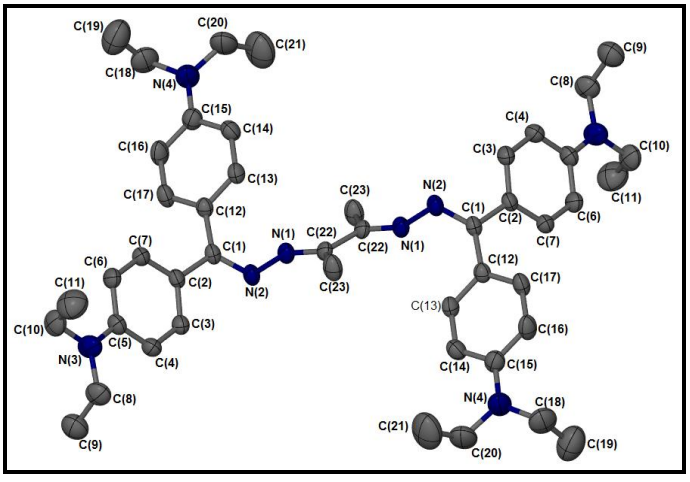


Figure 3.19 Thermal ellipsoid plot of the molecule of **Phase-I** at 27°C during cooling. Atoms are shown with 50% probability of thermal ellipsoids.

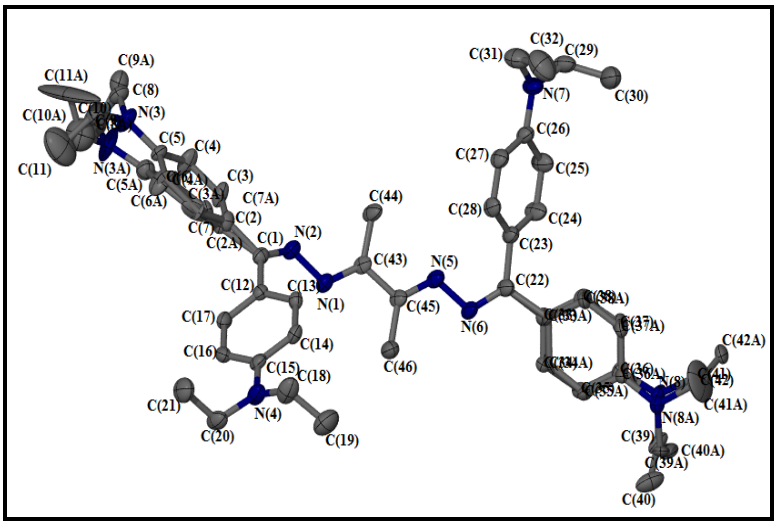


Figure 3.20 Thermal ellipsoid plot of the molecule of **Phase-IV** at -173°C. Atoms are shown with 70% probability of thermal ellipsoids.

CHAPTER-4

Polymorphism and Inclusion Properties of Two Bis-hydrazone Compounds of Butane-2,3-dione

4.1 Abstract

In this chapter I have discussed polymorphism and inclusion properties of two new bis-hydrazone compounds, 2,3-bis[2-bis{4-(dimethylamino)phenyl}methylene] hydrazone of butane-2,3-dione (**DMBHB**) and 2,3-bis[2-(ditolylmethylene)hydrazone] of butane-2,3-dione (**DTBHB**) (**Scheme 4.1**). Although, both **DMBHB**, **DTBHB** show inclusion properties, ability of inclusion of solvent by first compound is higher than the later. This may be due to different electronic effect of *N*,*N*-dimethyl and methyl groups. **DMBHB** forms varieties of inclusion compounds of large number of solvents while, **DTBHB** forms limited number of inclusion compounds, although same solvents have been used to crystallize both **DMBHB** and **DTBHB**. Two polymorphs of each of these bis-hydrazone compounds have been prepared by solvent mediated crystallization. Inclusion compounds and the polymorphs are characterized by X-ray diffraction and thermal analysis.

4.2 Introduction

Design of host molecule for successful inclusion of guest in the crystal lattice depends on various factors described by Edwin Weber in 1991.[1] Weber has shown the importance of shape and symmetry of host molecule for efficient inclusion properties.[2] Non-covalent interactions such as hydrogen bonding interactions between the functional groups present in the host and guest molecules are very much responsible for clathrate formation.[3-7] Bishop has utilized the awkward molecular shape in addition to the functional group like hydroxyl group to design new host molecules.[8] Substituent in the host molecule also determines the inclusion behaviour.[9]

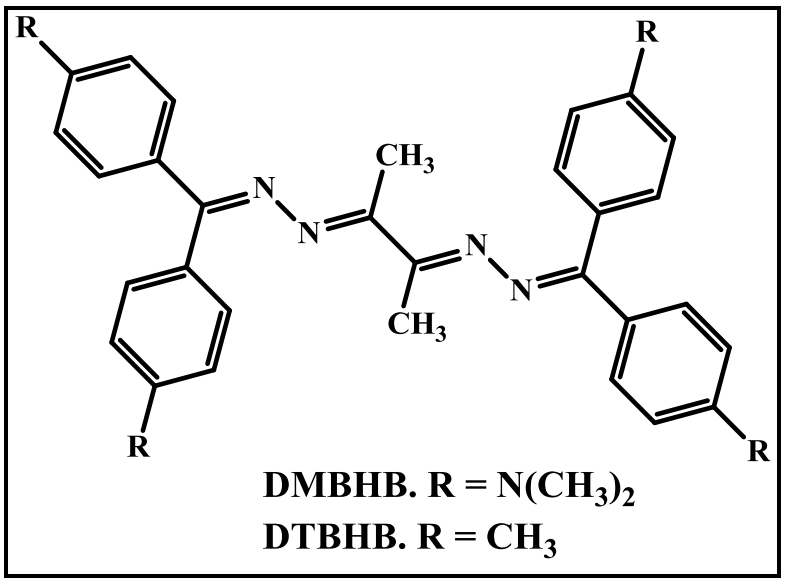
Although polymorphism of host compounds is not uncommon phenomenon, sometime it is very difficult to prepare the polymorphs of particular host molecule by solvent mediated crystallization.[10-13] Because, the host molecule always tends to include the solvent molecule in which the host is crystallized. Polymorphism arises due to the difference in intermolecular interactions in the polymorphs.[14-16] The difference in intermolecular interactions may occur due to conformational differences in the molecule,[17,18] although various crystallization conditions such as temperature, supersaturation, seeding strategy, agitation and cooling rate, solvent, additives, and pH influence the formation of different solid forms.[19,20] Therefore, some innovative crystallization methods have been employed to prepare the polymorphs of some host compounds.[13,21-24]

Large number of organic compounds are reported for inclusion phenomenon as well as polymorphism.[13,25-30] But, very few of them are known for the formation of series of inclusion compounds. Barnett *et al*. have reported six solvates of o-acetamidobenzamide,[31] 1,1-bis(4-hydroxyphenyl)cyclohexane forms seven solvates,[32-35] Das and Barbour have reported eight solvates of hexakis(4-Cyanophenoxy)benzene,[36,37] nine solvates of diethylstilbestrol were reported by Görbitz and Hersleth.[38] Olanzapine, an antipsychotic drug produced 56 crystalline solvates and three polymorphs.[39] Sulfathiazole, a sulfadrug used as antibiotics exhibits 100 solvates[40] and five polymorphs.[41-48] Similarly Gossypol, a biologically active phenolic pigment, shows exceptional clathrate formation ability. Record number of 110 inclusion compounds and seven polymorphs of gossypol have been prepared till date.[49-51]

Solvent molecules have critical role in the formation of inclusion compounds. P. van der Sluis and J. Kroon have described three main functions of solvent molecules in the inclusion compounds.[52] Solvent molecules act as (i) participants in hydrogen-bonding networks;[52-57] (ii) as space fillers, with no strong interactions between solvent and solute molecules;[40,58,59] and (iii) as ligands completing the coordination around a metal ion. In the context of inclusion compounds of organic material, solvent molecules mostly show either one of the first two functions.

Host molecule also have certain features for the formation of large number of solvates. Conformational flexibility and presence of multiple number of hydrogen bonding functional groups are two important structural requirements for host molecule for efficient solvation ability.[50] This chapter deals with the inclusion property of two new host compounds 2,3-bis[2-bis{4-(dimethylamino)phenyl}methylene]hydrazone of butane-2,3-dione (**DMBHB**) and 2,3-bis[2-(ditolylmethylene)hydrazone] of butane-2,3-dione (**DTBHB**) (see **scheme 4.1**) prepared by Schiff base condensation reaction. **DTBHB** and **DMBHB** compounds were synthesised to study the inclusion property of these two compounds. Among all the bis-hydrazone compounds prepared in our laboratory **DMBHB** is very unique Schiff base product, which has tremendous solvate formation ability. **DMBHB** forms varieties of inclusion compounds by crystallization in large number of solvents available in our laboratory. On the other hand, limited number of solvates or no solvate formation took place when **DTBHB** and other bis-hydrazone compounds (described in previous chapters) were crystallized in same solvents as these were used for **DMBHB**. In this chapter total twelve solvates of

DMBHB and four solvates of **DTBHB** have been described. Apart from solvate formation, two polymorphs for both **DMBHB** and **DTBHB** have been prepared and characterized. Other than inclusion compounds, two polymorphs of each of the host compounds have been prepared by solvent mediated crystallization and characterized by X-ray diffraction and thermal analysis. In case of **DTBHB**, two polymorphs were found concomitantly in some solvents in two different colour.



Scheme 4.1 Molecular structure of 2,3-bis[2-bis{4-(dimethylamino)phenyl}methylene] hydrazone of butane-2,3-dione (**DMBHB**) and 2,3-bis[2-(ditolylmethylene)hydrazone] of butane-2,3-dione (**DTBHB**).

4.3 Results and Discussion

4.3.1 Inclusion Compounds of DTBHB

Pure as-synthesized compound of **DTBHB** has been crystallized in various solvents in order to study the inclusion property (see the list of solvents in **Table 4.5**). Total 40 solvents were used for crystallization of **DTBHB**. But inclusion compounds of **DTBHB** have been isolated only from dichloromethane, chloroform, *o*-xylene and *p*-xylene. These four solvates are designated as **DTBHB•DCM**, **DTBHB•$CHCl_3$**, **DTBHB•*o*-Xylene** and **DTBHB•*p*-Xylene**. All of these solvates have been characterized by Single Crystal X-ray Diffraction (SCD) study and Thermogravimetric analysis (TGA).

4.3.1.1 Crystal Structures of Inclusion Compound, DTBHB•$CHCl_3$

DTBHB forms inclusion compound of $CHCl_3$ by slow evaporation of chloroform solution of **DTBHB**. The inclusion compound crystallizes in $P\bar{1}$ space group with 1 : 1 host to guest ratio. The asymmetric unit consists of a full molecule of **DTBHB** and a full molecule of $CHCl_3$. Two terminal carbons of the conjugated spine in the molecule is out of plane of N−N=C(CH_3)−C(CH_3)=N−N unit, making awkward shape of the molecule (see **Table 4.9** for torsion angle and dihedral angle between the mean plane of terminal phenyl rings). In the crystal structure, molecules are connected by weak C─H···π hydrogen bonds forming a layer parallel to *ac* plane (**Figure 4.1**). Hydrogen atoms of the methyl substituent in the benzene ring are participating in the formation of C─H···π hydrogen bonding. Two successive layers parallel to each other shifted along [001] direction forming bilayer structure. Solvent molecules are trapped in between two bilayers (**Figure 4.2**).

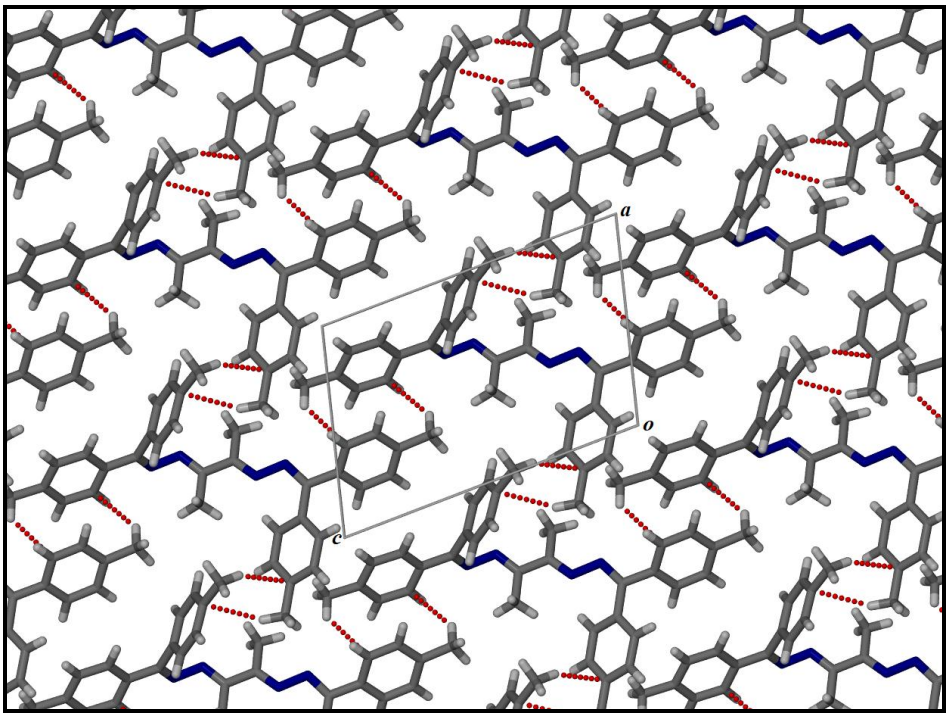


Figure 4.1 Packing diagram of **DTBHB•$CHCl_3$** viewed down *b* axis. Molecules are connected by C─H···π hydrogen bonds shown in red dotted line. Solvent molecules have been omitted for clarity.

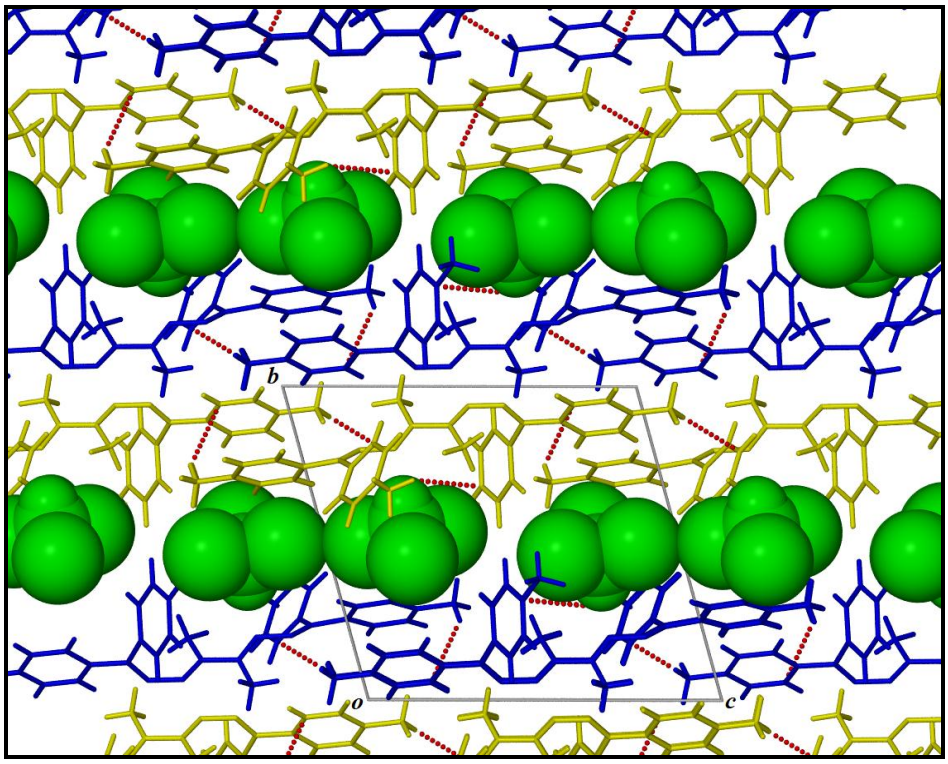


Figure 4.2 Packing diagram of **DTBHB•CHCl$_3$** viewed down *a* axis. Two parallel layers are shown in blue and yellow colour. $CHCl_3$ are shown in green colour. C─H···π hydrogen bonds are shown in red dotted line.

4.3.1.2 Crystal Structures of Inclusion Compound, DTBHB•DCM

Inclusion compound of **DTBHB** with dichloromethane (DCM) crystallizes in the space group *C*2/*c* with half molecule of host and a half molecule of guest in the asymmetric unit. Solvent molecules are disordered in two positions related by two-fold axis of symmetry parallel to *b* axis. Conjugated spine of **DTBHB** molecules are stacked one after another along *c* axis in a criss-cross fashion. Criss-cross arrangement of stacking units forms columns parallel to *b* axis (**Figure 4.3**). In each column, one-dimensional channels are generated parallel to *c* axis. Disordered dichloromethane molecules are situated in these channels. In the columns host molecules are connected by weak C─H···π hydrogen bonds (**Figure 4.4**).

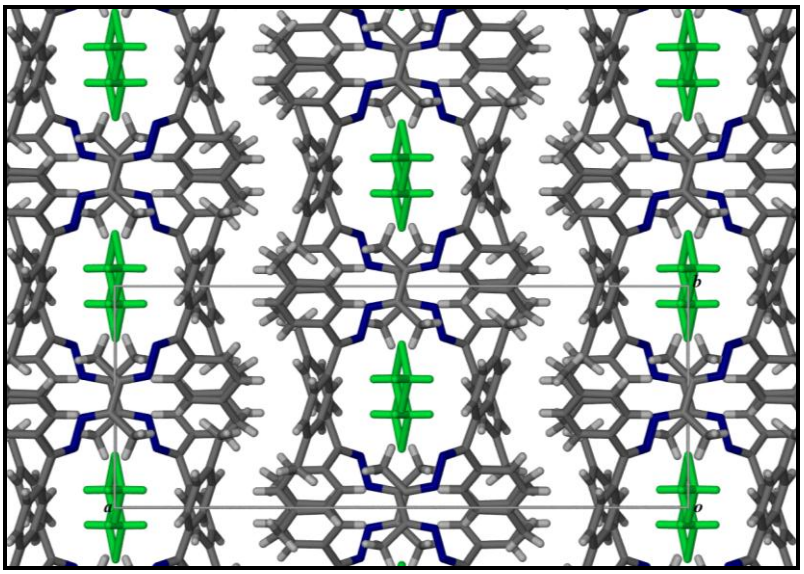


Figure 4.3 Packing diagram of **DTBHB•DCM** viewed down *c* axis. Solvent are shown in green.

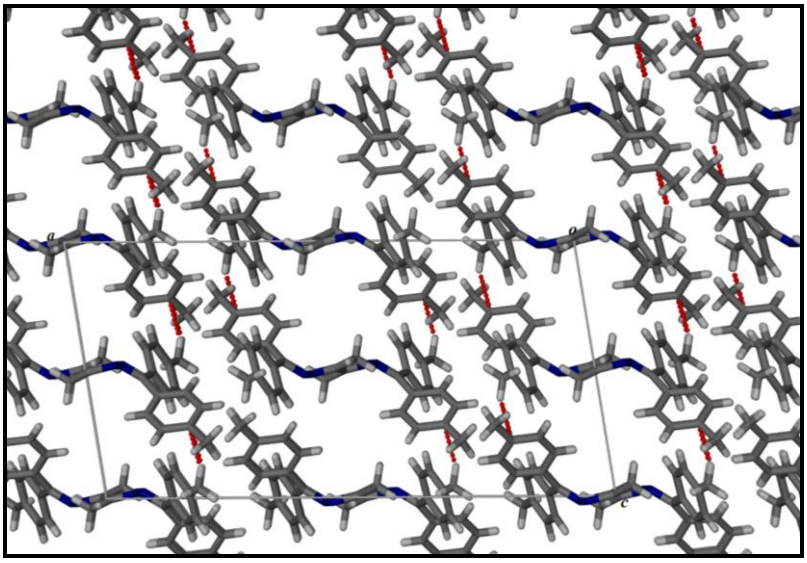


Figure 4.4 Packing diagram of **DTBHB•DCM** viewed down *b* axis. C─H···π hydrogen bonds along *c* axis between host molecules are shown in red dotted line. Solvent molecules are omitted for clarity.

4.3.1.3 Crystal Structure of Inclusion Compound, DTBHB•*p*-Xylene

Crystallization of **DTBHB** in *p*-xylene generates inclusion compound **DTBHB•*p*-Xylene**. This inclusion compound crystallized in $P\bar{1}$ space group with 1 : 2 host to guest ratio consisting of one full molecule of **DTBHB**, one and half molecules of *p*-xylene in the asymmetric unit. **DTBHB** molecules are stacked along *a* axis. Host molecules are connected by C─H···π hydrogen bonds with the *p*-xylene molecules forming columns parallel to *b* axis. One phenyl ring at each terminal of **DTBHB**

molecule is extended outward along the column. This arrangement of the molecules along the columns facilitates the formation of 1D channels running parallel to *a* axis by slight shifting of the adjacent columns along [010] direction. Two sites for the guest molecules have been observed in the crystal structure of **DTBHB•*p*-Xylene**. In one site, *p*-xylene molecules are present in the channels and in other site, the guest molecules are trapped in between the host molecules which are arranged along *b* axis (**Figure 4.5**).

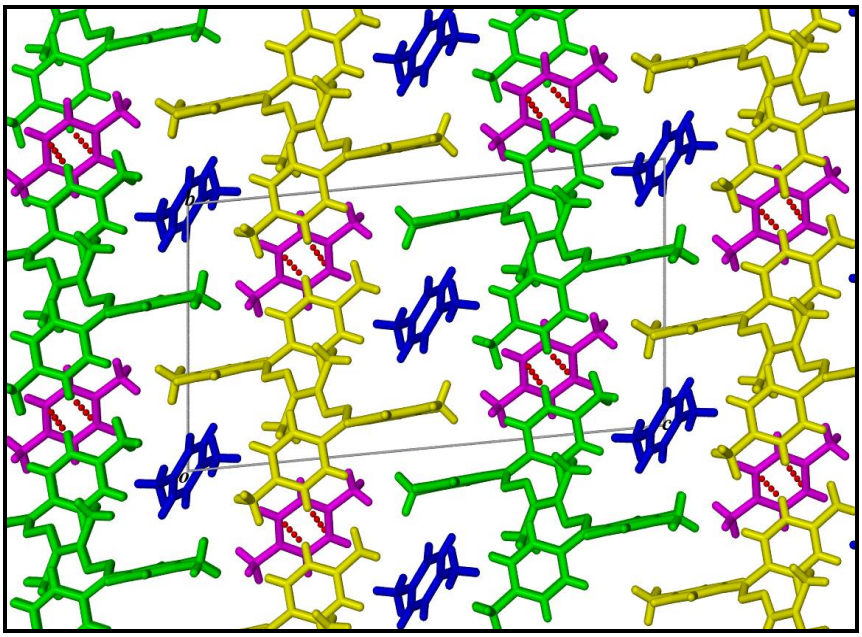


Figure 4.5 Packing diagram **DTBHB•*p*-Xylene** viewed down *a* axis. parallel columns are shown in green and yellow. *p*-Xylene molecules in two different sites are indicated by blue and magenta. C─H···π hydrogen bonds between host and magenta colour *p*-xylene molecules are shown in red dotted line.

4.3.1.4 Crystal Structure of Inclusion Compound, DTBHB•*o*-Xylene

Inclusion compounds of **DTBHB** with *o*-xylene crystallizes in $P\bar{1}$ space group. In the crystal structure of **DTBHB•*o*-Xylene** half molecule of **DTBHB** and two half molecules of *o*-xylene are present in the asymmetric unit making 1 : 2 of host to guest ratio. Both *o*-xylene molecules are disordered in the crystal structure. Packing of the host and guest molecules in the crystal structure of **DTBHB•*o*-Xylene** is almost similar to that in the crystal structure of **DTBHB•*p*-Xylene** (**Figure 4.6**). Molecular columns are formed parallel to *c* axis in this crystal structure.

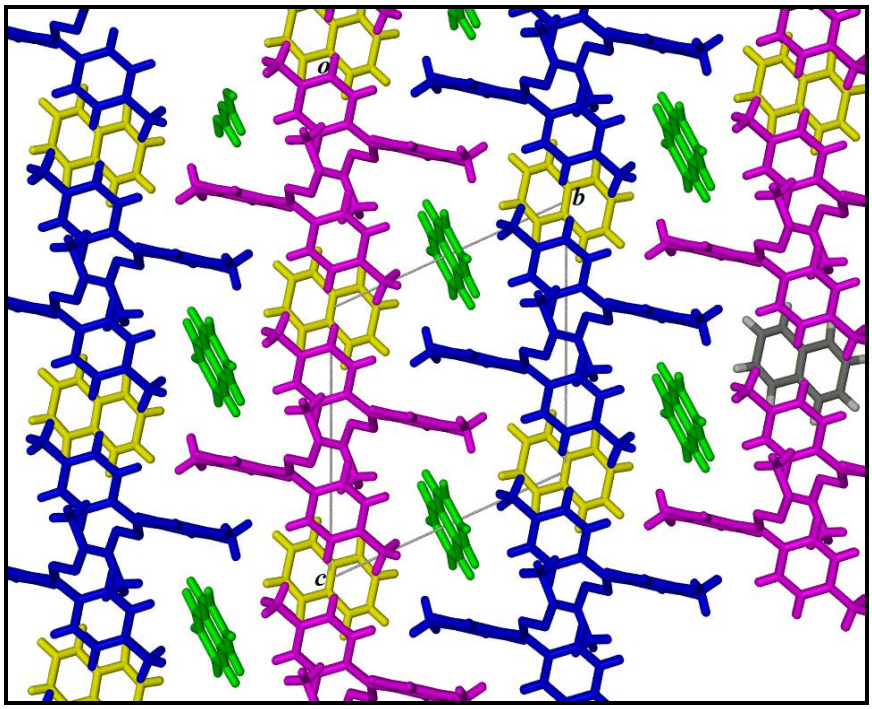


Figure 4.6 Packing diagram **DTBHB•*o*-Xylene** viewed down *a* axis. Parallel columns are shown in blue and magenta. Disordered *o*-Xylene molecules in two different sites are indicated by green and yellow.

4.3.2 Thermal Analysis of DTBHB

4.3.2.1 Thermogravimetric Analysis (TGA) of the Inclusion Compounds DTBHB

TGA were performed for all four inclusion compounds of **DTBHB** to understand the stability and desolvation of the inclusion compounds. TG plots are shown in (**Figure 4.7**). Percentage of mass loss due to desolvation and the host to guest ratio (calculated from TGA and SCD data) are shown in the (**Table 4.1**). In **DTBHB•$CHCl_3$** and **DTBHB•DCM** solvent loss was observed at around 100 °C and 80 °C respectively. This implies that the solvent molecules are bonded with the host molecules. Indeed, in **DTBHB•$CHCl_3$** solvent molecules are connected by C─H···N hydrogen bond (see **Table 4.10** for hydrogen bonding) with the **DTBHB** molecules. Although **DTBHB•DCM** forms channel structure, the solvent molecules are attached with the host molecules by C─H···π hydrogen bonds. In **DTBHB•*p*-Xylene** and **DTBHB•*o*-Xylene** solvent loss were observed at relatively low temperature (around 60 °C). This may be due to very weak interaction between the host and solvent molecules which have been observed in the channel formed by the host molecules as discussed before.

Table 4.1 Percentage of solvent loss and host to guest ratio in the inclusion compound of **DTBHB**

Inclusion compound	Experimental loss of guest (%)	Host to guest ratio calculated from TGA	Host to guest ratio from SCD data
DTBHB•$CHCl_3$	19.9467	1 : 1.035	1 : 1
DTBHB•DCM	13.7931	1 : 0.94	1 : 1
DTBHB•*p*-Xylene	29.5204	1 : 1.97	1 : 2
DTBHB•*o*-Xylene	31.4321	1 : 2.15	1 : 2

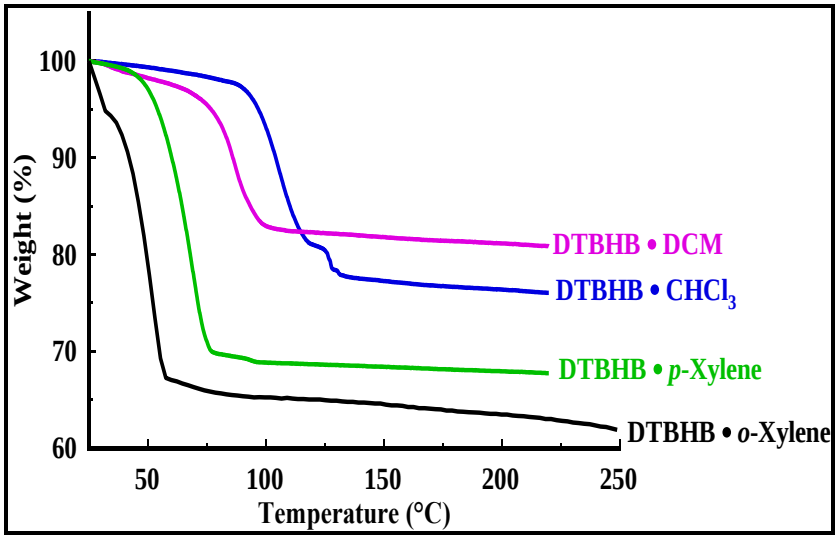


Figure 4.7 Thermogravimetric plot of the inclusion compounds of **DTBHB.**

4.3.2.2 Differential Scanning Calorimetric (DSC) Study of DTBHB

Differential scanning calorimetric analysis of **DTBHB** has been performed to understand the solid state character of the material. First heating segment of DSC thermogram of as-synthesized material indicates no solid to solid phase transformation before melting of the compound (red line in **Figure 4.8**). An exothermic peak was observed at 122 °C upon cooling of the melt phase indicating the crystallization phenomenon (blue line in **Figure 4.8**). Polymorphic nature of **DTBHB** has been confirmed by the observation of a small endothermic peak at 152 °C followed by melting at 165 °C during reheating of the compound (green line in **Figure 4.8**). DSC experiment implies that there are at least two polymorphs of **DTBHB** present. Indeed, two polymorphs have been prepared by solvent mediated crystallization. **Form-I** of

DTBHB can be prepared by crystallization in various solvents (see **Table 4.5**). Whereas **Form-II** has been isolated concomitantly with **Form-I** by crystallization of DTBHB only in DMSO, 1,4-dioxane and nitrobenzene. **Form-I** and **Form-II** of **DTBHB** can be distinguished visually due to different colour of these two polymorphs: **Form-I** is Red and **Form-II** is light yellow (**Figure 4.9**).

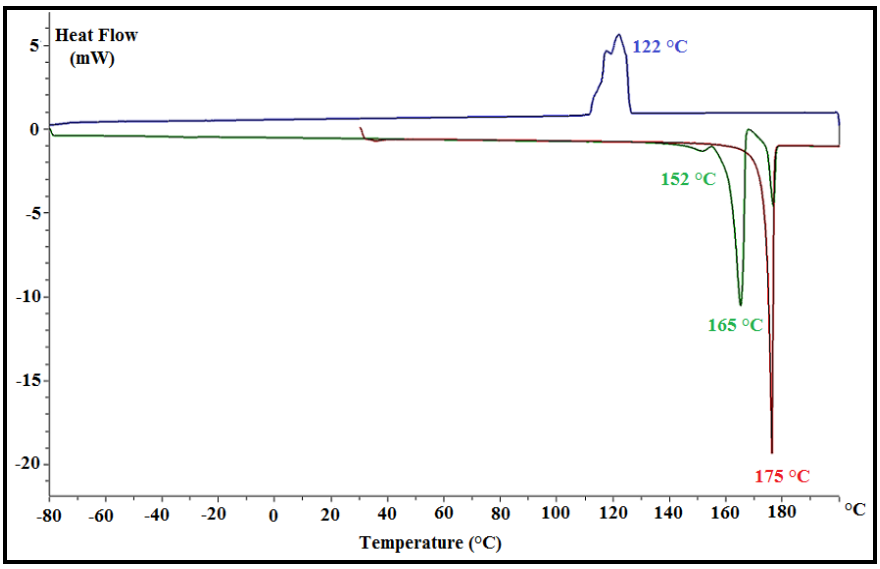


Figure 4.8 DSC thermogram of as-synthesized material of **DTBHB**. Red line shows the first heating segment. Blue line indicates cooling of the melt phase and green line shows the second heating segment.

4.3.3 Polymorphism of DTBHB

Polymorphic nature of **DTBHB** was found in the DSC experiment described before. DSC thermogram of **DTBHB** (**Figure 4.8**) shows that at least two polymorphs are present for this compound. First polymorph, **DTBHB-I** has been isolated as Red colour crystals during crystallization in various solvents (see **Table 4.5**). Light yellow colour second polymorph **DTBHB-II** was prepared concomitantly with **DTBHB-I** by crystallization of as-synthesized materials of **DTBHB** in DMSO, 1,4-dioxane and nitrobenzene. These polymorphs were characterized by SCD and PXRD.

Figure 4.9 Concomitant formation of **DTBHB-I** and **DTBHB-II**. Red crystals stand for **DTBHB-I** and Light yellow crystals indicate **DTBHB-II**.

4.3.3.1 Crystal Structure of Polymorph DTBHB-I

Crystal structure of Red polymorph **DTBHB-I** was solved in $P\bar{1}$ space group with two half molecules in the asymmetric unit. Conformation of the two molecules are different. The torsion angles of **(**−C=N−N=C−**)** unit in two symmetry independent molecules are 156.20 º and 123.99 º. Dihedral angle between the mean planes of the terminal phenyl rings in two symmetry independent molecules are 56.89 º and 66.47 º. Symmetry independent molecules from zigzag chains and columns parallel to *b* axis. The chains and columns are arranged one after another parallel to *b* axis. Molecules are stacked along *a* axis. Molecules are connected by C─H···π hydrogen bonds along the direction of chains and columns (**Figure 4.10**).

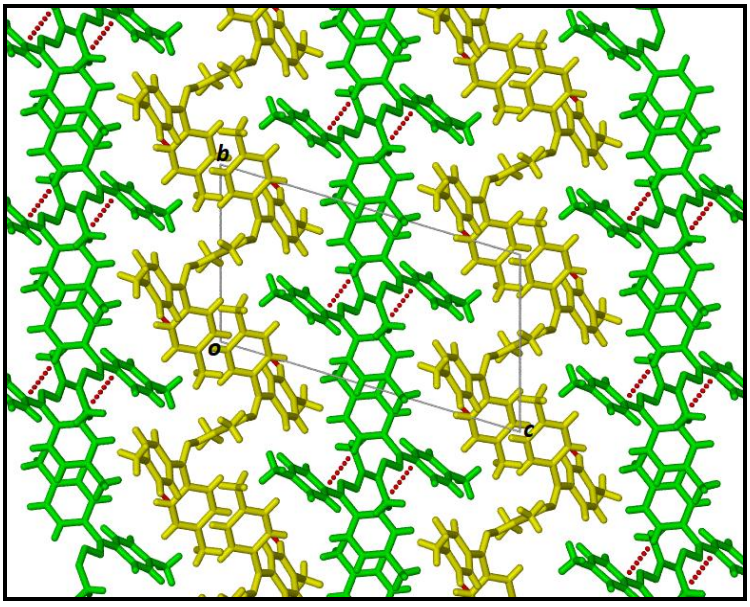


Figure 4.10 Packing diagram of molecules of **DTBHB-I** viewed down *a* axis. Chains and columns formed by two symmetry equivalent molecules are shown in yellow and green. Hydrogen bonds are shown in red dotted line.

4.3.3.2 Crystal Structure of Polymorph DTBHB-II

Crystal structure of **DTBHB-II** is completely different than that of **DTBHB-I**. Second polymorph of **DTBHB** was crystallized in noncentrosymmetric space group *P*1 consisting of a full molecule in the asymmetric unit. The torsion angles of **(**−C=N−N=C−**)** unit are 115.89 º and 104.07 º and dihedral angle between the mean planes of the terminal phenyl rings are 78.84 º and 67.88 º. Molecules, connected by C─H···π hydrogen bonds, are stacked along *a* axis. The stacking units are arranged in such a way to form zigzag chains along [001] direction. The chains are directed parallel to *c* axis (**Figure 4.11**).

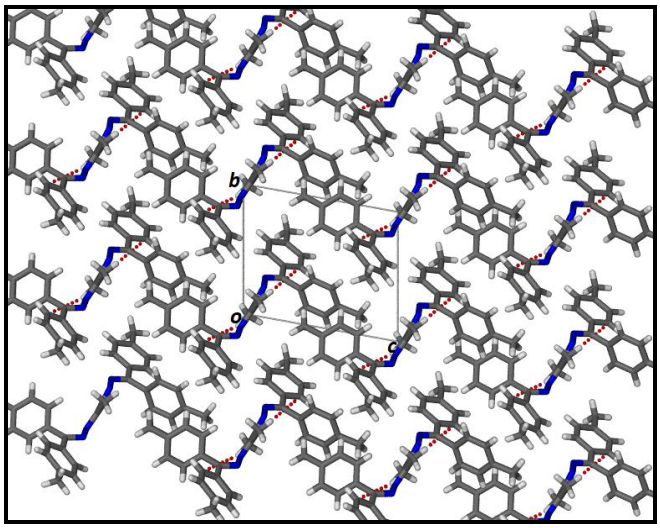


Figure 4.11 Packing diagram of **DTBHB-II** viewed down *a* axis. Hydrogen bonds are shown in red dotted line.

4.3.4 Powder X-ray Diffraction of the Polymorphs of DTBHB

After synthesis of the polymorphs by crystallization, each polymorph has been characterized by Powder X-ray Diffraction (PXRD). Experimental powder diffraction patterns and simulated patterns from single crystal data have been compared. Excellent match between these patterns (**Figure 4.12**) shows that polymorphism of DTBHB can be controlled bycrystallization method.

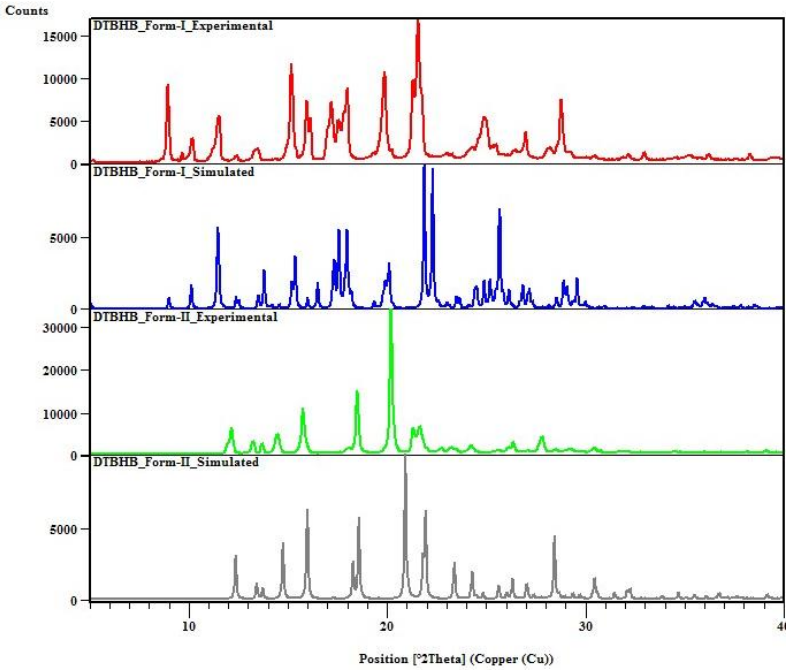


Figure 4.12 Experimental and simulated PXRD pattern of **DTBHB-I** and **DTBHB-II**.

4.3.5 Inclusion Compounds of DMBHB

DMBHB, a versatile host compound, has tremendous ability to form inclusion compounds. **DMBHB** formed 32 inclusion compounds out of 35 solvents used for crystallization (**Table 4.6**). Among 32 inclusion compounds, 12 were characterized by SCD and TGA. After analysis of these 12 crystal structures, the inclusion compounds of **DMBHB** can be classified into two broad categories on the basis of the arrangement of the host molecules in the crystal structure: columnar architecture and grid architecture. Columnar structures have been found in the inclusion compounds of **DMBHB** generated in $CHCl_3$, CH_2Cl_2, acetone, pyridine, THF, morpholine and in 1,4-dioxane (DIOX). Whereas solvent of all the aromatic hydrocarbon except mesitylene used in the crystallization such as benzene, *o*-xylene, *m*-xylene, *p*-xylene and toluene form inclusion compounds with grid structures.

4.3.5.1 Crystal Structures of Inclusion Compounds of DMBHB with Columnar Architecture

DMBHB molecules haves been organized in columnar fashion in the crystal structures of the inclusion compounds **DMBHB•$CHCl_3$**, **DMBHB•DCM**, **DMBHB•Acetone, DMBHB•Pyridine, DMBHB•THF**, **DMBHB•Morpholine**, **DMBHB•DIOX**. Crystal structure of all of these inclusion compounds were solved in $P\bar{1}$ space group.

DMBHB•$CHCl_3$ was crystallized with 1 : 2 host to guest ratio consisting of half molecule of host and a full molecule of guest in the asymmetric unit. **DMBHB** molecules are stacked upon one another along *a* axis. C─H···π hydrogen bonding is observed within these stacked molecules. These stacked molecules are arranged in columnar fashion along [010]. Columns are organized parallel to *b* axis creating voids parallel to *a* axis. Chloroform molecules, connected by weak C─H···N hydrogen bonds with the host molecules, have been found in the voids (**Figure 4.13**).

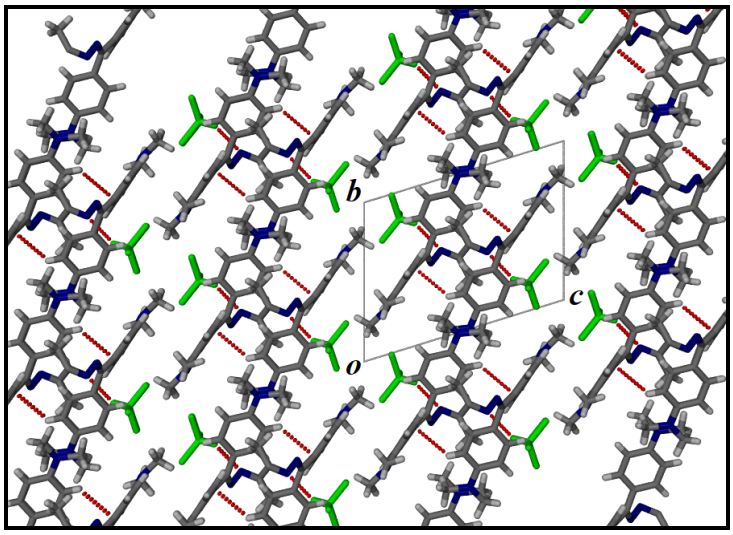


Figure 4.13 Packing diagram of **DMBHB•$CHCl_3$** viewed down *a* axis. Solvent molecules are shown in green. Hydrogen bonds are shown in red dotted line.

Crystal structures of both **DMBHB•CH_2Cl_2** and **DMBHB•Acetone** consist of half molecule of host and a full molecule of guest in the asymmetric unit. Acetone molecules have been found to be disordered in the crystal structure of **DMBHB•Acetone**. There are close similarities in unit cell parameters between the crystal structures of **DMBHB•$CHCl_3$**, **DMBHB•CH_2Cl_2** and **DMBHB•Acetone**. Packing of the host and guest molecules are also almost similar. Therefore, the crystal structures of **DMBHB•CH_2Cl_2** (**Figure 4.14**) and **DMBHB•Acetone** (**Figure 4.15**) are isostructural with that of **DMBHB•$CHCl_3$** (**Figure 4.13**).

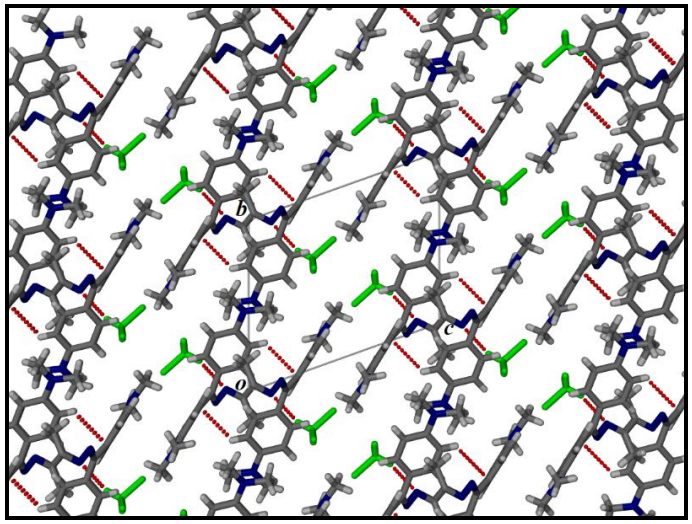


Figure 4.14 Packing diagram of **DMBHB•CH_2Cl_2** viewed down *a* axis. Solvent molecules are shown in green. Hydrogen bonds are shown in red dotted line.

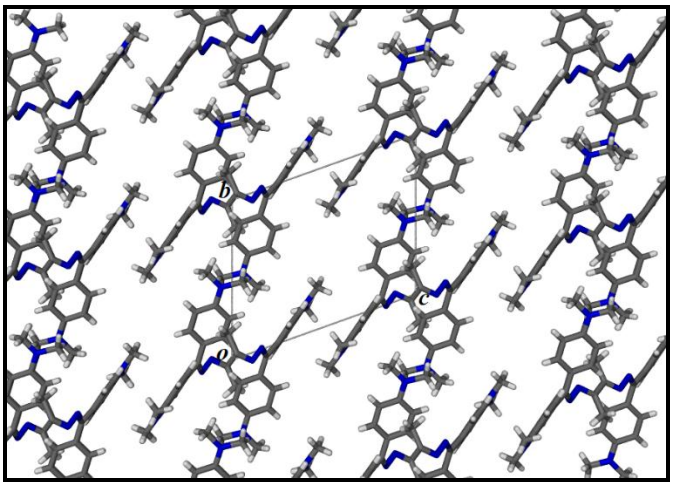


Figure 4.15 Packing diagram of **DMBHB•Acetone** viewed down *a* axis. Solvent molecules have been omitted due to severe disorder.

Similarly**,** crystal structures of **DMBHB•THF** and **DMBHB•Pyridine** are isostructural in terms of unit cell parameter as well as packing of host and guest molecules**.** In both the crystal structure, half molecule of host and a full molecule of guest are present in the asymmetric unit. In case of **DMBHB•Pyridine** structure pyridine molecule is disordered in two positions. **DMBHB** molecules, connected by C─H···π hydrogen bonds are stacked along *a* axis. The stacked units form columns parallel to *b* axis (**Figure 4.16** and **4.17**).

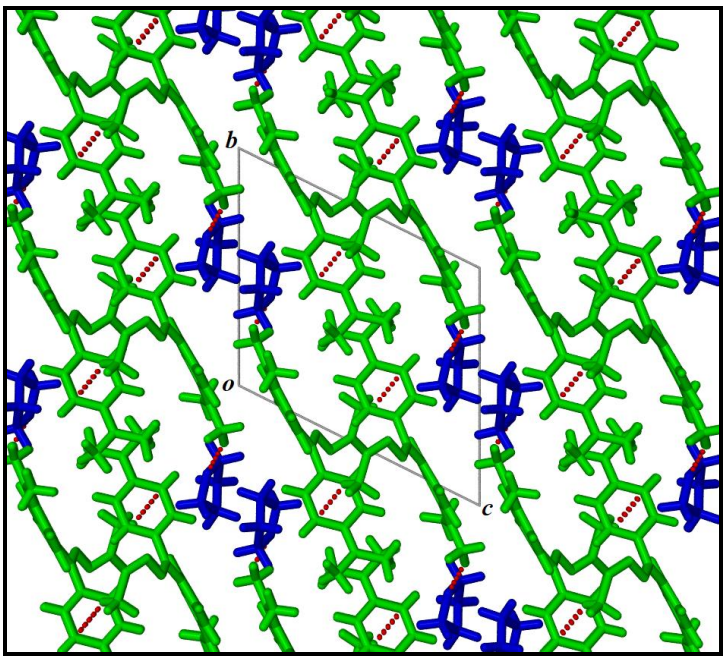


Figure 4.16 Packing diagram of **DMBHB•THF** viewed down *a* axis. THF molecules are shown in blue.

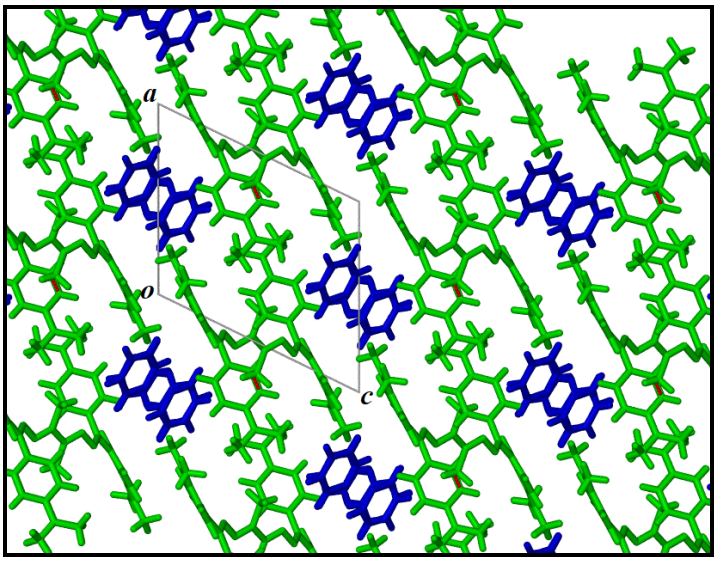


Figure 4.17 Packing diagram of **DMBHB•Pyridine** viewed down *a* axis. Solvent molecules are shown in blue.

DMBHB compound includes 1,4-dioxane (**DIOX**) in the crystal lattice with 1 : 1 host to guest ratio. Half molecule of each of host and guest are present in the asymmetric unit. Host molecules are stacked along *a* axis. The stacked molecules are connected by weak C─H···π hydrogen bond forming a columnar array. Adjacent columns are connected by C─H···π hydrogen bond generating voids parallel to *a* axis. The voids are occupied by **DIOX** molecules (**Figure 4.18**).

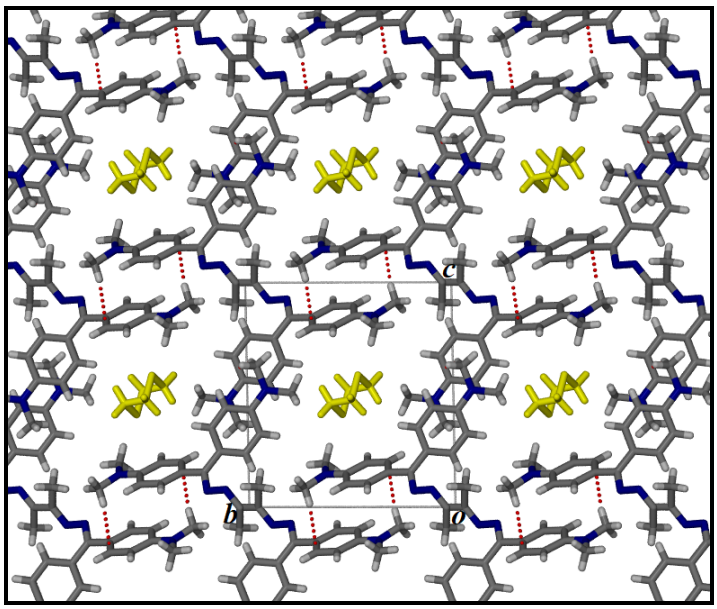


Figure 4.18 Packing diagram of **DMBHB•DIOX** viewed down *a* axis. 1,4-Doixane molecules are shown in yellow. C─H···π hydrogen bonds are shown in red dotted line.

Crystal structure of **DMBHB•Morpholine** is different from other inclusion compounds of **DMBHB** within the series of columnar architecture, although columnar arrangement of host molecules is also observed in **DMBHB•Morpholine**. Host to guest ratio in this crystal structure is 1 : 2. Similar to previously described structures, host molecule **DMBHB**, connected by C─H···π hydrogen bonds, are stacked along *a* axis. Morpholine molecules are present in voids generated by parallel arrangement of columns formed by the stacking units of **DMBHB** molecules (**Figure 4.19**). Guest molecules are inter-connected with each other by N─H···O and N─H···N hydrogen bonds. (see **Table 4.10** for hydrogen bonding parameters) Morpholine molecules are also connected with the **DMBHB** molecules by C─H···O hydrogen bonds.

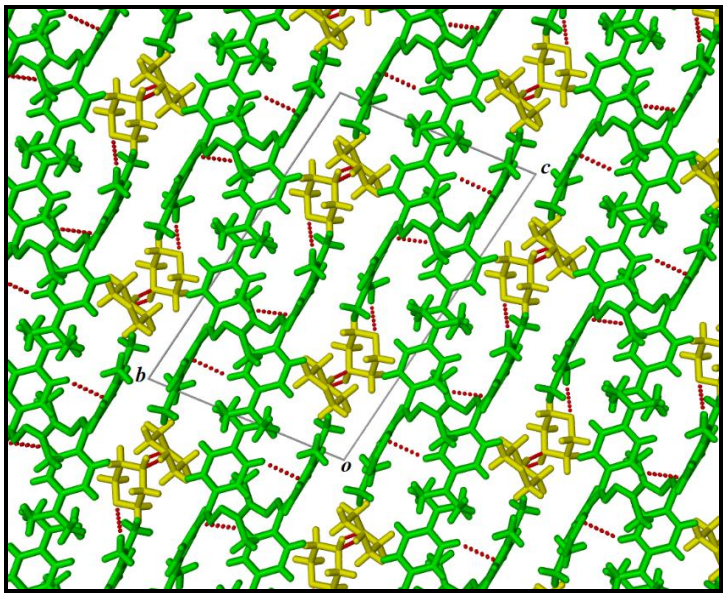
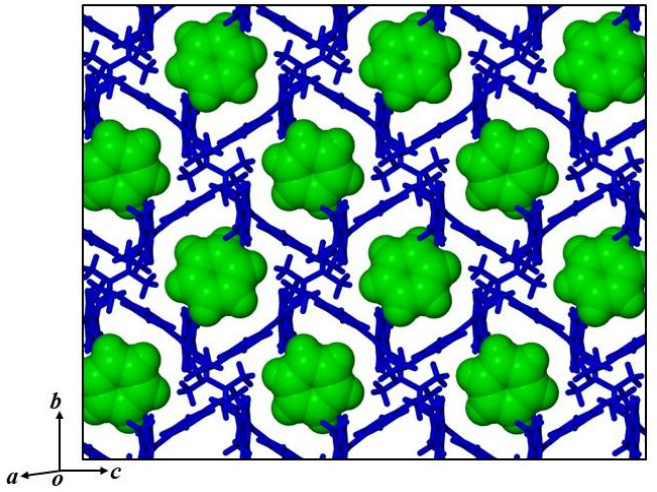


Figure 4.19 Packing diagram of **DMBHB•Morpholine** viewed down *a* axis. **DMBHB** and morpholine molecules are shown in green and yellow colour respectively. Hydrogen bonds are shown in red dotted line.

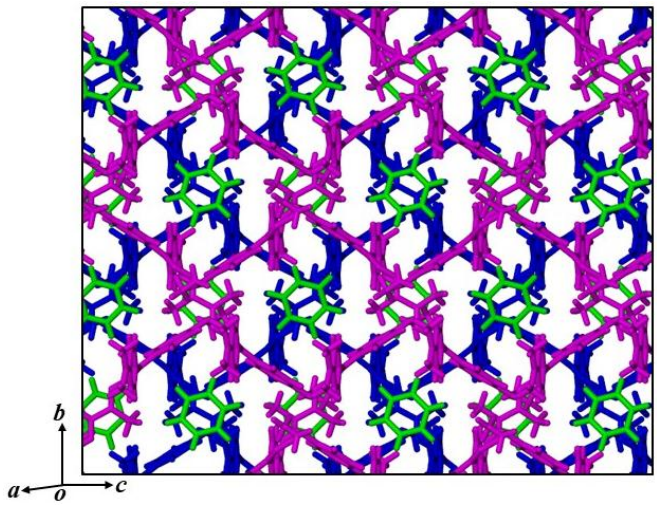
4.3.5.2 Crystal Structures of Inclusion Compounds of DMBHB with Grid Architecture

Compound **DMBHB** generates inclusion compounds in some aromatic hydrocarbon solvents like benzene, *o*-xylene, *p*-xylene, *m*-xylene and toluene. In the crystal structure of all these inclusion compounds **DMBHB** forms grid architecture. Benzene inclusion compounds of **DMBHB** was formed in 1 : 1 host to guest ratio. The crystal structure was solved in monoclinic space group *C*2/*c* with the presence of half molecule of both **DMBHB** and benzene in the asymmetric unit. Arrangement of

DMBHB molecules in the crystal structure of **DMBHB•Benzene** forms square grid architecture parallel to *bc* plane. The grids are filled by benzene molecules (**Figure 4.20a**). Adjacent square grids, parallel to each other, are offset to each other in order to make efficient packing and to avoid the host-host repulsion (**Figure 4.20b**). This also prevents the formation of channel structure. Host molecules are connected by weak van der Waals interaction, whereas benzene molecules are connected by C─H···π hydrogen bonds with **DMBHB** molecules in the square grid.



(**a**)



(**b**)

Figure 4.20 (**a**) Square grid arrangement of **DMBHB** molecules in the crystal structure of **DMBHB•Benzene** viewed down *a* axis. (**b**) Offset arrangement of two adjacent square grids parallel to each other are shown in blue and magenta. Benzene molecules are shown in green.

Inclusion compounds of *o*-xylene, *p*-xylene, *m*-xylene and toluene formed in 1 : 1 host to guest ratio. Crystal structures of these inclusion compounds were solved in $P\bar{1}$ space group except the crystal structure of **DMBHB•*m*-Xylene** which was solved in noncetrosymmetric space group *P*1. In case of **DMBHB•*o*-Xylene** two half molecules of **DMBHB** and two disordered *o*-xylene molecules are present in the asymmetric unit. Asymmetric unit of **DMBHB•*m*-Xylene** consists of two full molecules of **DMBHB** and two full molecules of *m*-xylene one of which is disordered. Whereas in both the crystal structures of **DMBHB•*p*-Xylene** and **DMBHB•Toluene** one full molecule and two half molecules of both host and guest are present in the asymmetric unit. Packing of the molecules in the crystal structures of **DMBHB•*o*-Xylene**, **DMBHB•*m*-Xylene**, **DMBHB•*p*-Xylene** and **DMBHB•Toluene** are almost similar.

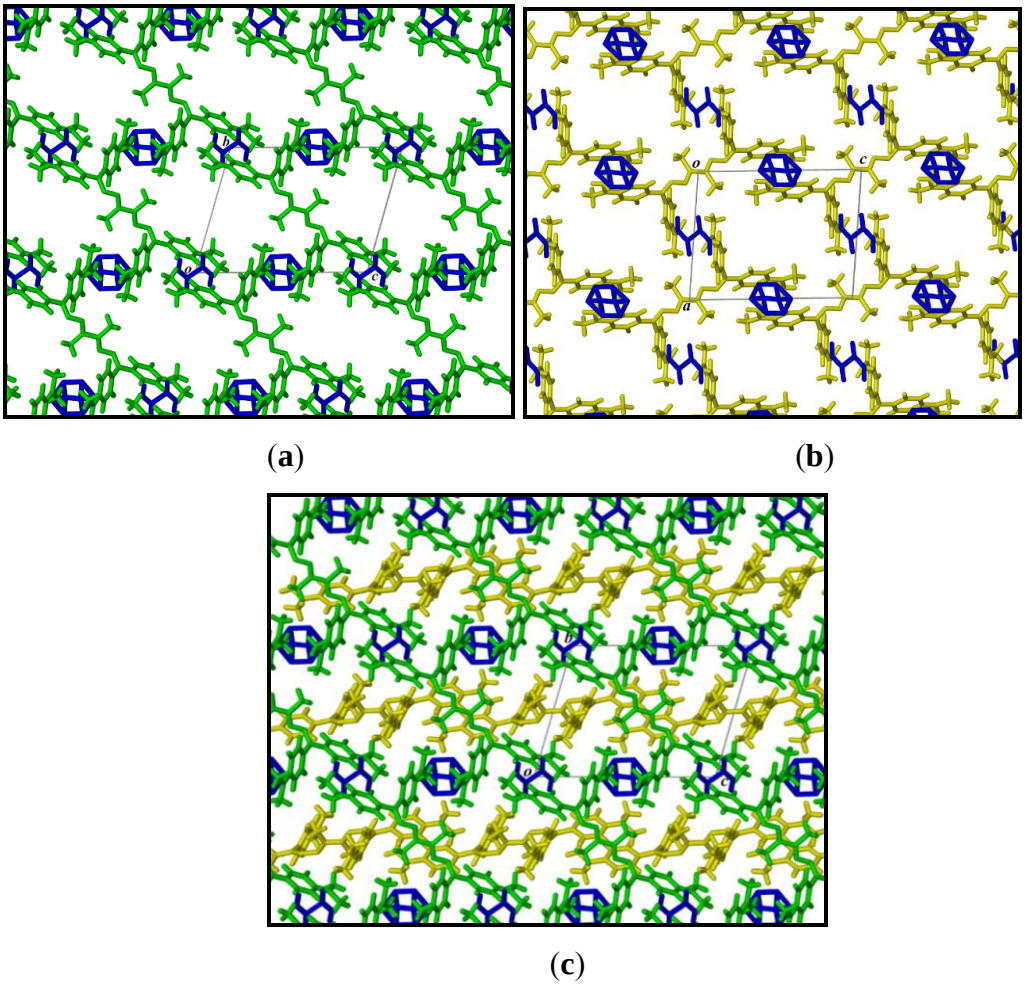
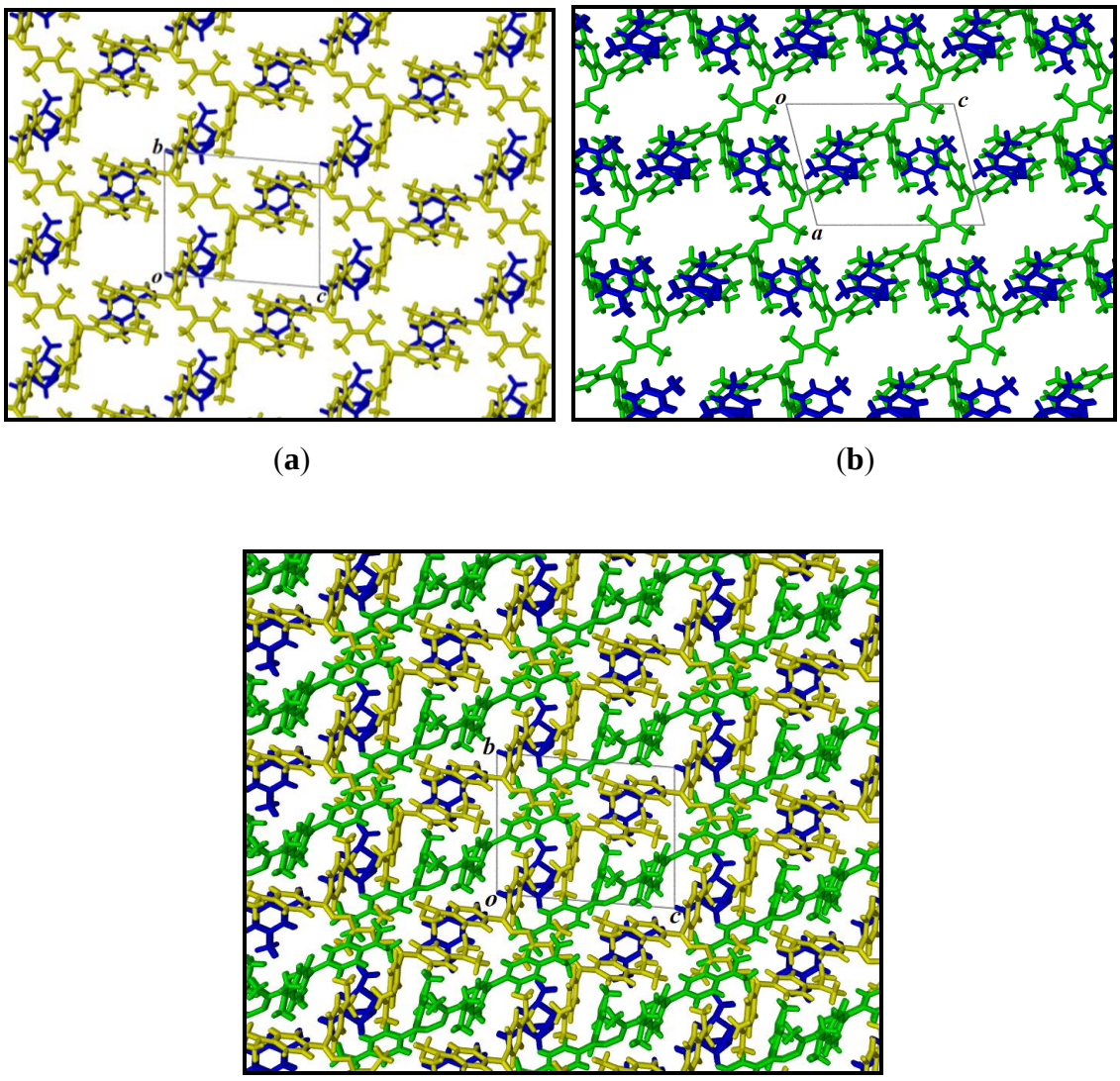


Figure 4.21 (**a**) Crystal structure of **DMBHB•*o*-Xylene** viewed down *a* axis. (**b**) Crystal structure of **DMBHB•*o*-Xylene** viewed down *b* axis. (**c**) Packing diagram of **DMBHB•*o*-Xylene**. Symmetry independent molecules are shown in yellow and green colour. Disordered *o*-xylene molecules have been shown in blue.



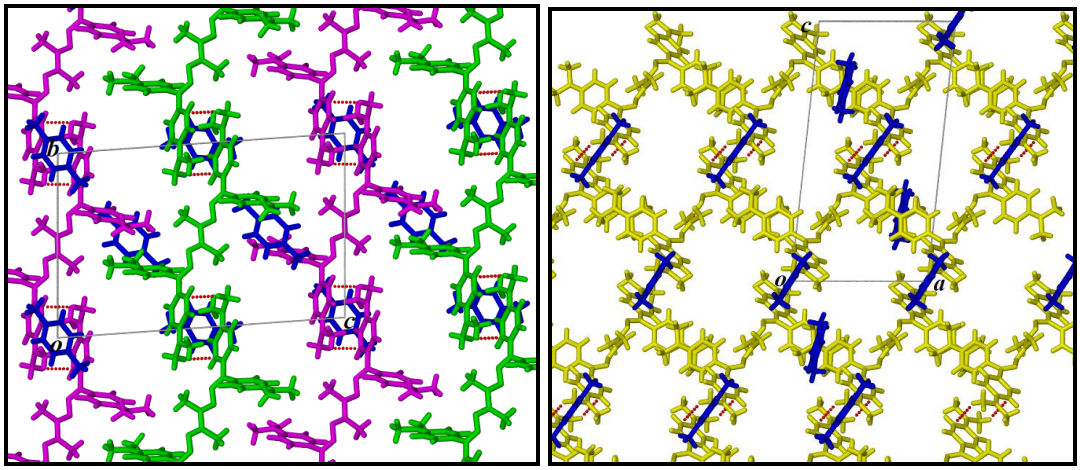
(**a**) (**b**)

(**c**)

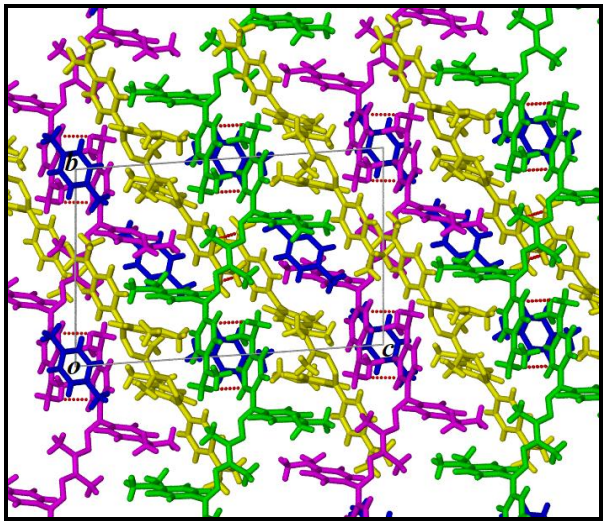
Figure 4.22 (**a**) Crystal structure of **DMBHB•*m*-Xylene** viewed down *a* axis. (**b**) Crystal structure of **DMBHB•*m*-Xylene** viewed down *b* axis. (**c**) Packing diagram of **DMBHB•*m*-Xylene**. Symmetry independent molecules are shown in yellow and green colour. *m*-Xylene molecules have been shown in blue.

Symmetry equivalent molecules in **DMBHB•*o*-Xylene** and **DMBHB•*m*-Xylene** form rectangular grids due to the arrangement of molecules in columnar fashion (Figure **4.21a** and **4.21b** for **DMBHB•*o*-Xylene**; **Figure 4.22a** and **4.22b** for **DMBHB•*m*-Xylene**). Guest molecules have been found in between two parallel grids. Non-parallel rectangular grids, formed by symmetry independent molecules, are interpenetrated each other to create close packed 3D structure (**Figure 4.21c** for **DMBHB•*o*-Xylene** and **Figure 4.22c** for **DMBHB•*m*-Xylene**).

In the crystal structure of **DMBHB•*p*-Xylene** and **DMBHB•Toluene** symmetry equivalent molecules, connected by C─H···π hydrogen bonds, are arranged in columns. Two parallel columns form rectangular grids. Two half molecules of host, present in the asymmetric, form one type of rectangular grid (**Figure 4.23a** for **DMBHB•*p*-Xylene** and **Figure 4.24a** for **DMBHB•Toluene**).



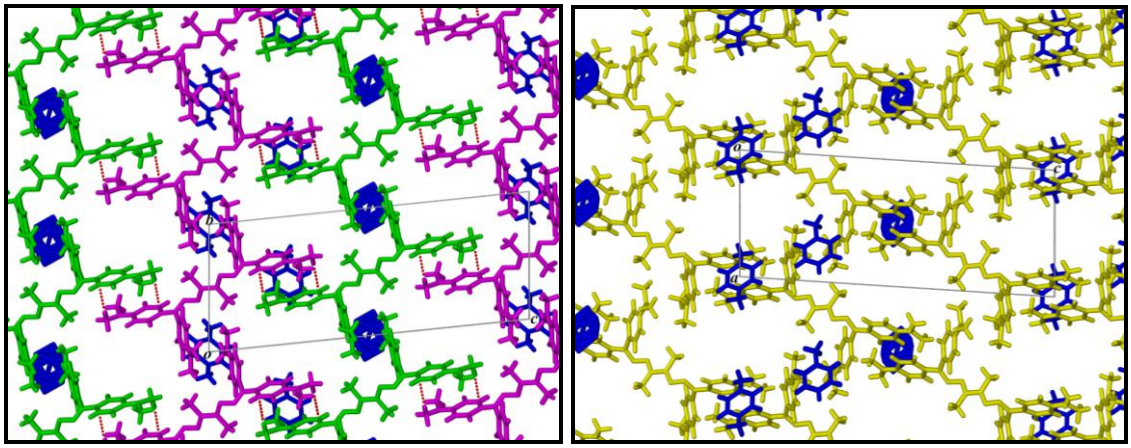
(**a**) (**b**)



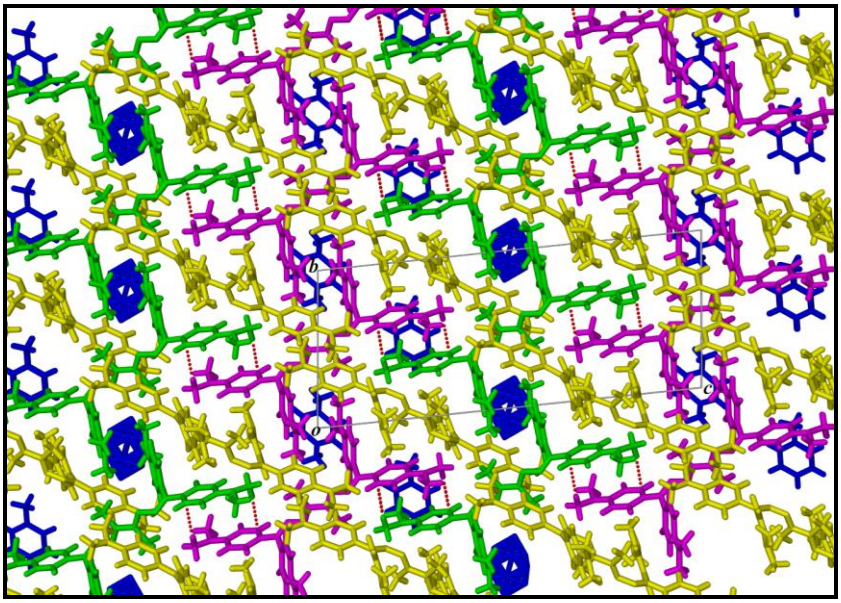
(**c**)

Figure 4.23 (**a**) Crystal structure of **DMBHB•*p*-Xylene** viewed down *a* axis showing the rectangular grid formed by the half molecules of **DMBHB** present in the asymmetric unit. Symmetry independent molecules are shown in magenta and green colour. (**b**) Crystal structure of **DMBHB•*p*-Xylene** viewed down *b* axis showing the rectangular grid formed by the full molecule of **DMBHB** present in the asymmetric unit shown in yellow colour. (**c**) Packing diagram of **DMBHB•*p*-Xylene** viewed down *a* axis showing interpenetration of two different grids. *p*-Xylene molecules are shown in blue colour.

Whereas full molecule of **DMBHB** present in the asymmetric unit also forms another rectangular grid inclined to the previous grid (**Figure 4.23b** for **DMBHB•*p*-Xylene** and **Figure 4.24b** for **DMBHB•Toluene**). These grids are interpenetrated in order to fill the voids in the crystal structure. Guest molecules are trapped between two parallel grids in the crystal structure of **DMBHB•*p*-Xylene** and **DMBHB•Toluene**.



(**a**) (**b**)



(**c**)

Figure 4.24 (**a**) Rectangular grids formed by **DMBHB** molecules in the crystal structure of **DMBHB•Toluene** viewed down *a* axis. Symmetry independent molecules are shown in green and magenta; (**b**) Rectangular grid formed by the full molecule of **DMBHB** present in the asymmetric unit in the crystal structure viewed down *b* axis; (**c**) Overall packing diagram of crystal structure of **DMBHB•Toluene** viewed down *a* axis. Toluene molecules are shown in blue.

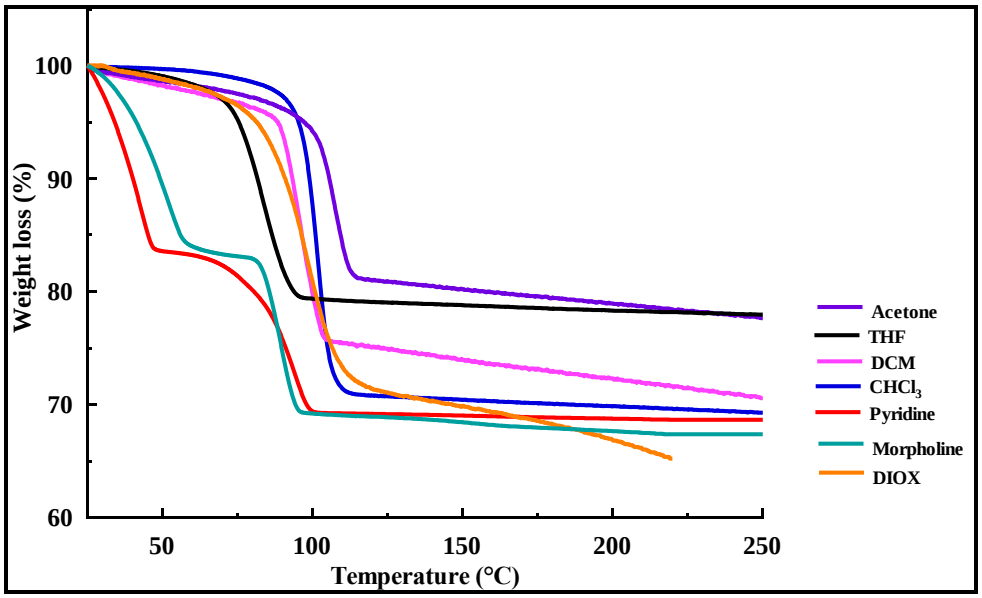
4.3.6 Thermal Analysis of DMBHB

4.3.6.1 Thermogravimetric Analysis (TGA) of the Inclusion Compounds DMBHB

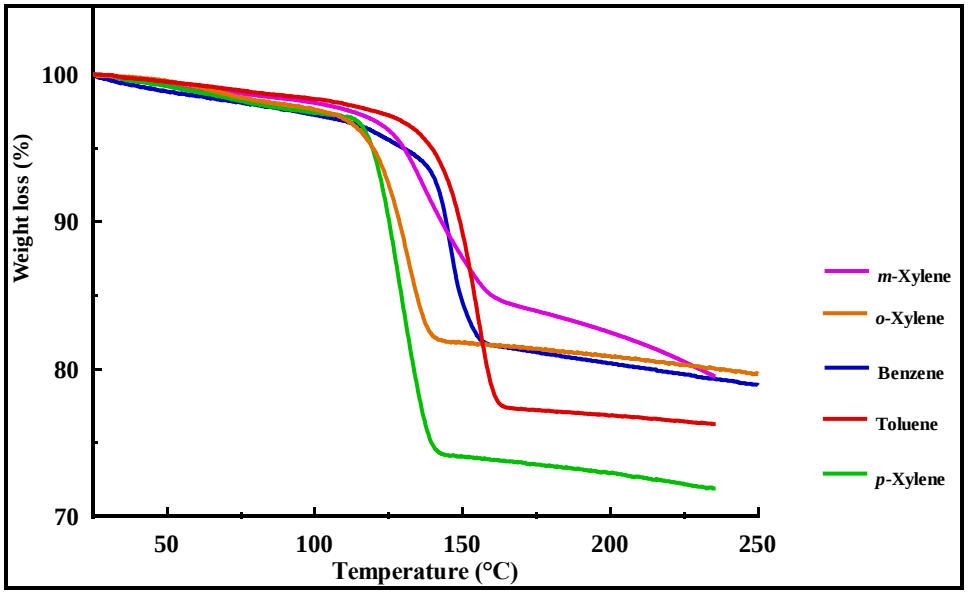
Thermogravimetric analysis of all the inclusion compounds of **DMBHB** was carried out to understand the desolvation phenomenon. Percentage of solvent loss and host to guest ratio is given in (**Table 4.2**). TG plots are shown in (**Figure 4.25a**) and (**Figure 4.25b**). In all the inclusion compounds solvent loss has been observed in one step except in case of **DMBHB•Pyridine** and **DMBHB•Morpholine** (**Figure 4.25a**). First step of solvent loss in these two inclusion compounds can be attributed to evaporation of solvent from the surface of the crystalline materials.

Table 4.2 Percentage of solvent loss and host to guest ratio in the inclusion compound of **DMBHB**

Inclusion Compound	Experimental loss of Guest (%)	Host to Guest ratio calculated from TGA	Host to Guest ratio from SCD data
DMBHB•$CHCl_3$	28.1862	1 : 2.0194	1 : 2
DMBHB•DCM	20.2068	1 : 1.83	1 : 2
DMBHB•Acetone	15.4037	1 : 1.93	1 : 2
DMBHB•THF	19.1349	1 : 2.02	1 : 2
DMBHB•Pyridine	16.7757	1 : 1.57	1 : 2
DMBHB•DIOX	12.6638	1 : 1.01	1 : 1
DMBHB•Morpholine	16.9729	1 : 1.45	1 : 2
DMBHB•Benzene	14.0033	1 : 1.28	1 : 1
DMBHB•*o*-Xylene	16.3410	1 : 1.13	1 : 1
DMBHB•*m*-Xylene	12.4724	1 : 0.82	1 : 1
DMBHB•*p*-Xylene	15.3287	1 : 1.05	1 : 1
DMBHB•Toluene	13.2590	1 : 1.02	1 : 1



(**a**)



(**b**)

Figure 4.25 (**a**) TG plots of the inclusion compounds of **DMBHB** generating columnar structure. (**b**) TG plots of the inclusion compounds of **DMBHB** forming grid architecture.

4.3.6.2 Differential Scanning Calorimetric (DSC) Study of DMBHB

Solid-state nature of **DMBHB** compounds has been analyzed by DSC studies. DSC experiments of as-synthesized materials were carried out by heat-cool-heat method. DSC thermogram is shown in (**Figure 4.26**). Endothermic peak at 240 °C in the first heating segment implies the melting of the compound. No thermal event has been observed during cooling of the melt phase. Exothermic peak at 127 °C during re-

heating of the sample attributes the crystallization followed by an endothermic peak at 235 °C indicating the melting again.

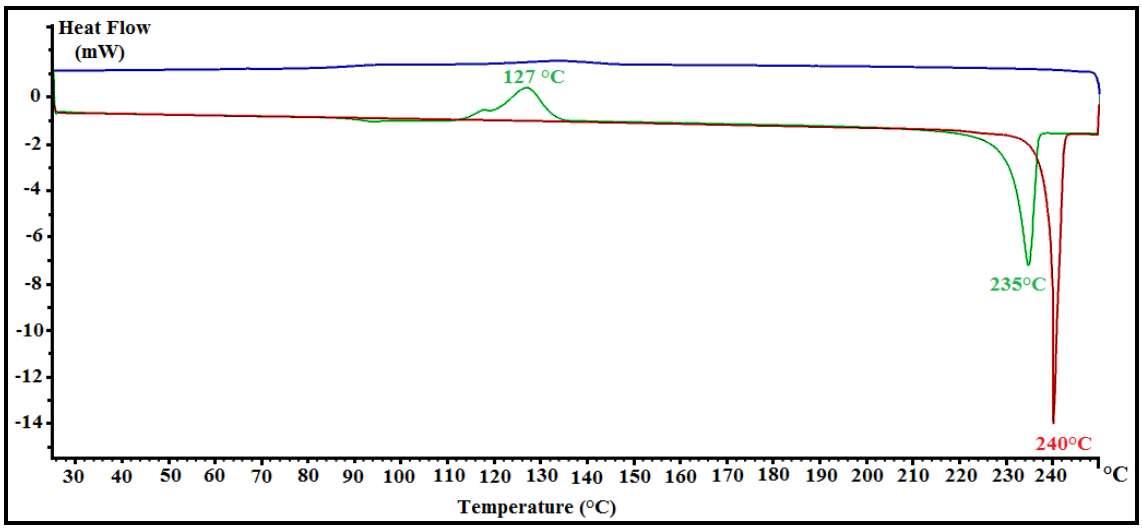


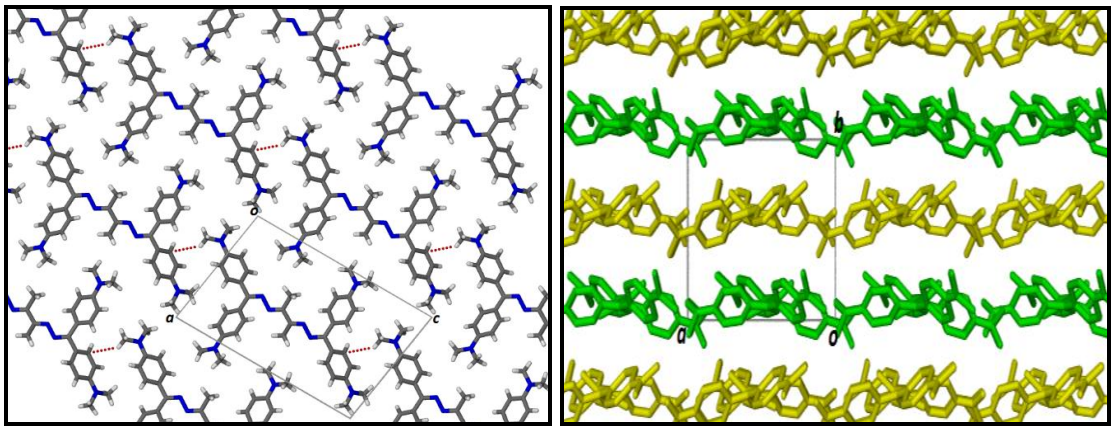
Figure 4.26 DSC thermogram of as-synthesized material of **DMBHB**. Red line indicates the first heating segment, blue line is for cooling of the melt phase and green line implies re-heating.

4.3.7 Polymorphism of DMBHB

Similar to **DTBHB** compounds two polymorphs of **DMBHB** have been isolated by crystallization in two different solvents (**Table 4.6**). **DMBHB-I** has been prepared by the crystallization of as-synthesized materials in ethyl acetate and acetonitrile. Whereas **DMBHB-II** has been obtained from mesitylene solution.

4.3.7.1 Crystal Structures of DMBHB-I

Crystal structure of **DMBHB-I** was solved in $P2_1$ space group consisting of a full molecule of **DMBHB** in the asymmetric unit. Molecules formed uneven 2D sheets parallel to *ac* planes (**Figure 4.27**). Linearly arranged molecules in the sheets are connected by C─H···π hydrogen bonds. These sheets are stacked along *b* axis generating 3D packing arrangement of the molecules.

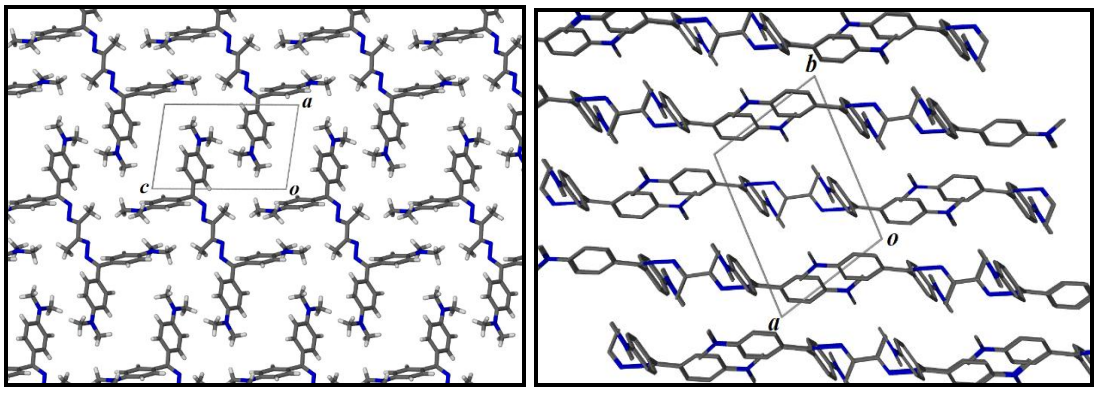


(**a**) (**b**)

Figure 4.27 Packing diagram of **DMBHB-I**. (**a**) Arrangement of **DMBHB** molecules in uneven sheet parallel to *ac* plane. C─H···π hydrogen bonds have been shown in red colour. (**b**) Stacking of uneven sheets along *b* axis. Alternative sheets have been shown in yellow and green. Hydrogen atoms have been removed for clarity.

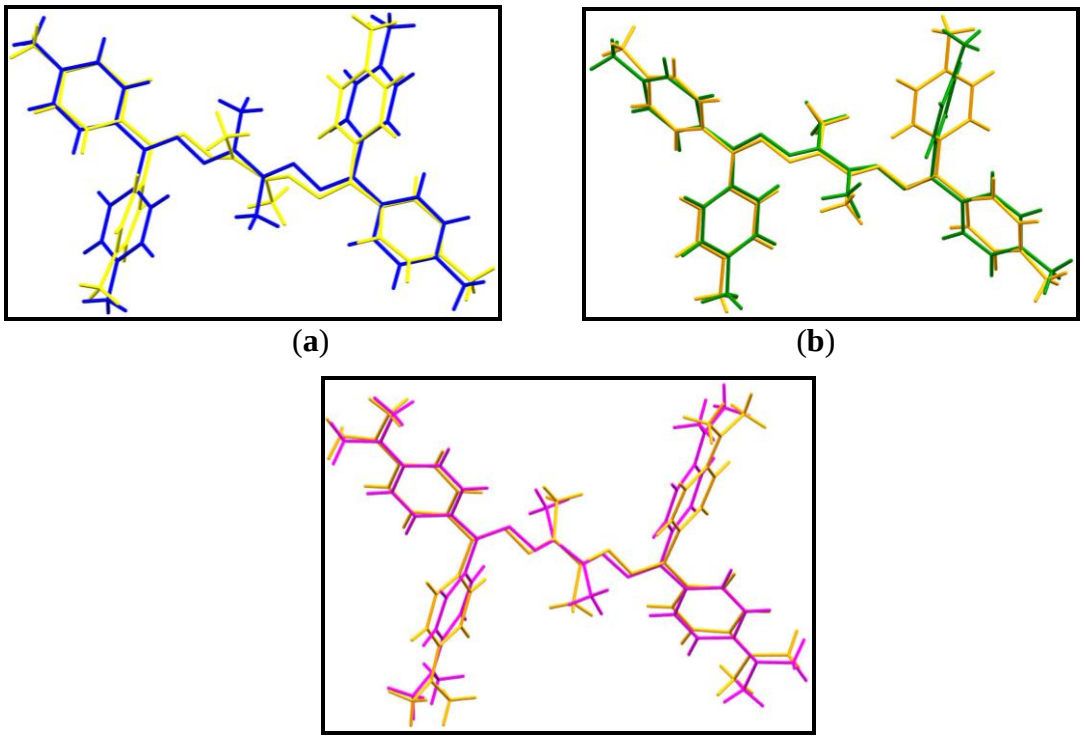
4.3.7.2 Crystal Structures of DMBHB-II

Molecules in the crystal structure of polymorph **DMBHB-II** form layer parallel to (1 -1 0) planes (**Figure 4.28a**). Adjacent layers are offset to each other in order to make close packing structure (**Figure 4.28b**).



(**a**) (**b**)

Figure 4.28. (**a**) A layer formed by **DMBHB-II** molecules parallel to (1 -1 0) planes viewed down *b* axis. (**b**) Stacking of layers parallel to (1 -1 0) planes. Hydrogen atoms have been removed for clarity.



(**a**) (**b**)

(**c**)

Figure 4.29 (**a**) Overlay diagram of the molecular structure of polymorphs **DTBHB-I_1** (blue) and **DTBHB-II** (yellow); (**b**) Overlay diagram of the molecular structure of polymorphs **DTBHB-I_2** (yellow) and **DTBHB-II** (green); (**c**) Overlay diagram of the molecular structure of polymorphs **DMBHB-I** (orange) and **DMBHB-II** (magenta). [**DTBHB-I_1** and **DTBHB-I_2** are molecular structure of two molecules present in the asymmetric unit].

Overlay diagram of the molecular structures of the molecules present in the asymmetric unit of the crystal structures of **DTBHB** and **DMBHB** (**Figure 4.29**) indicates that both the bis-hydrazone compounds exhibit conformational polymorphism.

4.4 Conclusion

Inclusion properties and polymorphism of two new bis-hydrazone compounds, **DTBHB** and **DMBHB** have been studied. The ability of the formation of inclusion compounds has been analyzed by changing substituent on the terminal phenyl ring of bis-hydrazone molecules described in this chapter**.** Crystallization of varieties of solvent showed that **DMBHB** exhibits better ability to form inclusion compounds than that of **DTBHB**. Upon crystallization of these two compounds in same solvents, **DTBHB** formed only four inclusion compounds whereas **DMBHB** formed 32 inclusion compounds out of which twelve inclusion compounds of **DMBHB** have been fully characterized by SCD and TGA and reported in this thesis**.** Analysis of the crystal

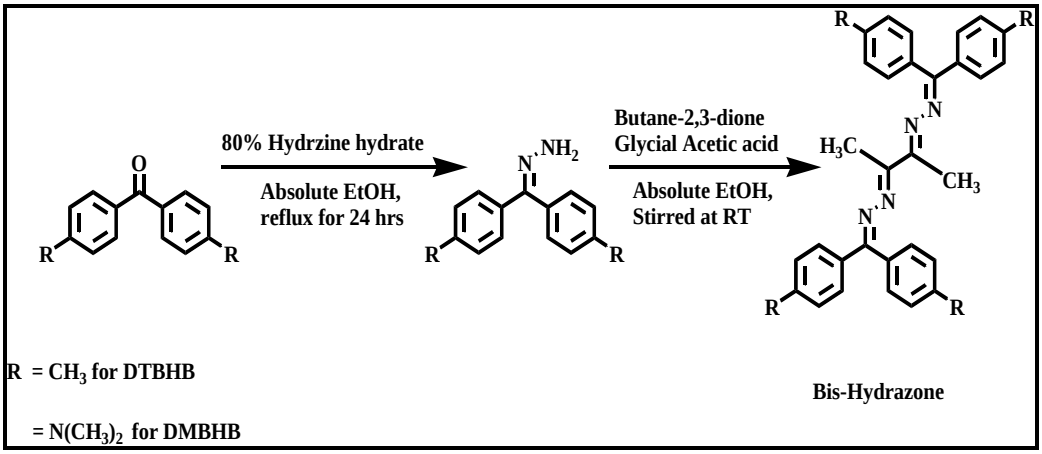
structures of all the inclusion compounds shows that **DMBHB** molecule is more flexible to adopt different conformations than that of **DTBHB**. In other words, *N,N*-Dimethyl group increases the flexibility of **DMBHB**.

In addition to the inclusion property, both **DTBHB** and **DMBHB** exhibit conformational polymorphism. DSC analysis shows the polymorphic nature of these compounds. Two polymorphs of each have been synthesized by solvent mediated crystallization. Crystal structures of all the polymorphs have been determined by Single Crystal X-ray Diffraction method.

4.5 Experimental Section

4.5.1. Synthesis of DTBHB and DMBHB

The starting materials and reagents used for synthesis of **DTBHB and DMBHB** compound were obtained from Alfa Aesar & Sigma-Aldrich and used without further purification. All solvents used in crystallization experiments were reagent grade. ^{1}H NMR spectra were recorded on a 500 MHz Bruker Advance III spectrometer in $CDCl_3$. The bis-hydrazone compounds **DTBHB** and **DMBHB** were synthesized after little modification of the procedure reported in literature.[60] Synthetic procedure has been shown in (**Scheme 4.2**). Some characteristic features of **DTBHB** and **DMBHB** are given in (**Table 4.3**) and (**Table 4.4**) respectively.



Scheme 4.2

Molecular structures were characterized by NMR spectroscopy and Mass spectrometry (MS).

NMR and MS data for compound **DTBHB:**
^{1}H NMR (500 MHz, $CDCl_3$): δ7.610 (d, 4H), δ7.230 (t, 8H), δ7.127 (d, 4H), 2.425 (d, 12H), δ2.022 (d, 6H).

TOF-MS (*m/z*): 499.2500 (100%).

NMR and MS data for compound **DMBHB:**
^{1}H NMR (500 MHz, $CDCl_3$): δ7.653 (d, 4H), δ7.177 (d, 4H), δ6.723 (d of d, 8H), 3.052 (quartet, 24H), δ2.093 (s, 6H).

TOF-MS (*m/z*): 615.3517 (100%), 499.2502(11%), 308.1725(10%), 266.1407(30%), 223.1011(15%).

Table 4.3 Physical Properties of DTBHB

DTBHB	Physical Properties
Physical State	Crystalline powder
Colour	Yellow
Melting Point	173 °C – 176 °C
Solubility	Soluble in all organic Solvents except alcohols
Yield	82.5 %

Table 4.4 Physical Properties of DMBHB

DMBHB	Physical Properties
Physical State	Crystalline powder
Colour	Bright yellow
Melting Point	235 °C – 240 °C
Solubility	Soluble in all organic Solvents except alcohols
Yield	83 %

4.5.2 Crystallization of DTBHB and DMBHB

All the inclusion compounds and polymorphs of **DTBHB** and **DMBHB** were prepared by slow evaporation of solvent. List of solvents used for crystallization are mentioned in **Table 4.5** and **Table 4.6**.

Table 4.5 Solvents used for crystallization of compound **DTBHB** and composition of crystals produced

S. No.	Solvent used for Crystallization	Crystalline form obtained
1.	Dichloromethane	Inclusion compound, **DTBHB•DCM**
2.	Chloroform	Inclusion compound, **DTBHB•$CHCl_3$**
3.	Carbon tetrachloride	Red colour polymorph (**DTBHB-I**)
4.	Ethyl acetate	Red colour polymorph (**DTBHB-I**)
5.	Acetone	Red colour polymorph (**DTBHB-I**)
6.	Diethyl ether + Acetone	Red colour polymorph (**DTBHB-I**)
7.	Dimethyl Sulfoxide	Concomitant formation of both Red (**DTBHB-I**) and Light Yellow (**DTBHB-II**) colour polymorphs
8.	Dimethylformamide	Red colour polymorph (**DTBHB-I**)
9.	Water + Acetone	Red colour polymorph (**DTBHB-I**)
10.	Nitromethane	Red colour polymorph (**DTBHB-I**)
11.	n-Hexane + Acetone	Red colour polymorph (**DTBHB-I**)
12.	Methanol + Acetone	Red colour polymorph (**DTBHB-I**)
13.	Ethanol + Acetone	Red colour polymorph (**DTBHB-I**)
14.	Isopropanol + Acetone	Red colour polymorph (**DTBHB-I**)
15.	n-Propanol + Acetone	Red colour polymorph (**DTBHB-I**)
16.	t-Butanol + Acetone	Red colour polymorph (**DTBHB-I**)
17.	Acetonitrile	Red colour polymorph (**DTBHB-I**)
18.	n-Butanol + Acetone	Red colour polymorph (**DTBHB-I**)
19.	Dimethylacetamide	Red colour polymorph (**DTBHB-I**)
20.	Tetrahydrofuran	Red colour polymorph (**DTBHB-I**)
21.	Furan	Red colour polymorph (**DTBHB-I**)
22.	1, 4-Dioxane	Concomitant formation of both Red (**DTBHB-I**) and Light Yellow (**DTBHB-II**) colour polymorphs
23.	Cyclohexanone	Red colour polymorph (**DTBHB-I**)
24.	Cyclohexane	Red colour polymorph (**DTBHB-I**)
25.	Benzene	Red colour polymorph (**DTBHB-I**)
26.	Pyridine	Red colour polymorph (**DTBHB-I**)
27.	Toluene	Red colour polymorph (**DTBHB-I**)

28.	Fluorobenzene	Red colour polymorph (**DTBHB-I**)
29.	Anisole	Red colour polymorph (**DTBHB-I**)
30.	Nitrobenzene	Concomitant formation of both Red (**DTBHB-I**) and Light Yellow (**DTBHB-II**) colour polymorphs
31.	*o*-Xylene	Inclusion compound, **DTBHB•*o*-Xylene**
32.	*m*-Xylene	Red colour polymorph (**DTBHB-I**)
33.	*p*-Xylene	Inclusion compound, **DTBHB•*p*-Xylene**
34.	Aniline	Red colour polymorph (**DTBHB-I**)
35.	Morpholine	Red colour polymorph (**DTBHB-I**)
36.	Piperidine	Red colour polymorph (**DTBHB-I**)
37.	Pyrrolidine	Red colour polymorph (**DTBHB-I**)
38.	*m*-Nitrotoluene	Red colour polymorph (**DTBHB-I**)
39.	Hexafluorobenzene	Red colour polymorph (**DTBHB-I**)
40.	Mesitylene	Red colour polymorph (**DTBHB-I**)

Table 4.6 Solvents used for crystallization of compound **DMBHB** and composition of crystals produced

S. No.	**Solvent used for Crystallization**	**Crystalline form obtained**
1.	Dichloromethane	Inclusion compound, **DMBHB•DCM**
2.	Chloroform	Inclusion compound, **DMBHB•$CHCl_3$**
3.	Acetone	Inclusion compound, **DMBHB•Acetone**
4.	Tetrahydrofuran	Inclusion compound, **DMBHB•THF**
5.	1,4-Dioxane	Inclusion compound, **DMBHB•DIOX**
6.	Pyridine	Inclusion compound, **DMBHB•Pyridine**
7.	Cyclohexane	Inclusion compound, **DMBHB•cyclohexane**
8.	Benzene	Inclusion compound, **DMBHB•Benzene**
9.	Toluene	Inclusion compound, **DMBHB•Toluene**
10.	*o*-Xylene	Inclusion compound, **DMBHB•*o*-Xylene**
11.	*m*-Xylene	Inclusion compound, **DMBHB•*m*-Xylene**
12.	*p*-Xylene	Inclusion compound, **DMBHB•*p*-Xylene**
13.	Morpholine	Inclusion compound, **DMBHB•morpholine**
14.	Nitromethane	Inclusion compound, **DMBHB•Nitromethane**
15.	Carbon tetrachloride	Inclusion compound, **DMBHB•CCl_4**
16.	Dimethylsulfoxide	Inclusion compound, **DMBHB•DMSO**
17.	Dimethylacetamide	Inclusion compound, **DMBHB•DMA**
18.	Dimethylformamide	Inclusion compound, **DMBHB•DMF**
19.	Nitrobenzene	Inclusion compound, **DMBHB•Nitrobenzene**
20.	Cyclohexanenone	Inclusion compound, **DMBHB•Cyclohexanone**

21.	Anisole	Inclusion compound, **DMBHB•Anisole**
22.	Aniline	Inclusion compound, **DMBHB•Aniline**
23.	*m*-Nitrotoluene	Inclusion compound, **DMBHB•*m*-Nitrotoluene**
24.	Hexafluorobenzene	Inclusion compound, **DMBHB•Hexafluorobenzene**
25.	Benzonitrile	Inclusion compound, **DMBHB•Benzonitrile**
26.	Fluorobenzene	Inclusion compound, **DMBHB•Fluorobenzene**
27.	Chlorobenzene	Inclusion compound, **DMBHB•Chlorobenzene**
28.	Bromobenzene	Inclusion compound, **DMBHB•Bromobenzene**
29.	Furan	Inclusion compound, **DMBHB•Furan**
30.	Piperidine	Inclusion compound, **DTBHB•Piperidine**
31.	Pyrrolidine	Inclusion compound, **DMBHB•Pyrrolidine**
32.	1, 2-Dichlorobenzene	Inclusion compound, **DMBHB•1,2-Dichlorobenzene**
33.	Ethyl acetate	Polymorph, **DMBHB-I**
34.	Acetonitrile	Polymorph, **DMBHB-I**
35.	Mesitylene	Polymorph, **DMBHB-II**

4.5.3 Single Crystal X-ray Diffraction (SCXRD) Study

Single crystal X-ray structures were collected on Bruker D8 Quest single crystal X-ray Diffractometer equipped with a microfocus anode (Mo) and a PHOTON 100 CMOS detector. Suitable single crystals of inclusion compounds and polymorphs of **DTBHB** and **DMBHB** for diffraction experiments were chosen under polarizable microscope. The crystals of solvates were cut and wrapped with paraton oil in order to prevent the loss of solvent. Diffraction data of most of the crystals described in this chapter have been collected at 100K using Oxford Cryosystream 800 Plus cryostat. Data for few crystals were collected at room temperature. All the data were integrated and scaled using the Bruker suite of programs.[61] The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using SHELX-2014.[62] All non-hydrogen host atoms were refined anisotropically and all hydrogen atoms were placed using calculated positions on riding models. Crystallographic data of all the structures and final refinement details are given (**Table 4.7**) and (**Table 4.8**).

4.5.4 Powder X-ray Diffraction (PXRD) Study

X-ray powder diffractograms were measured on Rigaku powder X-ray diffractometer, Miniflex-600 with CuK_α radiation, (λ = 1.54059 Å) operating in Bragg-Brentano geometry. The crystals of all the compounds were crushed gently and layered on a glass slide. In each case, data were collected at room temperature for approximately half an hour, scanning from 5º to 40º (2θ value).

4.5.5 Thermal Analysis (TA)

Differential scanning calorimetry (DSC) was performed on a Mettler Toledo DSC1 calorimeter with FRS5 DSC Sensor attached with HUBER TC100-MT chiller and STARe software V13.00. In all the cases 3 to 5 mg of sample were taken in Aluminum pan sealed with pierced lid. The samples were purged with a flow of dry nitrogen at 50 mL/min. DSC data were collected by heat-cool-heat method. In case of the compound **DTBHB**, sample was heated at the rate of 5 °C/min from 30 °C to 200 °C, cooled to -80 °C and then re-heated to 200 °C. Sample was heated from 30 °C to 250°C in case of compound **DMBHB**, then cooled to room temperature and re-heated again till 250 °C.

For TGA Mettler Toledo TGA1 was used in combination with Minichiller MT/230 and STARe software V13.00. Before analysis, crystals taken out of mother liquor were blotted dry using filter paper and placed on alumina crucible. The samples were purged with a flow of dry nitrogen at the rate of 50mL/min. Samples were heated at the rate of 5°C/min from 30 to 250°C.

4.6 References:

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4.7 Appendix:

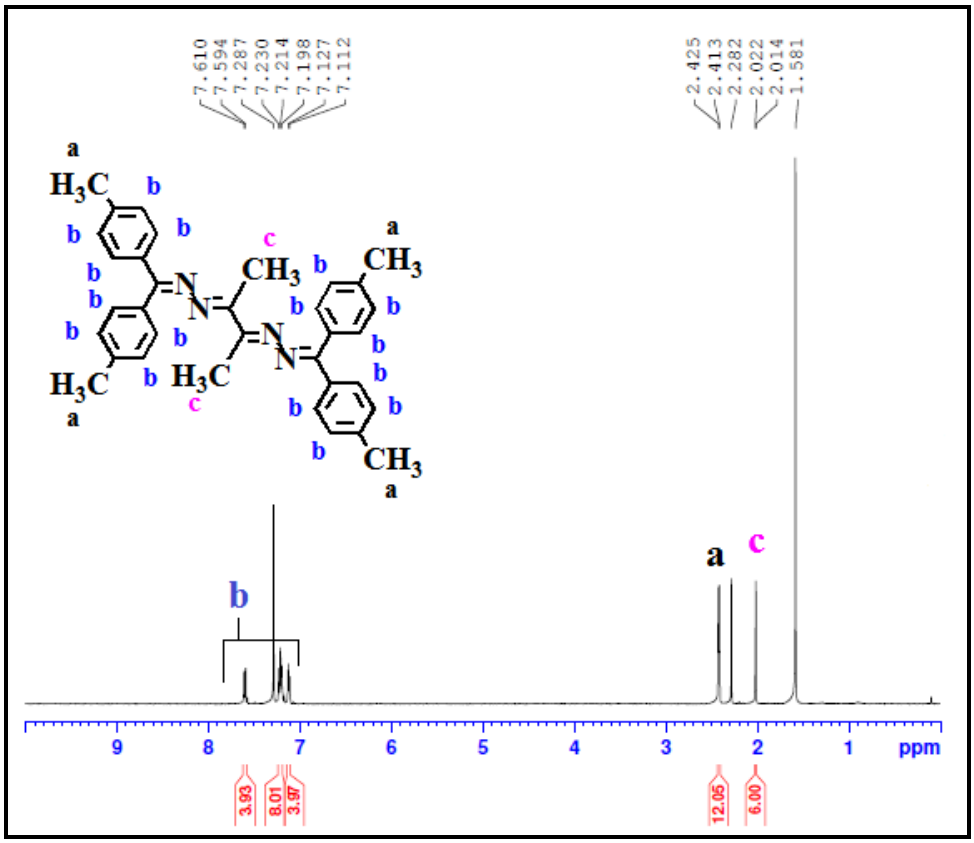


Figure 4.30 ^{1}H NMR Spectrum of **DTBHB** (500 MHz, $CDCl_3$).

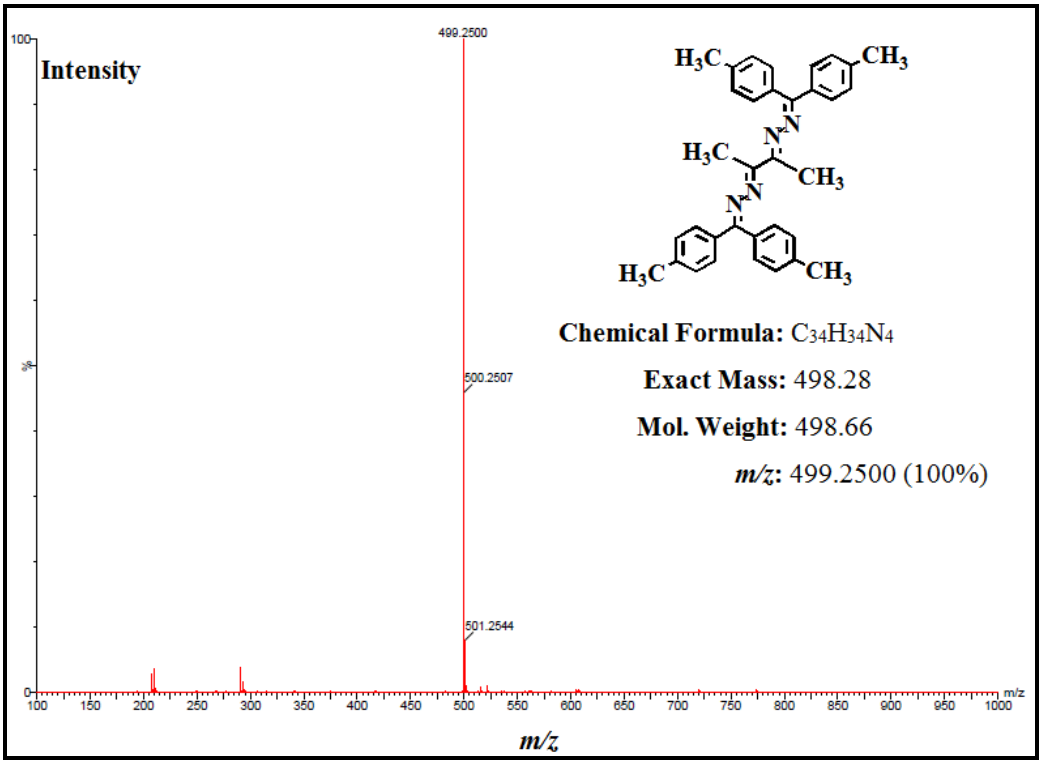


Figure 4.31 TOF Mass Spectrum of **DTBHB** TOF-MS (*m/z*).

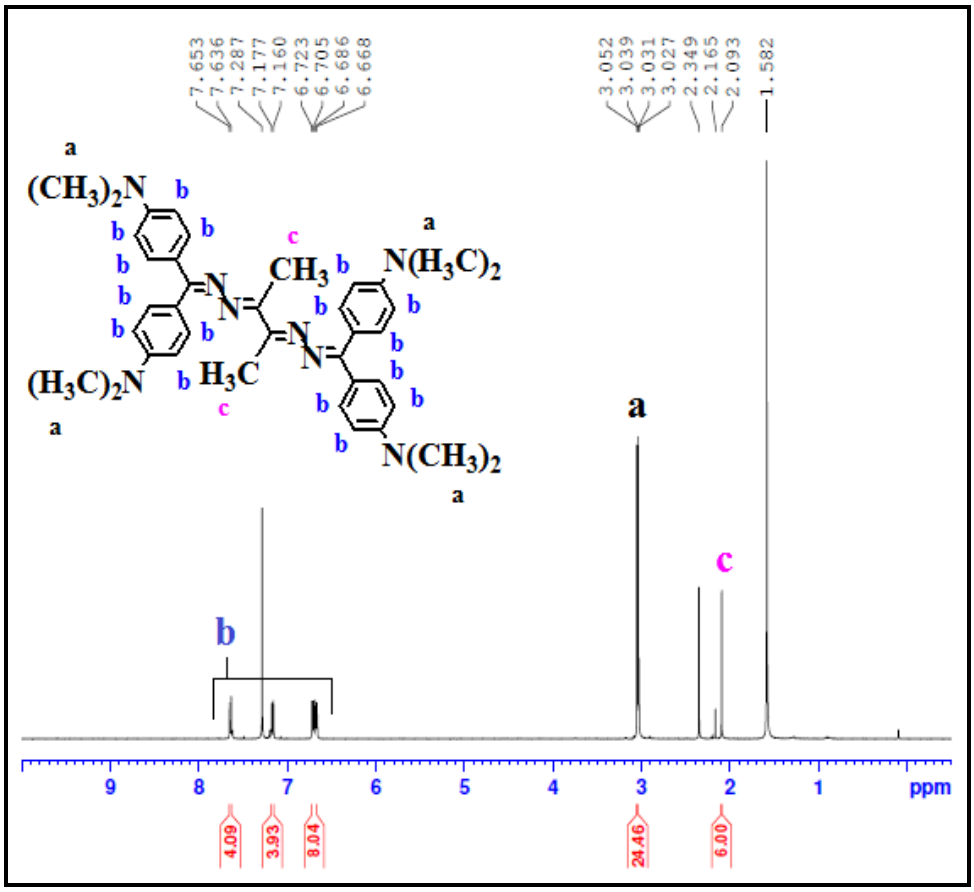


Figure 4.32 ^{1}H NMR Spectrum of **DMBHB** (500 MHz, $CDCl_3$).

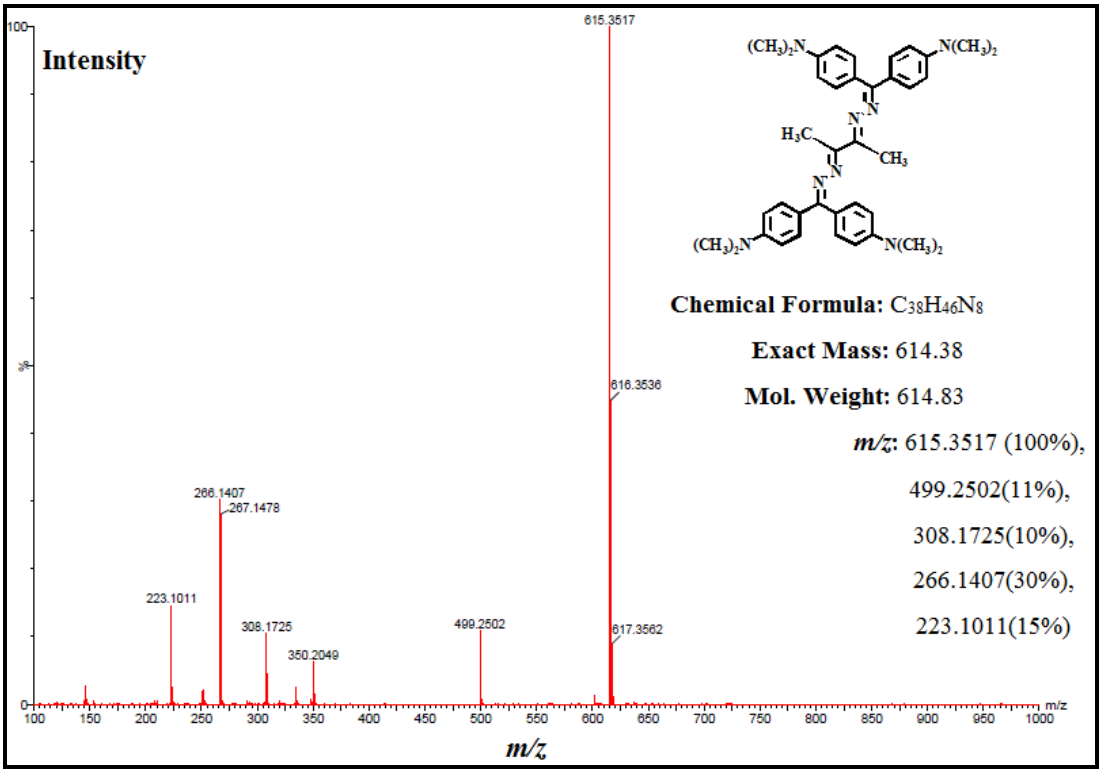


Figure 4.33 TOF Mass Spectrum of **DMBHB** TOF-MS (*m/z*).

Table 4.7 Crystal Data and Structure Refinement for all the Crystal Structures of DTBHB

Compound	**DTBHB•$CHCl_3$**	**DTBHB•DCM**	**DTBHB•*o*-Xylene**	**DTBHB•*p*-Xylene**	**DTBHB-I**	**DTBHB-II**
Moiety formula	$C_{34}H_{34}N_4$•1($CHCl_3$)	$C_{34}H_{34}N_4$•1(CH_2Cl_2)	$C_{34}H_{34}N_4$•2(C_8H_{10})	$C_{34}H_{34}N_4$•2(C_8H_{10})	$C_{34}H_{34}N_4$	$C_{34}H_{34}N_4$
Crystal system	triclinic	monoclinic	triclinic	triclinic	triclinic	triclinic
Space group	$P\bar{1}$	*C2/c*	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	*P*1
Crystal size (mm^3)	0.38 x 0.22 x 0.18	0.42 x 0.31 x 0.15	0.33 x 0.21 x 0.14	0.31 x 0.15 x 0.08	0.43 x 0.32 x 0.21	0.42 x 0.31 x 0.11
a/*Å*	9.5652(4)	25.7069(14)	7.5560(3)	7.4652(6)	7.6122(4)	7.7270(15)
b/*Å*	12.9807(7)	9.8183(5)	12.0130(5)	11.9604(10)	10.7586(6)	8.9264(17)
c/*Å*	14.0148(7)	12.5615(6)	12.1730(5)	22.937(2)	18.3363(11)	10.491(2)
α/(*deg*)	101.898(2)	90	113.881(2)	84.830(3)	104.238(2)	97.989(7)
β/(*deg*)	101.089(2)	99.430(2)	90.094(2)	88.207(3)	95.169(2)	96.215(7)
γ/(*deg*)	104.386(2)	90	96.276(2)	88.655(3)	107.232(2)	106.294(7)
V/$Å^3$	1593.96(14)	3127.7(3)	1003.01(7)	2038.2(3)	1368.51(13)	679.5(2)
Z	2	4	1	2	2	1
D_{cal}/g cm^{-3}	1.288	1.239	1.237	1.158	1.210	1.219
T/K	100	100	100(2)	100(2)	100(2)	100(2)
μ/mm^{-1}	0.318	0.238	0.072	0.067	0.072	0.072
F_{000}	648	1232	394	764	532	266
Reflections measured	69077	32825	22323	84994	63984	28324
Unique reflections	7922	3885	4959	10165	6794	6741
Observed reflections	6181	3109	3663	6409	5759	6027
Parameters	387	195	283	493	349	350
R_{int}	0.0484	0.0379	0.0417	0.0838	0.1030	0.0364
final *R* [I >2σ(I)]	0.0414	0.0670	0.0764	0.0766	0.0521	0.0402
final *R* (all data)	0.0624	0.0846	0.1054	0.1277	0.0627	0.0495
GOF on F^2	1.024	1.045	1.035	1.044	1.051	1.046

Table 4.8 Crystal data and Structure Refinement for all the Crystal Structures of DMBHB

Compound	**DMBHB•$CHCl_3$**	**DMBHB•DCM**	**DMBHB•Acetone**	**DMBHB•THF**	**DMBHB•DIOX**
Moiety formula	C_{38} H_{46} N_8•2($CHCl_3$)	C_{38} H_{46} N_8•2(CH_2Cl_2)	C_{38} H_{46} N_8•2(C_3H_6O)	C_{38} H_{46} N_8•2(C_4H_8O)	C_{38} H_{46} N_8•1($C_4H_8O_2$)
Crystal system	triclinic	triclinic	triclinic	triclinic	triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
Crystal size (mm^3)	0.510 x 0.28 x 0.07	0.41 x 0.32 x 0.21	0.28 x 0.15 x 0.14	0.31 x 0.28 x 0.11	0.44 x 0.18 x 0.09
$a/Å$	8.4230(8)	8.1927(4)	8.1092(5)	8.0742(6)	6.9918(4)
$b/Å$	10.0671(10)	10.6046(6)	10.9272(7)	11.3565(7)	11.9065(6)
$c/Å$	13.3531(13)	13.0226(7)	13.4057(8)	12.6694(8)	12.5312(6)
$\alpha/(deg)$	71.174(4)	68.768(2)	68.893(3)	115.729(2)	87.182(3)
$\beta/(deg)$	76.553(4)	72.007(2)	78.350(3)	91.789(2)	83.199(3)
$\gamma/(deg)$	80.621(4)	81.741(2)	79.869(3)	99.817(3)	74.316(3)
V/Å^3	1037.56(18)	1002.39(9)	1078.42(12)	1023.94(12)	997.13(9)
Z	1	1	1	1	1
D_{cal}/g cm^{-3}	1.366	1.300	0.947	1.231	1.171
T/K	100(2)	100(2)	298(2)	100(2)	293(2)
μ/mm^{-1}	0.454	0.335	0.058	0.077	0.074
F_{000}	446	414	330	410	378
Reflections measured	24812	44331	46633	48980	31629
Unique reflections	5145	5006	5450	5094	4995
Observed reflections	4328	4017	2921	4046	1797
Parameters	249	240	215	258	252
R_{int}	0.0585	0.0301	0.0585	0.0578	0.1870
final R $[I>2\sigma(I)]$	0.0703	0.0508	0.0748	0.0469	0.0784
final R (all data)	0.0820	0.0649	0.1529	0.0651	0.2531
GOF on F^2	1.076	1.041	1.044	1.038	0.989

Compound	**DMBHB•Benzene**	**DMBHB•*o*-Xylene**	**DMBHB• *m*-Xylene**	**DMBHB•p-Xylene**	**DMBHB•Toluene**
Moiety formula	C_{38} H_{46} N_8•1(C_6H_6)	C_{38} H_{46} N_8•1(C_8H_{10})	C_{38} H_{46} N_8•1(C_8H_{10})	C_{38} H_{46} N_8•1(C_8H_{10})	C_{38} H_{46} N_8•1(C_7H_8)
Crystal system	monoclinic	triclinic	triclinic	triclinic	triclinic
Space group	$C2/c$	$P\bar{1}$	$P1$	$P\bar{1}$	$P\bar{1}$
Crystal size (mm^3)	0.31 x 0.21 x 0.20	0.35 x 0.28 x 0.14	0.50x 0.32 x 0.21	0.42 x 0.32 x 0.10	0.40 x 0.27 x 0.12
$a/\AA$	20.1415(16)	12.487(2)	12.0682(6)	12.1863(7)	12.1492(10)
$b/\AA$	14.3355(10)	12.537(2)	12.4198(6)	15.0056(9)	12.2872(10)
$c/\AA$	14.5028(11)	15.306(3)	15.0152(8)	23.0348(13)	28.911(2)
$\alpha/(deg)$	90	74.693(5)	89.461(2)	84.538(3)	82.270(4)
$\beta/(deg)$	115.798(2)	88.474(5)	76.629(2)	82.957(3)	83.791(4)
$\gamma/(deg)$	90	67.601(4)	68.461(2)	77.464(3)	68.201(4)
$V/\AA^3$	3770.2(5)	2129.4(6)	2029.54(18)	4070.5(4)	3962.8(5)
Z	4	2	2	2	4
D_{cal} /g cm^{-3}	1.221	0.959	1.180	1.176	1.181
T/K	100(2)	295(2)	100(2)	100(2)	100(2)
μ/mm^{-1}	0.074	0.058	0.071	0.071	0.071
F_{000}	1488	660	776	1552	1511
Reflections measured	30611	22538	98979	182291	155004
Unique reflections	4720	2600	20124	20298	19803
Observed reflections	3383	1830	15336	13808	13394
Parameters	240	427	1047	999	981
R_{int}	0.0684	0.0983	0.0524	0.0662	0.0926
final R [I >2σ(I)]	0.0615	0.0733	0.0514	0.0552	0.1253
final R (all data)	0.0901	0.1042	0.0813	0.0958	0.1737
GOF on F^2	1.050	1.075	1.024	1.035	1.098

Compound	**DMBHB•Pyridine**	**DMBHB•Morpholine**	**DMBHB-I**	**DMBHB-II**
Moiety formula	$C_{38}\ H_{46}\ N_8$•2($C_5H_5\ N$)	$C_{38}\ H_{46}\ N_8$•2(C_4H_9NO)	$C_{38}\ H_{46}\ N_8$	$C_{38}\ H_{46}\ N_8$
Crystal system	triclinic	triclinic	monoclinic	triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1$	$P\bar{1}$
Crystal size (mm^3)	0.33 x 0.11 x 0.08	0.35 x 0.22 x 0.05	0.43 x 0.31 x 0.11	0.24 x 0.22 x 0.12
$a/Å$	8.0436(4)	8.0756(3)	11.8988(4)	7.5278(8)
$b/Å$	11.3138(5)	13.1500(5)	8.1189(3)	10.1875(11)
$c/Å$	13.0333(6)	20.8773(8)	18.4205(6)	12.0834(13)
$\alpha/(deg)$	114.413(2)	100.845(2)	90	104.338(5)
$\beta/(deg)$	94.504(2)	92.889(2)	98.961(2)	95.713(5)
$\gamma/(deg)$	101.394(2)	101.525(2)	90	98.717(4)
$V/Å^3$	1041.56(9)	2124.61(14)	1757.80(11)	878.30(16)
Z	1	2	2	1
$D_{cal}/g\ cm^{-3}$	1.232	1.233	1.162	1.162
T/K	100(2)	100(2)	298(2)	293(2)
μ/mm^{-1}	0.075	0.078	0.071	0.071
F_{000}	414	852	660	330
Reflections measured	46163	91565	36032	33918
Unique reflections	5190	10588	8687	4357
Observed reflections	4205	7461	4605	2552
Parameters	318	542	426	213
R_{int}	0.0331	0.0608	0.0462	0.0393
final R $[I>2\sigma(I)]$	0.0566	0.0543	0.0548	0.0564
final R (all data)	0.0715	0.0887	0.1274	0.1042
GOF on F^2	1.024	1.020	1.012	1.015

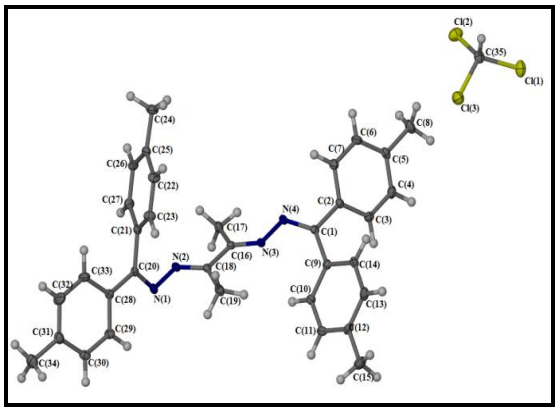
Table 4.9 Torsion angle **(−C=N−N=C−)** and Dihedral angle between the planes of terminal phenyl rings**:**

Crystal	Torsion angle of (−C=N−N=C−) unit	Dihedral angle
DTBHB•$CHCl_3$	102.99 º and 150.80 º	76.09 º and 69.74 º
DTBHB•CH_2Cl_2	132.54 º	63.99 º
DTBHB•*p*-Xylene	140.81 º and 140.82 º	63.04 º and 67.12 º
DTBHB•*o*-Xylene	142.92 º	64.70 º
DTBHB-I	156.20 º; 123.99 º	56.89 º; 66.47 º
DTBHB-II	115.89 º and 104.07 º	78.84 º and 67.88 º
DMBHB•$CHCl_3$	125.10 º	67.85 º
DMBHB•CH_2Cl_2	131.01 º	68.83 º
DMBHB•Acetone	132.40 º	64.84 º
DMBHB•DIOX	131.31 º	65.10 º
DMBHB•THF	132.70 º	67.59 º
DMBHB•Benzene	126.63 º	60.93 º
DMBHB•Pyridine	129.82 º	67.95 º
DMBHB•Morpholine	132.00 º and 128.99 º	68.40 º and 68.18 º
DMBHB•*p*-Xylene	120.00 º and 128.02 º; 121.93 º; 130.66 º	65.98 º and 67.18 º; 84.40 º; 74.37 º
DMBHB•*o*-Xylene	127.78 º; 127.33 º	66.62 º; 75.69 º
DMBHB•*m*-Xylene	124.90 º and 128.51 º; 123.89 º and 120.19 º	75.83 º and 76.22 º; 66.49 º and 72.96 º
DMBHB•Toluene	117.99 º and 127.74 º; 122.72 º; 125.00 º	73.54 º and 71.36 º; 83.81 º; 72.93 º
DMBHB-I	146.51 º and 159.00 º	70.36 º and 62.55 º
DMBHB-II	125.81 º	69. 89 º

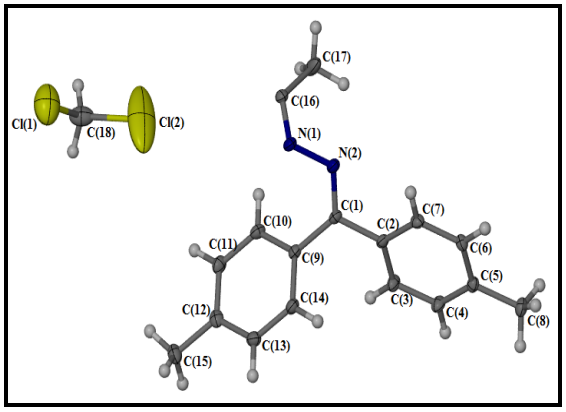
Table 4.10 Details of hydrogen bonding in the crystal structures described in this chapter

Compound	Hydrogen bond	H···A distance (Å)	D···A distance (Å)	D–H···A angle (°)
DTBHB.$CHCl_3$	C–H···π	2.899	3.668	136.04
	C–H···π	2.805	3.717	155.15
	C–H···π	2.912	3.712	139.51
	C–H···N	2.344	3.211	144.56
DTBHB.CH_2Cl_2	C–H···π	2.769	3.591	141.87
	C–H···π	2.820	3.726	152.50
DTBHB.*p*-Xylene	C–H···π	2.873	3.689	144.74
	C–H···π	2.920	3.730	143.95
DTBHB-I	C–H···π	2.844	3.723	154.39
	C–H···π	2.956	3.760	143.15
DTBHB-II	C–H···π	2.77	3.569(3)	142
	C–H···π	2.85	3.652(3)	140
	C–H···π	2.87	3.783(3)	163
	C–H···π	2.88	3.591(3)	130
DMBHB.$CHCl_3$	C–H···π	2.872	3.531	127.48
	C−H···N	2.32	3.263(5)	145
DMBHB.CH_2Cl_2	C–H···π	2.885	3.475	121.35
	C–H···N	2.33	3.353(3)	157
DMBHB.DIOX	C–H···π	2.935	3.734	141.45
	C–H···π	2.843	3.799	173.55
DMBHB.*p*-Xylene	C–H···π	2.774	3.701	157.97
	C–H···π	2.829	3.787	165.72
	C–H···π	2.758	3.597	143.95
DMBHB.THF	C–H···π	2.891	3.726	143.78
	C–H···O	2.659	3.571	154.97
DMBHB.Pyridine	C–H···π	2.794	3.662	148.01
DMBHB.Morpholine	C–H···π	2.750	3.527	139.58
	C–H···π	2.672	3.547	148.82
	C–H···O	2.466	3.437	170.49
	N–H···O	2.220	3.084	148.62
	N–H···N	2.242	3.218	170.25
DMBHB.Toluene	C–H···π	2.762	3.717	164.84
	C–H···π	2.783	3.694	154.81
DMBHB-I	C–H···π	2.928	3.724	141.00
DMBHB-II	C–H···π	2.86	3.745(2)	154

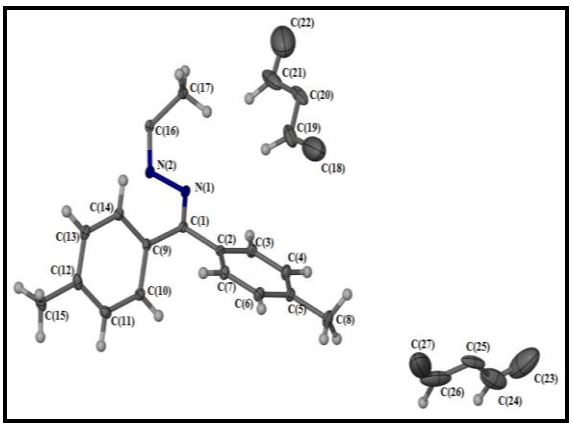
Thermal Ellipsoid Plots: (In all the cases atoms are shown in 50% probability)



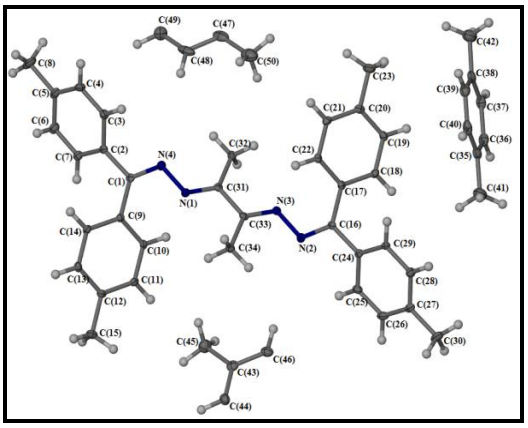
DTBHB•$CHCl_3$



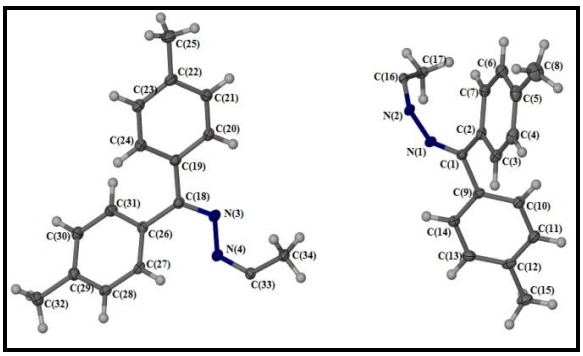
DTBHB•DCM



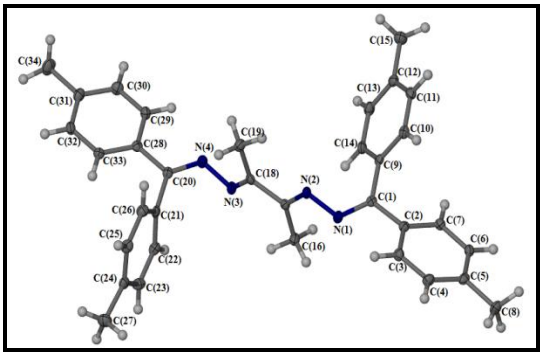
DTBHB•*o*-Xylene



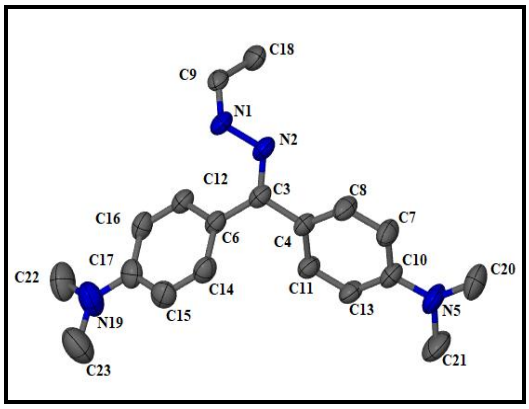
DTBHB•*p*-Xylene



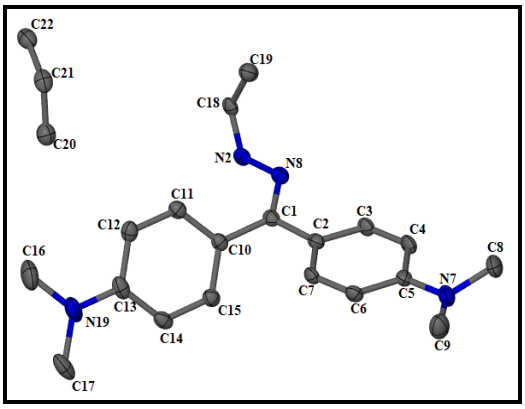
DTBHB-I



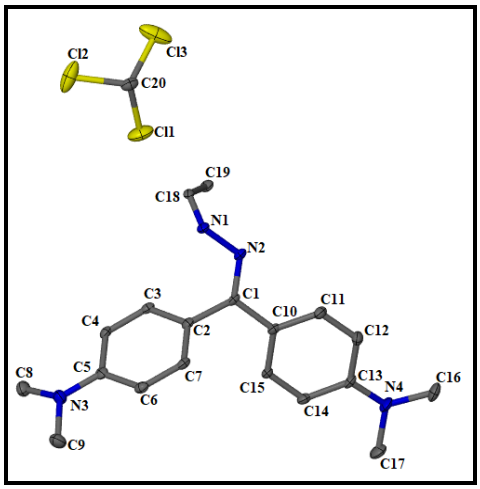
DTBHB-II



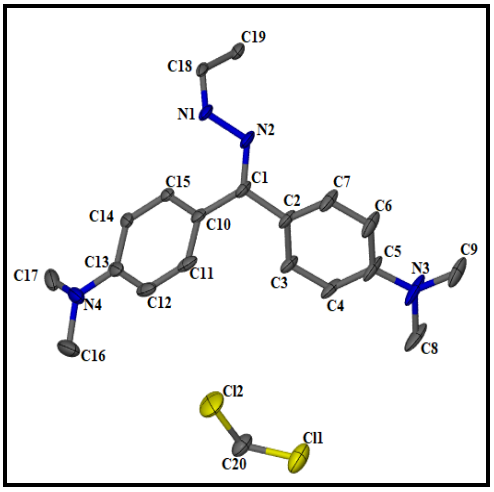
DMBHB•Acetone
(Acetone has been removed due to severe disorder)



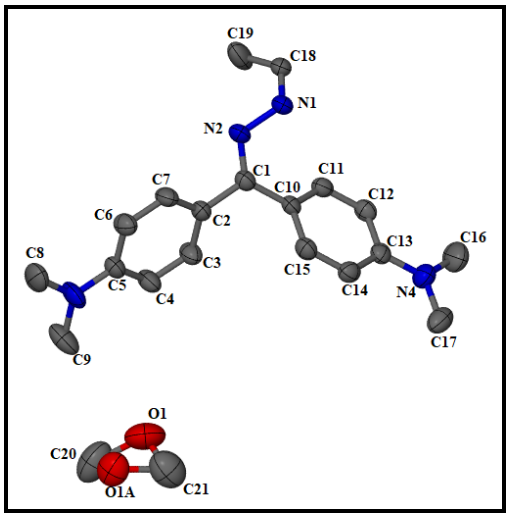
DMBHB•Benzene



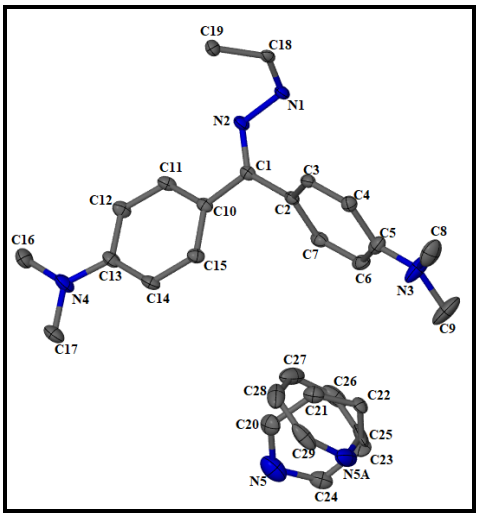
DMBHB•$CHCl_3$



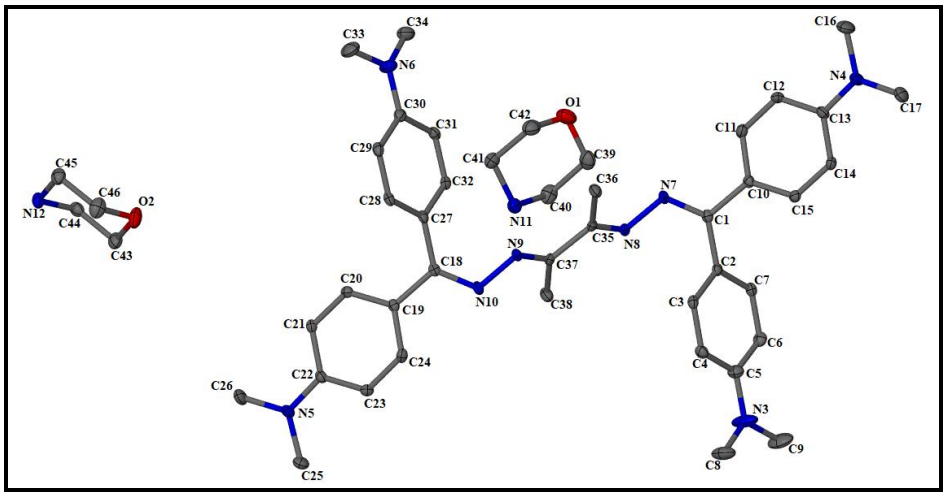
DMBHB•DCM



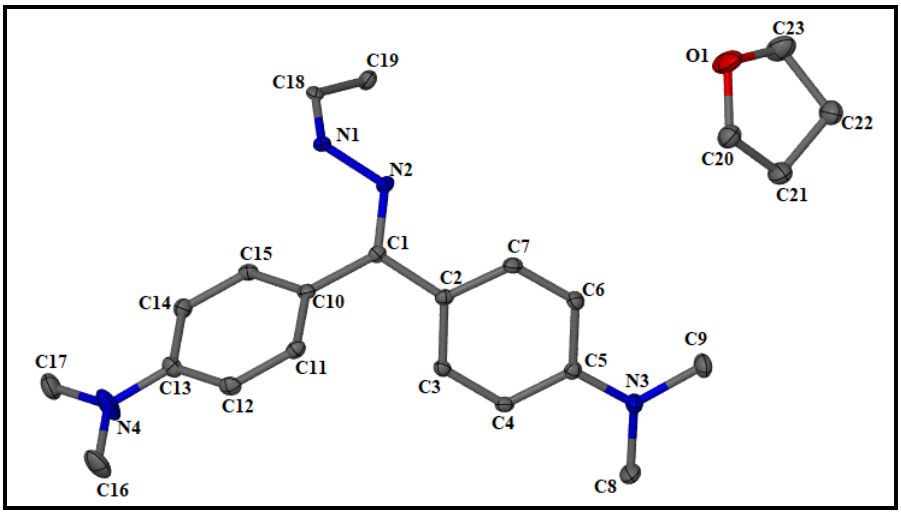
DMBHB•DIOX



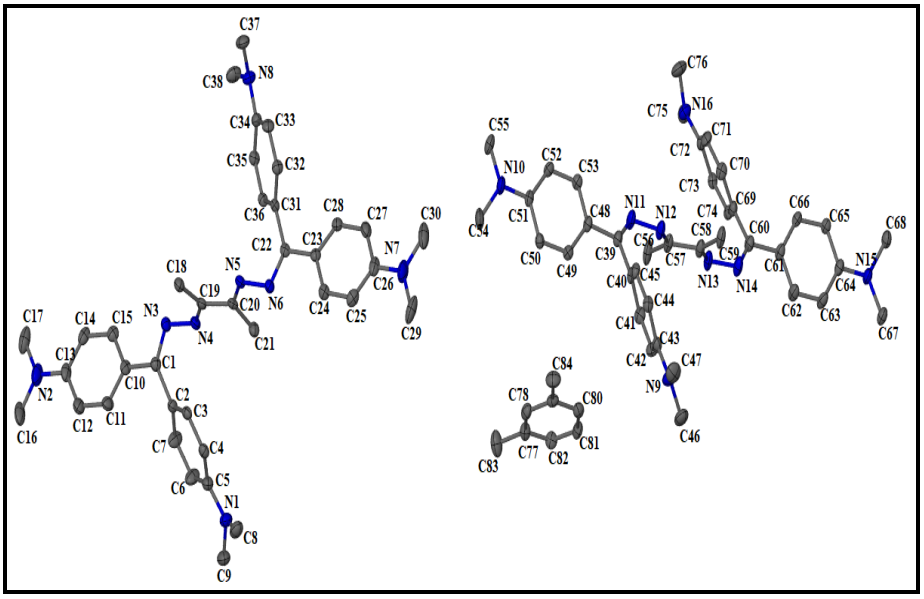
DMBHB•Pyridine



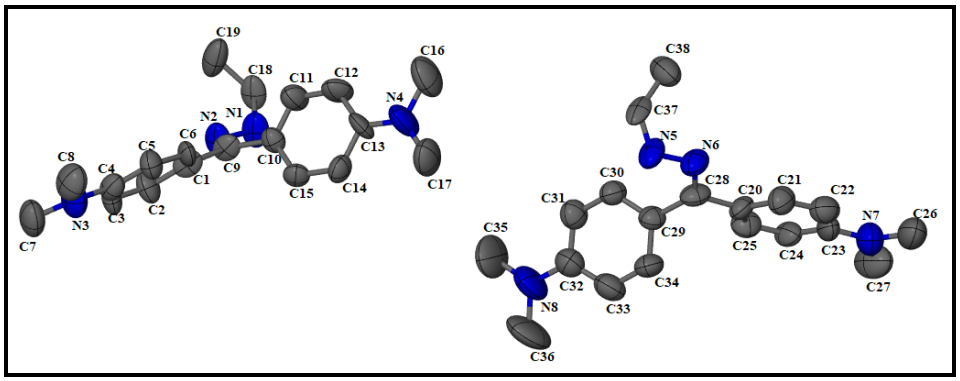
DMBHB•Morpholine



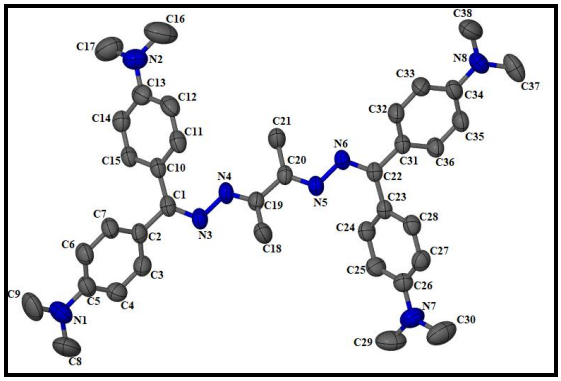
DMBHB•THF



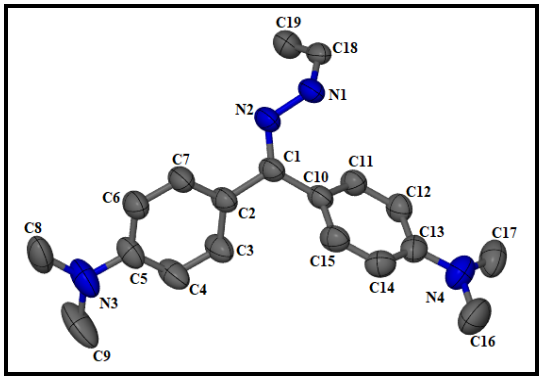
DMBHB•m-Xylene



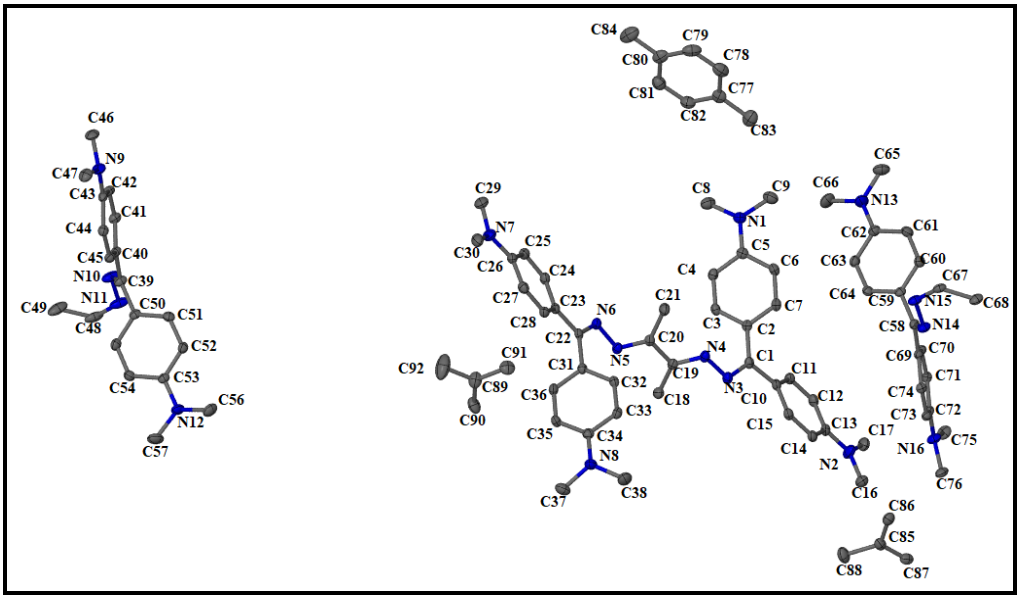
DMBHB•o-Xylene



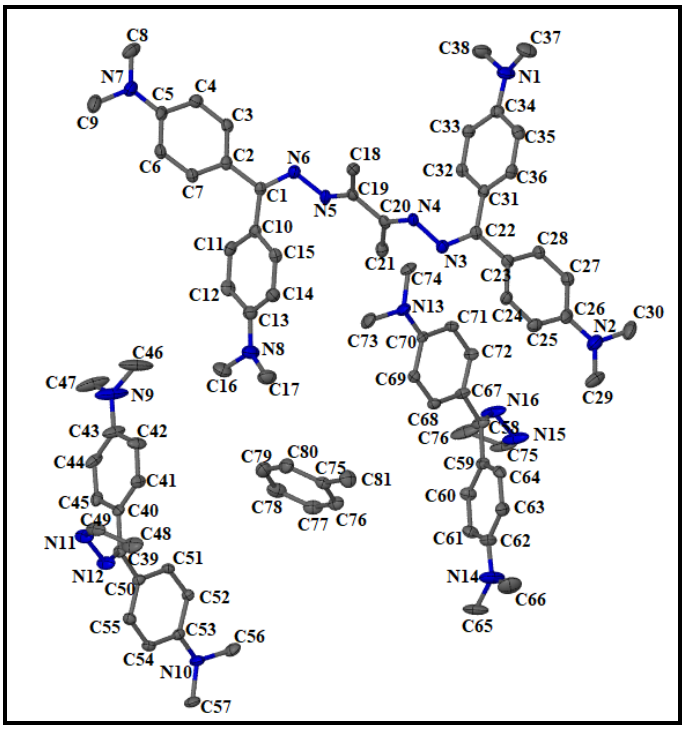
DMBHB-I



DMBHB-II



DMBHB•*p*-Xylene



DMBHB•Toluene

List of Publications

1. 1, 4-Dioxane-Specific Organic Hosts and Their Polymorphism:
Vikrant Jayant; Dinabandhu Das, *Cryst. Growth Des.*, **2016**, *16*, 4183−4189.

2. Temperature Induced Reversible Polymorphic Phase Transformations in a Bis-hydrazone Compound:
Vikrant Jayant; Dinabandhu Das, *Journal of Molecular Structure*, **2018**, *1155*, 628-633.

3. Solvatomorphism in Bis-hydrazone Compounds:
Vikrant Jayant; Dinabandhu Das, to be communicated.

Author's Profile

Vikrant Jayant

(विक्रान्त जयन्त)

Room No-340, Jhelum Hostel, Right Wing,

JNU, New Delhi, India-110067

Email: vikrantjayant@gmail.com

Contact: 9971295854, 8920498560.

Education

2012 **Pre. Ph. D In Physical Sciences**
School of Physical Sciences
Jawaharlal Nehru University **(JNU)**, New Delhi-110067, India

2012 **M. Sc. Organic Chemistry** (1st Division, 63.55 %)
Jamia Millia Islamia **(JMI)**, New Delhi-110025, India

2009 **B. Sc.** (1st Division, 68.14 %)
Indira Gandhi National Open University**(IGNOU)**, Maidan Garhi, New Delhi-110068, India

Achievements and Awards

2012 Cleared **Graduate Aptitude Test in Engineering (GATE)** in Chemical Sciences
Indian Institutes of Technology (IITs)

Conferences

1. National Science Day: Department of Science and Technology, Jawaharlal Nehru University, New Delhi, India, **Vikrant Jayant** *et al*. (**2016**) Poster Presentation.
2. Quantum Optics and Optics of Quantum Systems, School of Physical Sciences, Jawaharlal Nehru University, New Delhi, India, **Vikrant Jayant** *et al*. (**2016**) Attended the Conference.

Workshops

1. Attended the Workshop on "Circular Dichroism Spectroscopy", **Vikrant Jayant** *et al*. (**2013**), In AIRF of JNU, New Delhi.
2. Attended the Workshop on "FT-IR, Raman and NMR (1D & 2D) in Solution State'' **Vikrant Jayant** *et al*. (**2013**), In AIRF of JNU, New Delhi.
3. Attended the Workshop on "Time Resolved Fluorescence Spectroscopy'' **Vikrant Jayant** *et al*. (**2013**), In AIRF of JNU, New Delhi.
4. Attended the Workshop on "X-ray Diffraction (XRD) Powder" & "Surface Plasmon Resonance (SPR)", **Vikrant Jayant** *et al*. (**2013**), In AIRF of JNU, New Delhi.
5. Attended the March Meeting on "Nanoscience & Condensed Matter Interface", **Vikrant Jayant** *et al*. (**2013**), In SPS of JNU, New Delhi.
6. Attended the Workshop on "Computational Material Sciences" **Vikrant Jayant** *et al*. (**2014**), In SPS of JNU, New Delhi.
7. Plagiarism: "Issues and Challenges" A National Work Shop, Jawaharlal Nehru University, New Delhi, India, **Vikrant Jayant** *et al*. (**2014**).
8. Attended the Workshop on "Electron Paramagnetic Resonance Spectroscopy" (EPR), **Vikrant Jayant** *et al*. (**2016**), In AIRF of JNU, New Delhi.