Supramolecular Chemistry with Phthalimide Derivatives

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Abstract: Recent reports on various aspects of chemistry of phthalimide are being reviewed. The emerging development of supramolecular aspects of phthalimide derivatives are critically analyzed by examining the structures of host-guest complexes and also inorganic complexes. The role of weak interactions in deciding structures in solid states is discussed to reveal meta-stable species involved in nucleation process.

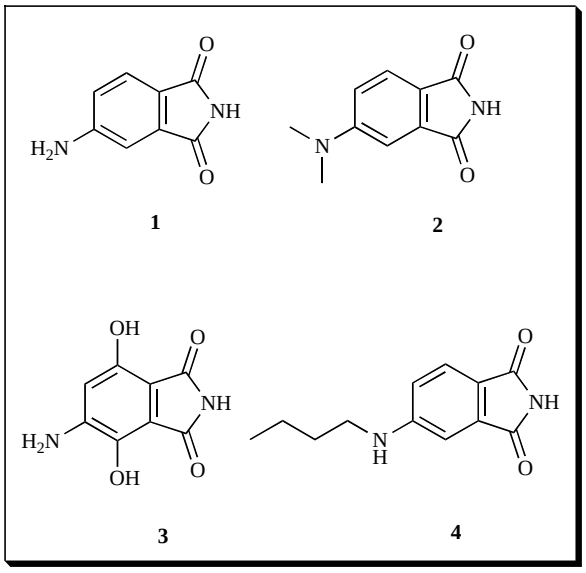
INTRODUCTION

Phthalimides are indispensable in protection and deprotection of primary amines, for which Grabriel synthesis [1] and Ing Manske reactions [2] are extensively studied. Phthalimide derivatives also find important application in catalytic reactions [3] and have been used for synthesis of chiral esters [4]. The presence of two carbonyl groups at next to a nitrogen atom makes them attractive for supramolecular host design. Thus, they have been used as novel biological modifiers for tumor necrosis factor alpha that plays an important role in certain physiological immune systems [5]. Phthalimide derivatives find application as biological probe and the fluorescence properties of them are highly environment sensitive [6]. The derivatives of phthalimides are useful in photochemical synthesis [7]. Some of the phthalimide derivatives are biologically active and find application as drugs [8]. In closely related system naphthalimide derivative tethered by peptide bonds shows helical structure [9].

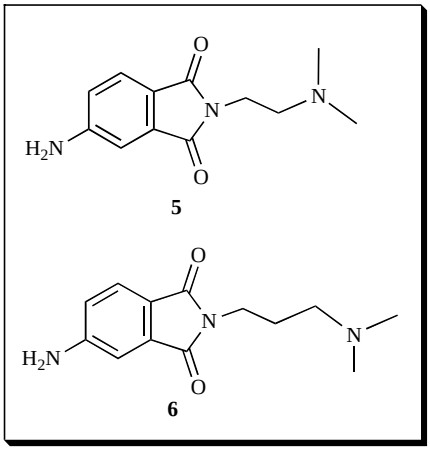
There is further necessity of understanding the properties and the reactivity of phthalimide derivatives so as to make a generalized approach to recognize the basic properties of this class of compounds and take them to practical application. In this article we make systematic discussion on the different aspects of phthalimide derivatives.

Photochemical Aspects of Phthalimide:

Phthalimide derivatives having electron-donating substituents in the aromatic ring show interesting photo-physical properties, which are sensitive to the environment. For example, 4-aminophthalimide (**1**) and its derivatives such as 4-*N*,*N*´-dimethylaminophthalimide (**2**), 4-amino-2,6-dihydroxyphthalimide (**3**) and 4-*N*-pentylaminophthali- mide (**4**) have environment sensitive fluorescence properties [10]. Protic solvents, confined media such as micelles and inclusion ofthese derivatives in macrocylic hosts such as β-cyclodextrin effects the emission maxima, fluorescence quantum yield and lifetime of these phthalimide derivatives. This indicates that specifically designed phthalimide derivatives may have application as molecular environment probe. 4-aminonaphthalimide (**2**) is an excellent probe for miceller environment [11].



Direct communication between the phthalimide fluorophore such as **5** and **6** and the metal center are observed in certain first row transition metal complexes; thus they can be regarded as structurally simple fluorescence sensors for the first row transition metal ions.



Analogous 6-dimethylamino-2,3-naphthalimide derivatives (**7** and **8**) show interesting fluorescence properties. They can be used for biochemical studies [12]. These groups can be easily incorporated into a peptide chain and hence by various bio-molecules could be monitored by fluorescence spectroscopy.

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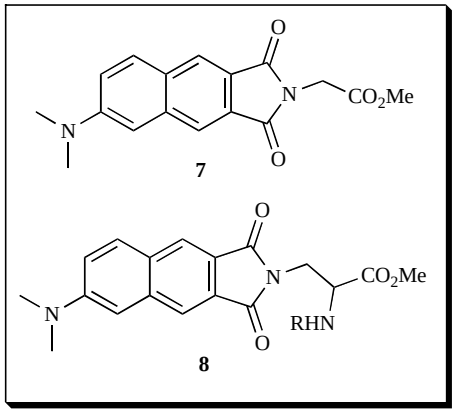
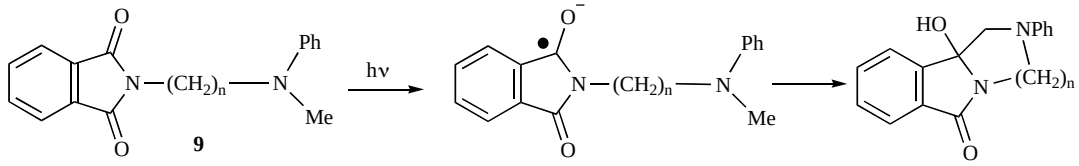


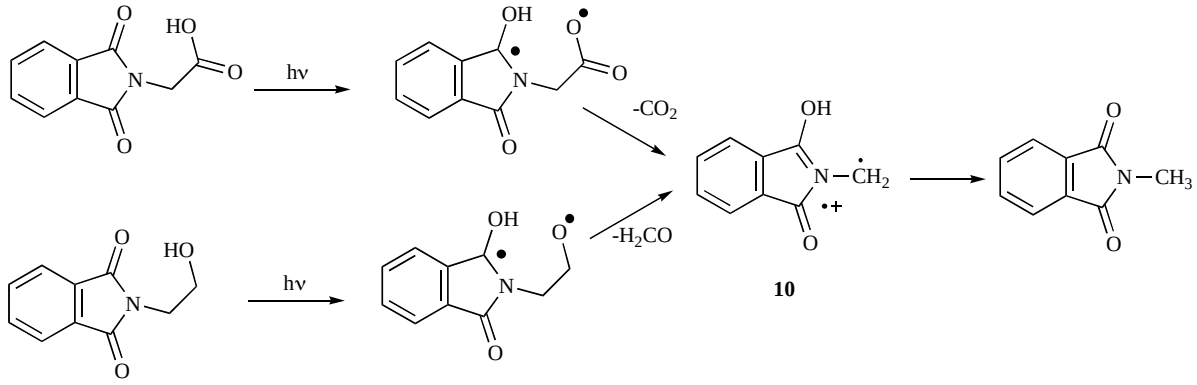
Stereochemical assignment could be made from the excited state of the phthalimide chromophore and their exciton couplings [13]. Phthalic anhydride undergoes condensation reactions with 1,8-naphthalene diamine to give heterocyclic compounds. These substrates have ability to bind to polyhydroxy aromatics and the fluorescence properties of them are dependent on the binding sites [14].

Phthalimide derivatives undergo numerous photochemical reactions. Owing to their high singlet triplet exited-reduction potentials, phthalimide participates in photo induced single electron transfer (SET) with a wide variety of electron donors [15]. Analogous to aromatic ketones, phthalimides in excited states participates in hydrogen atom abstraction. Irradiation of *N*-alkyl phthalimides (**9**) leads to preferential γ-hydrogen abstraction as a part of *N*-hererocyclic ring forming reactions [16] (equation **1**) with the exception [17] that in presence of good electron donors in the alkyl group the process is unlikely.

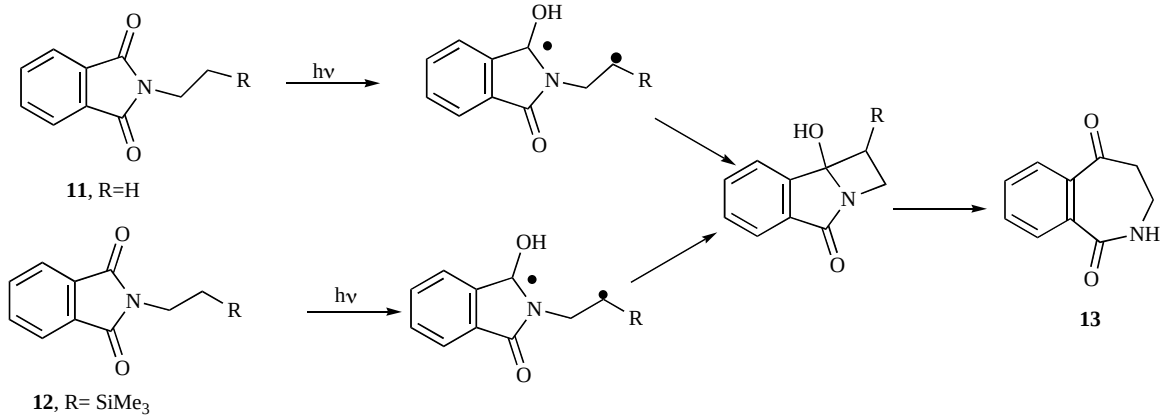
The *N*-phthaloyl-α-amino acids undergo high yielding photodecarboxylation reactions to produce the corresponding *N*-alkylphthalimides. *N*-phthaloyl derivatives of β-amino alcohols participate in a similar photochemical reaction. Based on the mechanistic and exploratory investigations [18] it has been suggested that these reactions proceed through azomethine ylide intermediate (**10**) (equation **2**). Laser flash photolysis studies of *N*-phthaloylglycine support the intermediacy of the azomethine ylide in these photochemical reactions [19].



Equation 1.



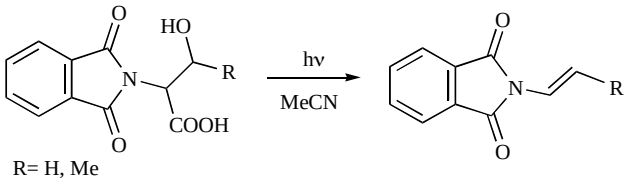
Equation 2.



Equation 3.

Hydrogen atom abstraction predominates in the photoexcited state of *N*-alkyl phthalimides. For example, in the case of *N*-ethyl phthalimide (**11**), initial γ-hydrogen abstraction followed by biradical coupling and ring opening leads to cyclic amide (equation **3**). However, photo-irradiation of *N*-silylethylphthalimide (**12**) in acetonitrile results in selective formation of benzazepinedione (**13**) [20].

However, in the case of *N*-phthaloyl derivatives of β-hydroxyamino acids a facile β-elemination takes place leading to the corresponding *N*-vinylphthalimide [7] (equation **4**).



Equation 4.

There are many more examples of photochemical reactions of phthalimide derivatives leading to useful products.

Weak Interactions in Phthalimides

The hydrogen bonding motifs in acyclic imides are well studied [21]. Acyclic imides can have three conformations, *cis-cis*, *cis-trans* and *trans-trans*, differentiated by the relative orientations of the carbonyl groups with respect to the central –NH group (Fig. **1**) out of which the *cis-cis* conformation is not observed either in solution or solid state. The *cis-trans* conformer is the most stable and was observed in most cases in the solid-state structure of the most of the acyclic amide.

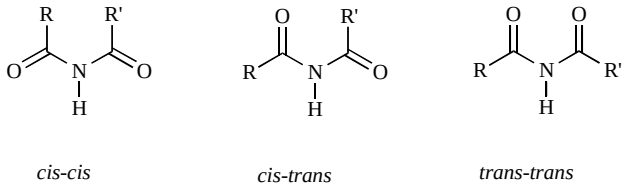
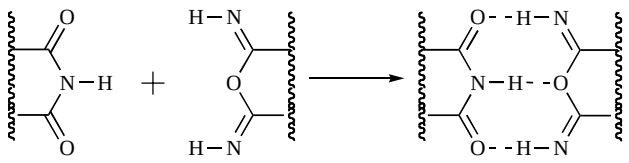


Fig. (1). Conformers due to restricted rotation of amide bond.

Three imide hydrogen-bonding types are generally observed with the most common pattern involving cyclic imide dimers as shown in Fig. (**2**).

Cyclic imides such as phthalimide can be regarded to show *cis-cis* conformation due to the rigid aromatic ring frame. Molecular recognition properties of imides are of interest and are based mostly on the complementarities in hydrogen bonding [22] (Scheme **1**).



Scheme 1. Complentarity in hydrogen bonding of an imide.

Single crystal X-ray diffraction studies [23] on phthalimide at low temperature revealed that molecules are

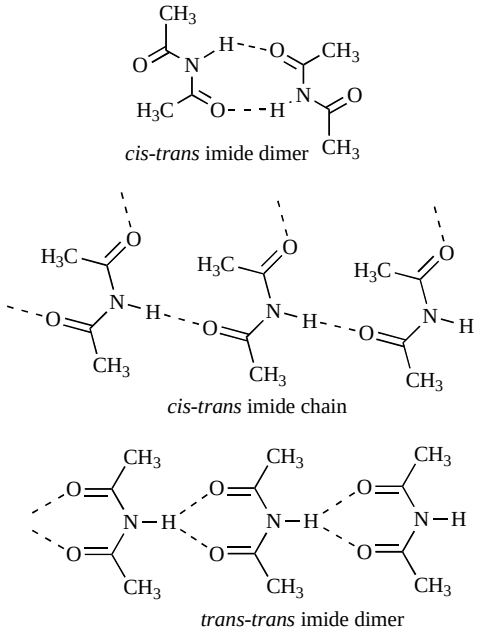
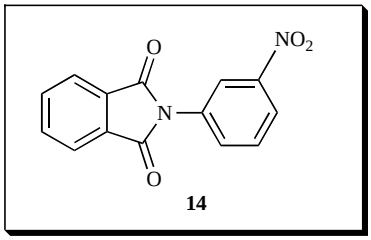


Fig. (2). Different types of intermolecular hydrogen bond in imides.

linked by N−H···O hydrogen bonds (dN···O2.8781Å; <D–H···A 167.0°) and C−H···O(dC···O3.3874Å and 3.4628 Å; <D–H···A 159.0° and149.0°) into molecular ribbons with centrosymmetric $R^2_2(8)$ and non-centrosymmetric $R^2_2(9)$ motif each containing N−H···O hydrogen bonds and C−H···O intermolecular interactions (Fig. **3**). The main features of the solid-state structure of phthalimide are that the individual units are self assembled in the lattice through intermolecular hydrogen bond and aromatic π-π stacking interactions [23].



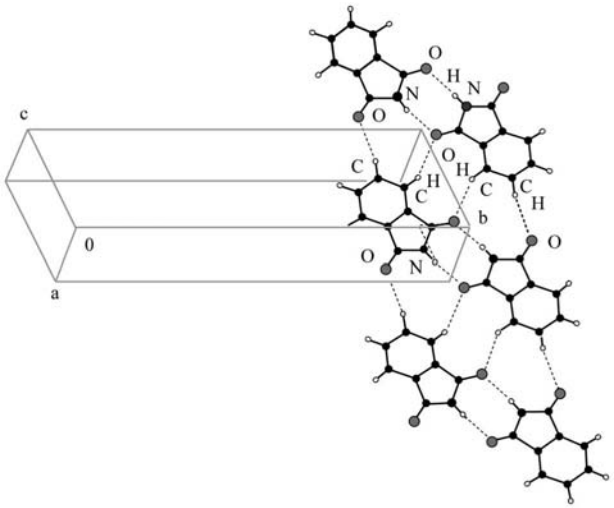


Fig. (3). Self-assembly of phthalimide.

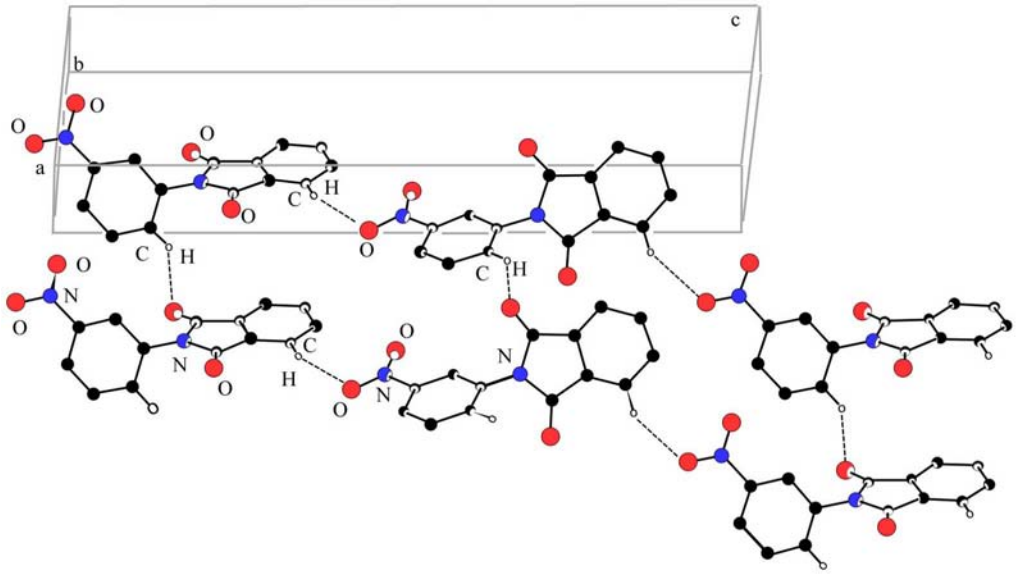
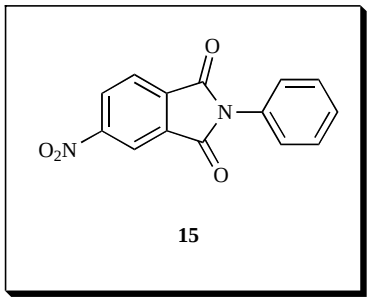


Fig. (4). Self-assembly of *N*-(3-nitrophenyl) phthalimide.

The presence of weak C−H···O interactions is also found [24] in the solid state assembly of other phthalimide derivatives such as *N*-(3-nitrophenyl) phthalimide (**14**). The molecules are linked into three-dimensional network by four different C−H···O interactions (dC···O3.105Å-3.432 Å; <D–H···A 128.0°-167.0°). The molecules lie across two fold rotation axes in the space group P2/n and are linked by a single C−H···O hydrogen bond interaction (dC···O 3.410 Å; <D–H···A 147.0°) into chains of rings. Chains are held together in a sheet by weak intermolecular C−H···O and N−H···O dipolar interactions as shown in Fig. (**4**).

On the other hand, solid-state structure of *N*-phenyl-4-nitrophthalimide (**15**) revealed similar weak C−H···O hydrogen bonding along with aromatic π-π stacking interactions among the phthalimide rings [25]. The molecules are held together by two sets of C−H···O hydrogen bonds (dC···O 3.118 and 3.294 Å; <D–H···A 147.0 and139.0°) into chains which were further linked into sheets by weak aromatic π-stacking interactions between the phthalimide rings as shown in Fig. (**5**).



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Structure of *N*-(4-fluorophenyl) phthalimide (**16**) show that the molecules are held together by two C−H···O hydrogen bonds [26] (dC···O 3.173 and 3.323 Å; <D–H···A 134.0 and157.0°) as shown in Fig. (**6**) . The dihedral angle between the planes of the heterocyclic ring and the fluorinated aryl rings is 50.5(4)°.

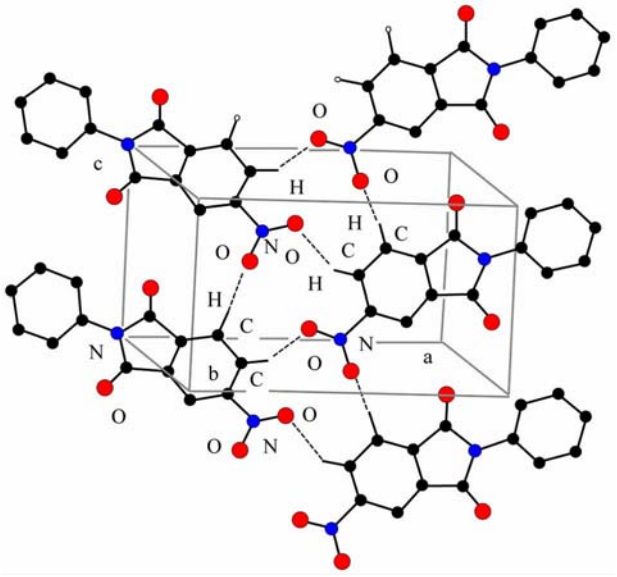
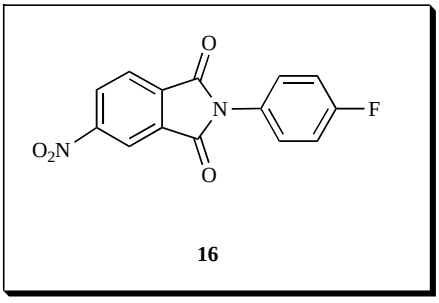


Fig. (5). The hydrogen bonded self-assembly of *N*-phenyl-4-nitrophthalimide.



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Phthalimide units linked to biologically important pyrimidine derivatives like 4, 6-*bis* (methyl sulphenyl)-1-phthalimido-propyl-1H-pyrazolo[3,4-d]pyrimidine derivatives (**17**) has folded conformation in solid state [27] as shown in Fig. (**7**). The molecule forms a fourfold

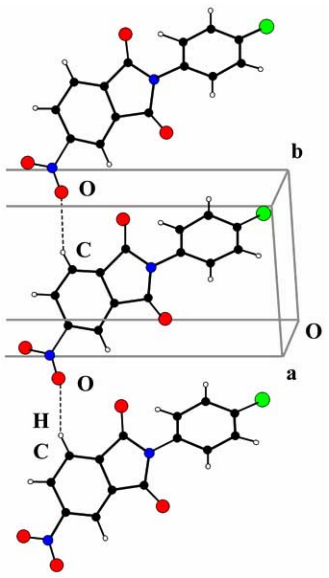
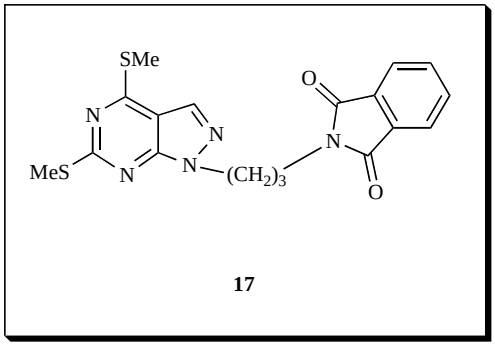


Fig. (6). Inter-molecular hydrogen bonding in self-assembly of *N*-(4-fluorophenyl)phthalimide.

arrangement of phthalimide-pyrimidine-pyrimidine-phthal-imide stacked rings.



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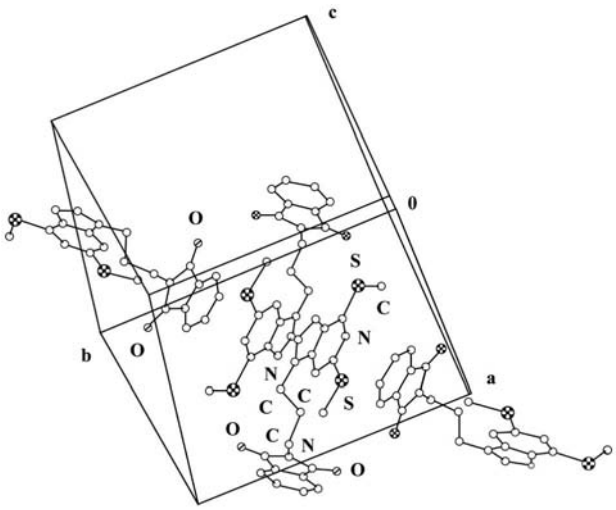
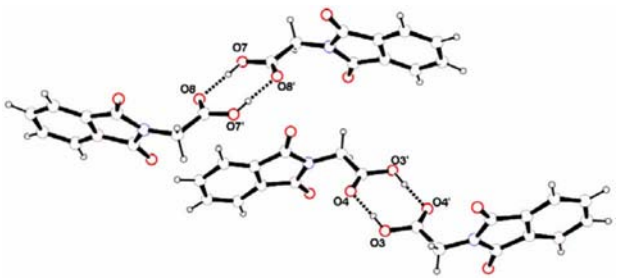


Fig. (7). Stacking of aromatic rings in the solid state structure of 4, 6-*bis*(methyl sulphenyl)-1-phthalimidopropyl-1H-pyrazolo[3,4-d] pyrimidine (hydrogen atoms are omitted for clarity).

N-phthaloylglycine (**18**) generally crystallizes in monoclinic unit cell with a water of crystallization and it has an extended hydrogen bonded structure [28a] resulting from the hydrogen bonding interactions among the carboxylic acid groups with the lattice water molecules. In this assembly, it is shown that there are extensive aromatic π-stacking interactions among the planar aromatic phthalimide units. The dimeric form of the compound can be crystallized from a mixer of acetone and diethyl ether [28b] (Fig. **8**). Crystal structure of the compound **18** shows that it crystallizes in triclinic P-1 space group. The carboxylic acid groups of **18** forms hydrogen bonded bridges in $R^2_2(8)$ motif involving O3−H···O4 and O7−H···O8 intermolecular interaction. The dimeric step-like structure extends along ab plane with two phthaloyl units disposed in *trans* manner (Fig. **8**) with respect to the dimeric hydrogen bonded carboxylic acid groups. The phthaloyl rings are stacked each other in an offset manner.



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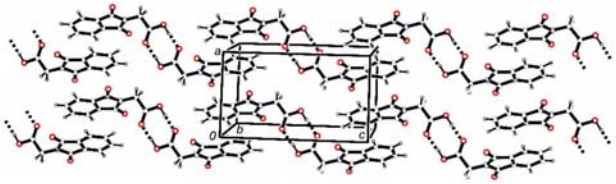


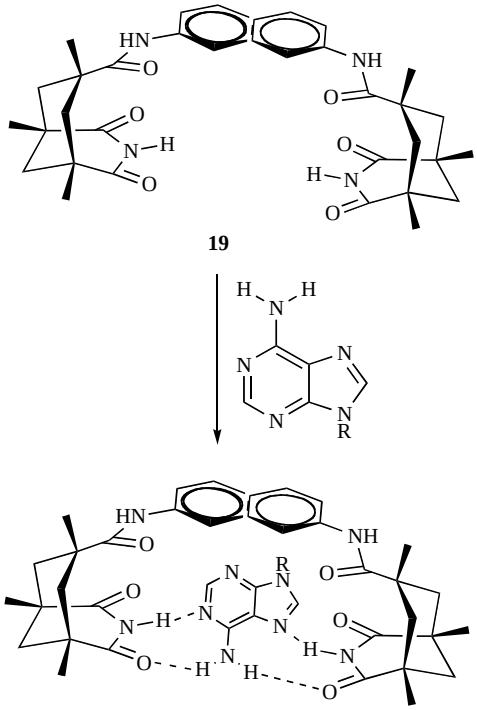
b)

Fig. (8). a) Dimeric structure of **18** b) Packing pattern.

Host-Guest Chemistry of Phthalamide and Analogues

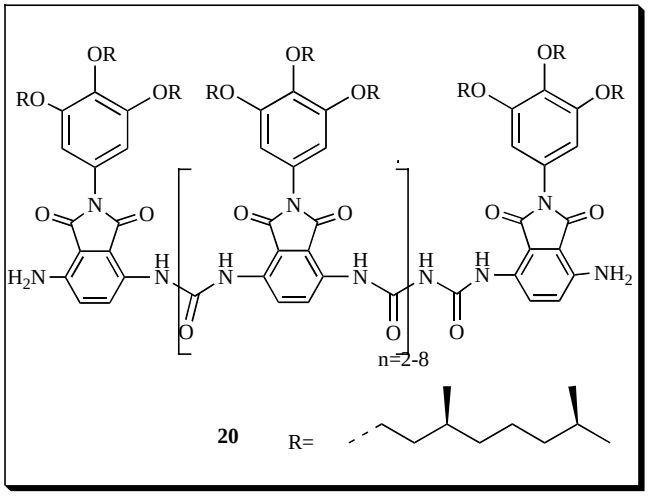
The imide derivative (**19**) binds to adenine derivative [29] and capable of extracting it to non-aqueous solvents like chloroform from water (Scheme **2**). The recognition is basically due to the complementary N−H•••N and N−H•••O hydrogen bond between the receptor, and the adenine derivative.

The self-assembly and the molecular recognition properties of the imide derivatives derived from glycoluril and Kemp's tri acid are extensively studied. The self-complementary hydrogen bonding in imides is utilized [30] in chiral chromatographic separation of heterocyclic drugs such as barbiturates, gluterimides and hydantoins. It is also used for designing molecular tapes and sheets [31] as well as for the synthesis of liquid crystalline materials [32]. Circular dichroism studies on polyureido phthalimide derivatives (**20**)

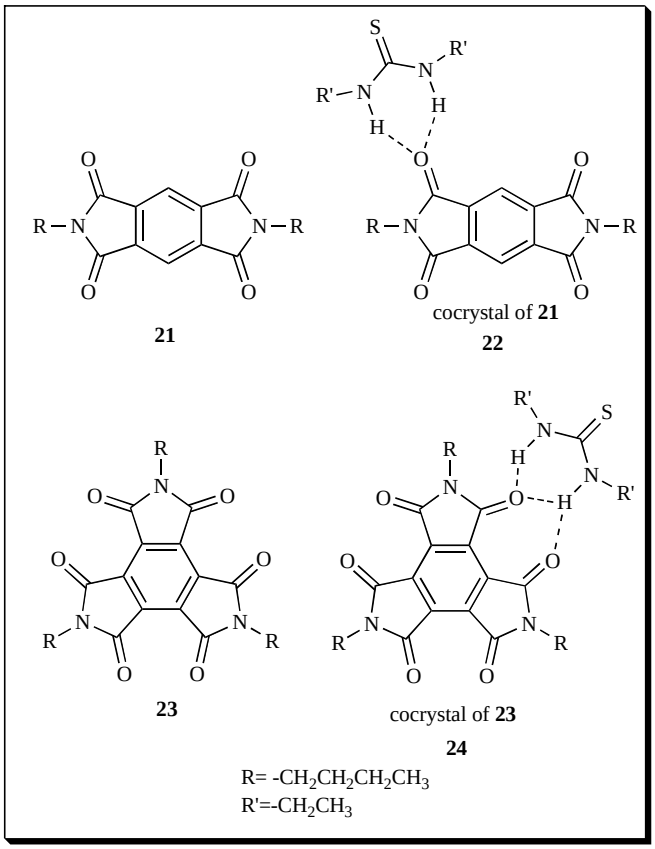


Scheme 2. Encapsulation of adenine derivative by an imide derivative (**19**).

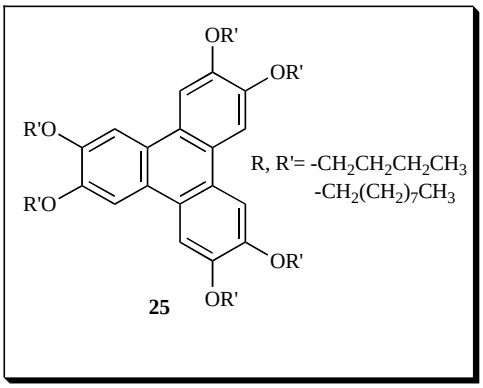
show that these oligomers fold into chiral helical architecture in tetrahydrofuran through intramolecular hydrogen bonding [33].



Cyclic imide derivatives such as *bis*-(*N*,*N*´-*n*-butyl) pyrromelliticdiimide (**21**) and *tris*-(*N*,*N*´,*N*"-*n*-butyl) mellitic triimide (**22**) interacts with alkylthiourea derivatives. Such assemblies are formed by hydrogen bonding interaction between amide N−H group of thiourea derivatives and the imide carbonyl group; which in turn affects the redox potentials of the parent imide derivatives [34]. It has been shown that mellitic triimide undergo three sequential one electron reduction processes whose potential are significantly lowered in presence of alkyl thiourea derivatives. Calculations of the relative free energy change between the different electronic states of the imide acceptors and their corresponding hydrogen bonded alkyl thiourea complexes indicates dramatic increases in the hydrogen bond strength with increase in the acceptor charge density.

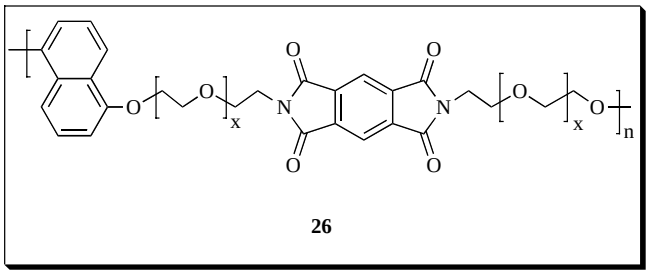


Electron poor alkyl mellitic triimide derivatives (**24**) were shown to form 1:1 charge transfer complex with hexa-alkoxytriphenylene (**25**) with π-facial interaction in solid state [35]. The C3-symmetric triimide, although not liquid crystalline itself, exhibit crystalline to isotropic phase transitions when mixed with suitable electron rich components like **25** and display significantly enhanced enantiotopic columnar mesophases with respect to those observed for either of the pure parent components.



Recently it has been demonstrated [36] that by proper design flexible synthetic polymers (**26**) based on pyromellitic diimide can be made to fold under influence of relatively weak intra chain inter-segment interactions such as charge transfer interaction assisted in tandem by solvophobic effects and metal ion complexation of a flexible oligoethylene oxide loop leading to a stacking of aromatic

donor acceptor segments enveloped by hydrophilic oligoethylene oxide loop that wrap around suitable alkali metal ions such as K^+, Na^+.



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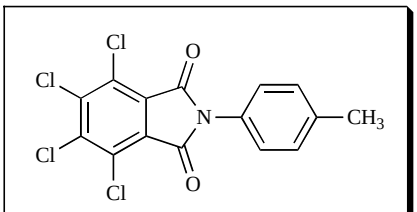
N-(*p*-Tolyl)tetrachlorophthalimide (**27**) forms channel type inclusion compounds with aromatic guest molecules with appropriate size such as benzene [37]. Pharmaceutically important phthalimide derivatives such as 1,4-diphenyl-3-phthalimido-2-azitidinone (**28**) are found [38] to form 1:1 and 2;1 inclusion compounds with benzene and 1,4-dioxane respectively.



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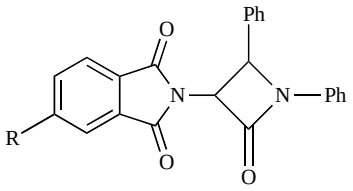
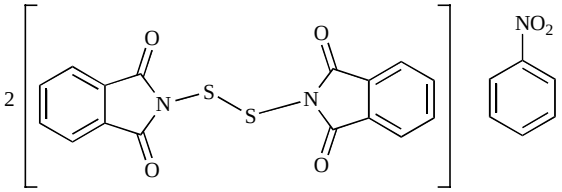


28 R= H, NO_2

N,*N*´-Dithio-*bis*-phthalimide (**29**) forms 2:1 inclusion compound with solvents like nitrobenzene (Fig. **9**), chlorobenzene and toluene [39]. The molecules are linked by C−H···O hydrogen bonds and by aromatic π-π stacking interactions to form channels along [100] direction and the nitrobenzene molecules lie in these channels involving C−H···O hydrogen bonds and C−H···π interactions with the *bis*-phthalimide moiety (Fig. **9**). Unlike nitrobenzene, chlorobenzene molecules lie in isolated cavities and the toluene molecules lie within the continuous channels formed by the phthalimide stacks.

Racemic *N*-azitidinone (**30**) substituted phthalimide forms inclusion complex (Fig. **10**) with optically active 10,10´-dihydroxy-9,9´-biphenanthryl (**31**) host leading to the optical resolution of the azitidinone derivative [40]. The crystal-packing diagram in the lattice of the co-crystal is shown in Fig. (**10**).



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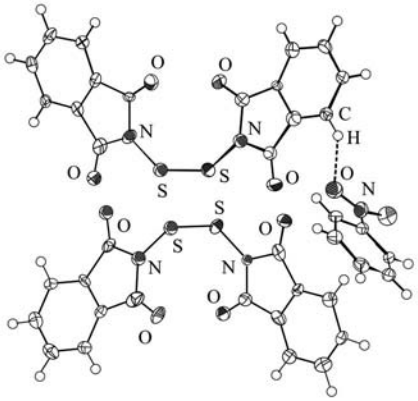
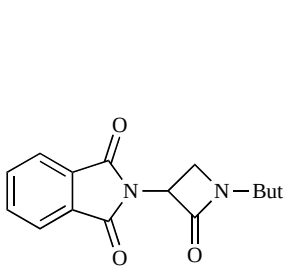
a)

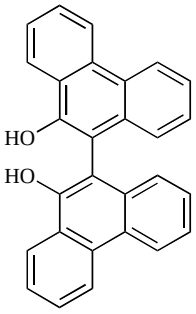


b)

Fig. (9). a) Co-crystal of **29** with nitrobenzene and its (b) structure of the co-crystal.

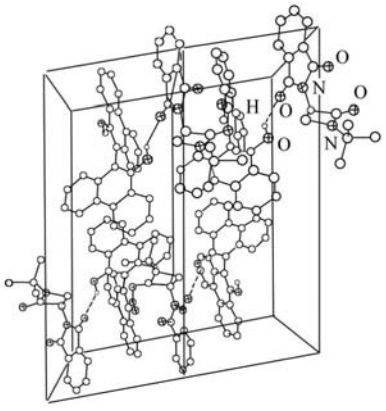


30 (±)



31 (s)-(-)

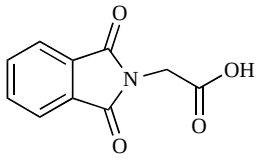
a)



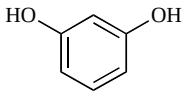
b)

Fig. (10). a) Co-crystal of **30** with 10,10´-dihydroxy-9,9´-biphenanthryl and b) its packing in the unit cell (hydrogen atoms are omitted for clarity).

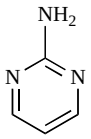
The *N*-phthaloylglycine (**18**) either can form adduct or salts with different aromatic amines (chart **1**). The *N*-phthaloylglycine forms 2:1 co-crystal (**33**) with 1,3-dihydroxybenzene [28b]. The co-crystals are in the orthorhombic Pccm space group. From the crystal structure of co-crystal **32** it is observed that two molecules of *N*-phthaloylglycine (**18**) are in the form of H-bonded cyclic dimer in $R^2_2(8)$ motif involving O3−H···O2 intermolecular interaction with which a 1,3-dihydroxybenzene interacts with the imide carbonyl groups of *N*-phthaloylglycine through O4−H···O1 intermolecular hydrogen bonding as shown in Fig. (**11**).



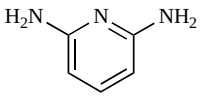
18



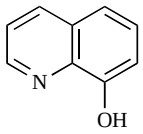
1,3-dihydroxybenzene



2-aminopyrimidine



2,6-diaminopyridine



8-hydroxyquinoline

Chart 1.

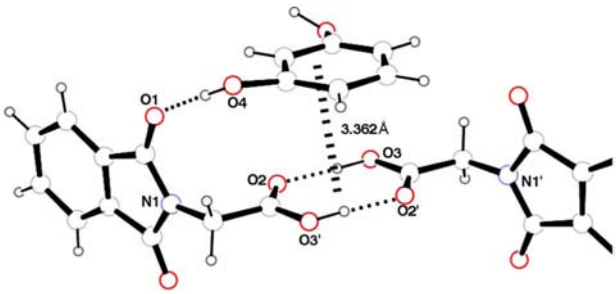


Fig. (11). The structure of co-crystal of 1,3-dihydroxybenzene with *N*-phtahloylglycine.

In the dimeric units formed by the hydrogen bonding between the carboxylic acid groups the phthaloyl groups are disposed in *trans* to each other. In this co-crystal the aromatic rings of phthaloyl units are packed with a separation of 3.39 Å along the a-axis whereas along c-crystallographic axis the distances between two consecutive 1,3-dihydroxybenzenes are 6.704 Å; the interplanar distance along c-axis between the aromatic rings of 1,3-dihydroxybenzenes and the carboxylic acid ring are 3.362Å (which implies that the 1,3-dihydroxybenzene units are aligned along ab-plane, 3.362Å apart from the dimeric –COOH groups. Crystal structure of the co-crystal **33** formed between **18** and 2-aminopyrimidine [28b] shows that it crystallises in orthorhombic Pbcn space group and 2-aminopyrimidine does not deprotonate *N*-phthaloylglycine but forms hydrogen bonded co-crystals through complementary O4−H···N3 and N2−H···O3 intermolecular hydrogen bonding interactions as shown in Fig. (**12**). In this co-crystal the complementary effect of the N=C-NH_2 part of the 2-aminopyrimidine with the carboxylic group of **18** leads to $R^2_2(8)$ hydrogen bonding motif. Theses hydrogen bonded units are further held together in the lattice through weak C2−H···O1 intermolecular interaction leading to extended hydrogen bonded zig-zag assembly along c-axis. One of the imide carbonyl group interacts with 2-aminopyrimidine molecules through C11−H···O2 intermolecular interaction (Fig. **12**).

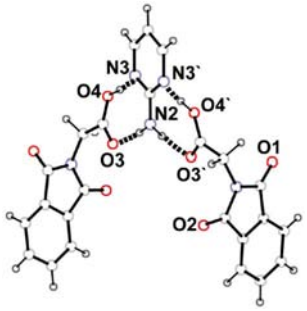


Fig. (12). The structure of co-crystal of 2-aminopyrimidine with N-phthaloylglycine.

Single crystal X-ray diffraction studies of the co-crystal of **18** with 2,6-diaminopyridine **35** shows 2,6-diamino-pyridine deprotonates **18** to form a 1:1 salt [28b]. One amino groups involve in hydrogen bonding with the carboxylate unit through N3−H···O1 and N4−H···O1intermolecular interaction. The pyridine nitrogen atom is involved in hydrogen bonding with carboxylic acid group of **18** through N2−H···O2 intermolecular interaction. The hydrogen bonding involving the pyridine N-atom and one of the amino acid groups of 2,6-diaminopyridine with the carboxylate group of **18** can be described as $R^2_2(8)$ hydrogen bonding motif (Fig. **13**).

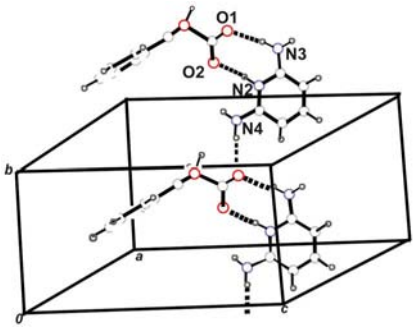


Fig. (13). The structure of salt of N-phthaloylglycine with 2,6-diaminopyridine.

Single crystal X-ray diffraction studies of the co-crystal **18** with 8-hydroxyquinoline **35** reveals [28b] it to be an assembly of one neutral molecule of **18** with the salt of 8-

hydroxyquinoline by **18**. The self-assembled structure is formed through hydrogen bonding and aromatic-π stacking interactions as illustrated in Fig. (**14**).

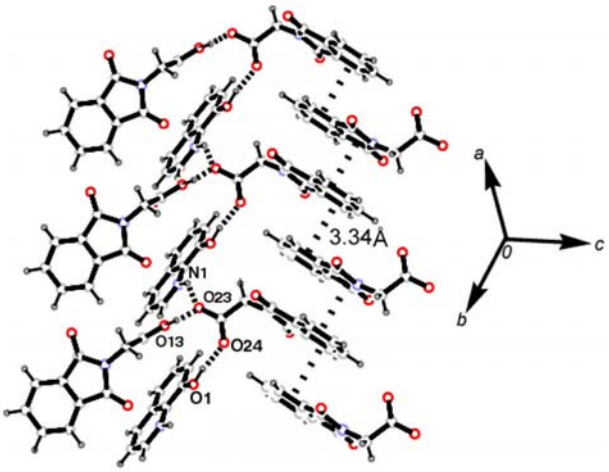
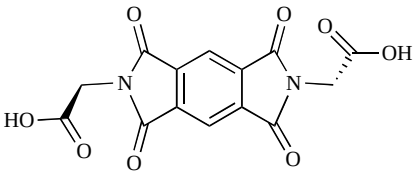
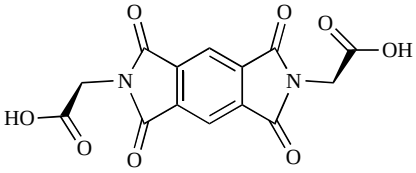


Fig. (14). Hydrogen-bond and aromatic stacking in the salt of *N*-phthaloylglycine with 8-hydroxyquinoline.

The guest-host chemistry is also extended to similar electron poor π-conjugated host *N,N′-bis*-(glycinyl) pyromellitic diimide (**34**). This molecule has two carboxylic acid groups at distal ends and may have *syn* or *anti* form (Chart **2**).



anti

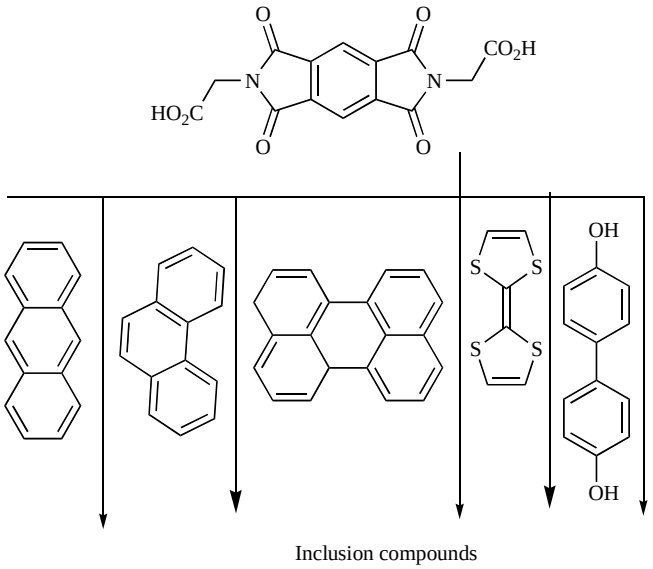


34

syn

Chart 2. Two conformers of *N,N′-bis*-(glycinyl)pyromellitic diimide.

This compound (**34**) has the central planar pyromellitic diimide unit, which is electron poor and interacts with electron rich guest molecules through donor acceptor interaction [41]. It has been shown [42] that the *N,N′-bis* (alkyl)pyromellitic diimide derivatives are very suitable synthons which provide different kind of space for co-crystal formation when it is in *syn* or *anti*- orientation and selectively in substrate recognition can be achieved . The compound **34** has been used for encapsulation of aromatic polynuclear compounds [40] such as shown in Scheme **3**. Recently it is also demonstrated the type of interactions varies in encapsulation of polynuclear aromatic hydrocarbons [28c].



Scheme 3. Different molecules forming inclusion compound with *N,N′-bis*-(glycinyl)pyromellitic diimide.

On the other hand, with 2,6-diaminopyridine, compound **34** forms co-crystal in mixture of ethanol/acetonitrile as orange red crystals [41] and characterized spectroscopically as 1:1 co-crystal (**35**). The co-crystal **35** are formed in monoclinic P2(1)/c space group. 2-Aminopyrimidine does not deprotonate **34** but behaves as hydrogen bond donor and acceptor. The assembly is formed by the complementary N−H···N, N−H···O and O−H···N intermolecular hydrogen bonding interactions (Fig. **15**).

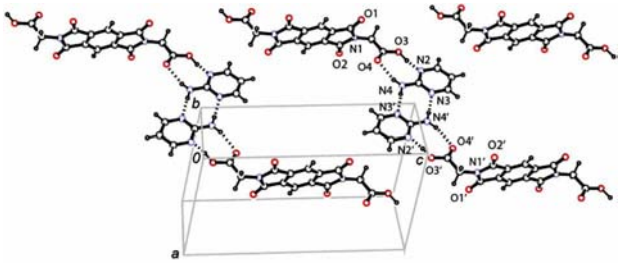


Fig. (15). Crystal structure of co-crystal of 2,6-diaminopyridine with **34**.

Crystal structure of the co-crystal of **34** with 2,6-diaminopyridine [28b] reveals that the cocrystal has two carboxylic acid end-groups of *N,N′-bis* (glycinyl) pyromellitic diimide in *syn*-disposition. However, one of the carboxylic acid group gets deprotonated by 2,6-diaminopyridine, thus it may not be considered to be a rotamer of the neutral *anti* form. The N^{+}–H thus formed participates in N+–H···O hydrogen bonding to a water molecule. These water molecules are held through N3−H···O1w (dN3···O1w 2.724(5)Å; <N3–H···O1w 171.5°) intermolecular interaction (Fig. **16**).

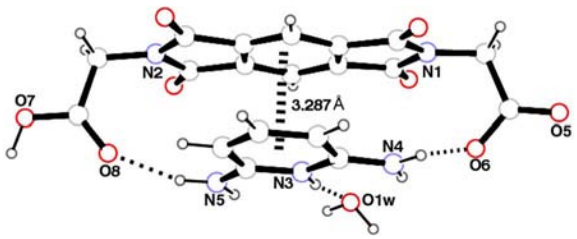


Fig. (16). Structure of salt of **34** with 2,6-diaminopyridine.

It is apparent from the figure that one molecule of 2,6-diaminopyridinium cation and a water molecule are anchored between the carboxylic acid/carboxylate groups of the *N*,*N*′-*bis*(glycinyl)pyromellitic diimide to show *syn*-disposition with respect to the central planar pyromellitic unit. The water molecule is further weakly hydrogen bonded to the imide carbonyl group of another such unit. The two amino groups are hydrogen bonded to the carboxylic acid/carboxylate end groups. It is observed that the carboxylate end group of **34** is hydrogen bonded to an undeprotonated carboxylic acid group from another unit leading to a hydrogen bonded assembly of the 2,6-diaminopyridinium salt of **34**. Moreover, it is observed that the interplanar distance between the aromatic ring of 2,6-diaminopyrimidine and the central pyromellitic diimide unit is 3.29Å which indicates a strong donor-acceptor interaction.

Recently phenol-pyridine hydrogen bonded synthon is shown [43] as persistent recognition pattern in a family of molecular complexes of isonicotinamide and phenols and carboxy-substituted phenol. Hydroxy aromatics such as 1,3-dihydroxybenzene and 1,3,5-trihydroxybenzene are used [44] as building blocks for designing various supramolecular architectures. The 2-hydroxyethyl phthalimide **36** has interesting hydrogen bonded structure [45] as illustrated in Fig. (**17**).

The hydroxyl groups of **36** are involved in intermolecular hydrogen bonding to one of the imide carbonyl groups of through O1−H···O2 interaction. This moderate hydrogen bonding can be represented by $C^1_1(3)$ motif. These hydrogen-bonded chains are further linked together by weak intermolecular C8−H···O2 interactions. No aromatic π-stacking interactions were observed between the phthalimide rings. Structural study on analogous *N*-(3-iodopropyl) phthalimide derivative shows similar folded step like structure in solid state assembled through C−H···O hydrogen bonding [46]. Compound **36** forms 1:1 co-crystal **37** with 1,3-dihydroxybenzene [45]. Solid-state structure of co-crystal **37** at room temperature shows that the co-crystal **37**

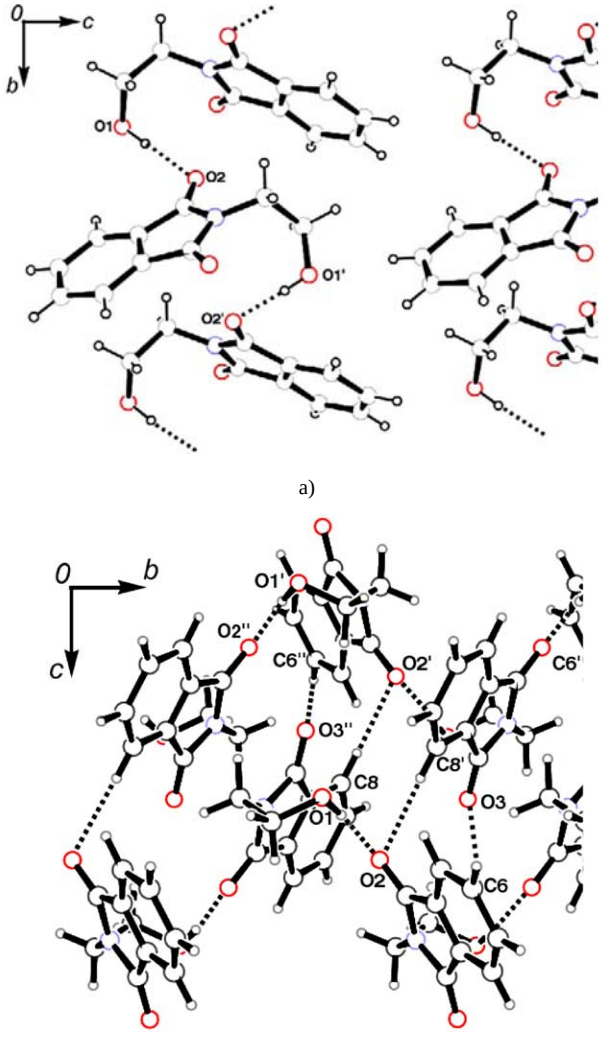


Fig. (17). a) The crystal structure of **36** and b) self-assembly of 2.1 through C-H···O interactions.

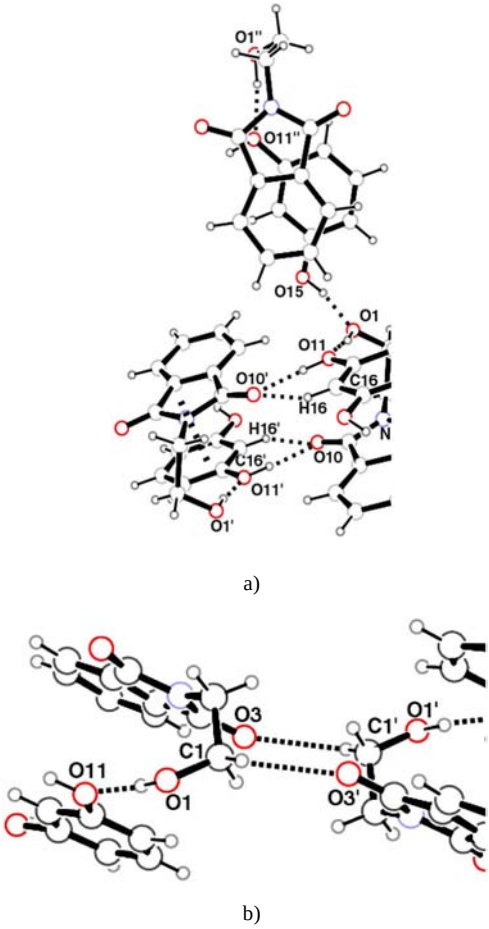


Fig. (18). a) hydrogen bonded assembly of **36** and 1,3-dihydroxybenzene b) weak C−H···O interaction in the co-crystal **37**.

crystallizes in monoclinic C2/c space group. The assembly of the components is governed by the hydrogen bonding, weak C−H···O and aromatic π-stacking interactions. The hydroxy group of **36** interacts with one of the phenolic-OH group of 1,3-dihydroxybenzene through intermolecular O1−H···O11 and O11−H···O10 hydrogen bonding interaction (Fig. **18**).

Transition Metal Complexes of Phthaloyl Derivatives

N-phthaloylglycine is reported to form dinuclear complex with silver(I) where the ligand *N*-phthaloylglycine coordinates to the metal center through a monodentate carboxylate unit and through the imide carbonyl as neutral ligand [47]. Moreover, tetranulclear tin(IV) complex of *N*-phthaloylglycine is synthesized and it is shown [48] that the ligand *N*-phthaloylglycine coordinates to the metal center in monodentate fashion. There are good number of examples on pyridine substituted *N*-*N*'-pyromellitic diimide complexes of tin and silver [49]. The Co(II) complex [50] of *N*-phthaloylglycine has composition $[Co(L)_2(H_2O)_4]2H_2O$. It has a distorted octahedron environment with four aqua ligands occupying one plane of the octahedron. There are two monodentate carboxylate groups at the axial positions (Fig. **19**).

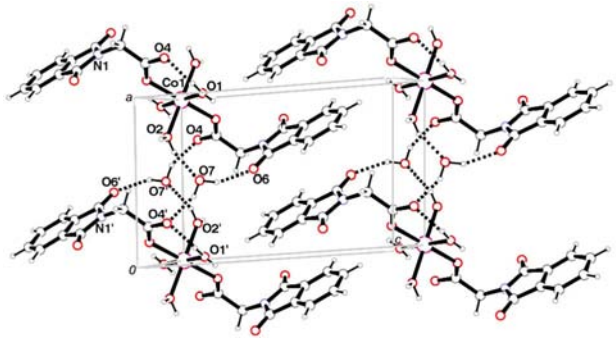


Fig. (19). Crystal structure showing two units of tetra-aqua *bis*-*N*-phthaloylglycinato cobalt(II)dihydrate.

Since the cobalt complexes is coordinated through carboxylate group it's coordination may be compared with the supramolecular construction that is made from analogous carboxy-phosphonate complex reported in the literature [51]. It is found that water molecules are involved in a tight packed structure in our cobalt complex, in contrast to the supramolecular assembly reported from carboxylate phosphate that has interesting S-shaped voids filled with water molecules. In that case, it is observed hexa coordinated cobalt with two water molecules occupying coordination site and had observed it be a cluster containing three cobalt centers. But in the case of tetra-aqua *bis*-*N*-phthaloylglycinato cobalt(II)dihydrate four water molecules are coordinated to Co(II), which are in two different environments with a three dimensional network.

The Ni(II) complexes of *N*-phthaloylglycine may have different compositions [52] depending on the synthetic procedure as shown in the scheme **4**.

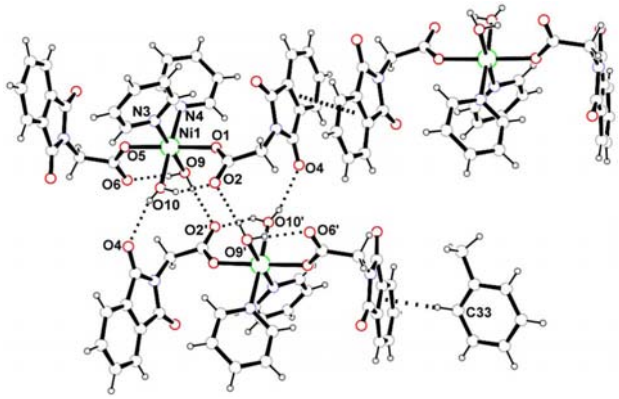
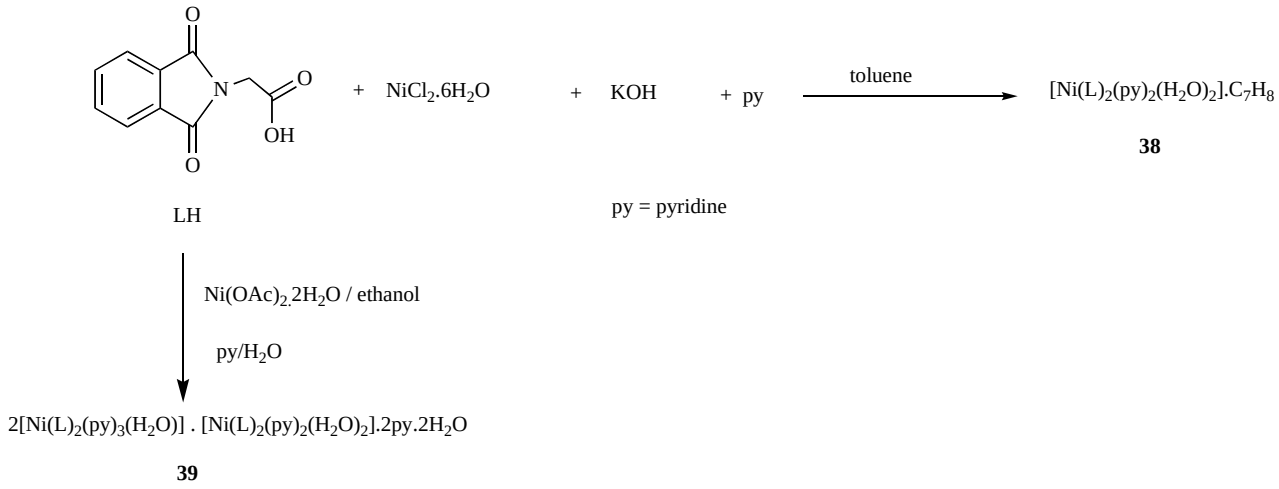


Fig. (20). Hydrogen bonded self-assembly of *bis*-(pyridine)-*bis*(aqua)-*bis*-(*N*-phthaloylglycinato) nickel(II).toluene (**38**).

Single crystal X-ray diffraction study of the complex **38**, namely *bis*-(pyridine)-*bis*(aqua)-*bis*-(*N*-phthaloylglycinato) nickel(II).toluene, shows that the Ni(II) centres are in octahedral environment (Fig. **20**). The monodentate *N*-phthaloyl glycinate ligands are occupying the axial positions with Ni1−O1 and Ni1−O5 bond distances of 2.076(1) and 2.058(1)Å and O1−Ni1−O5 bond angle of 178.91(6)°



Scheme 4. The variation in complex formation of Ni(II) with *N*-phthaolylglycine on changing reaction procedure.

respectively in a *cis* disposition with respect to the phthaloyl units. Two pyridine and two water molecules are occupying the equatorial positions in a *cis* disposition to each other. The coordinated water molecules are involved in intra-molecular hydrogen bonding with the carbonyl group of the monodentate carboxylate unit.

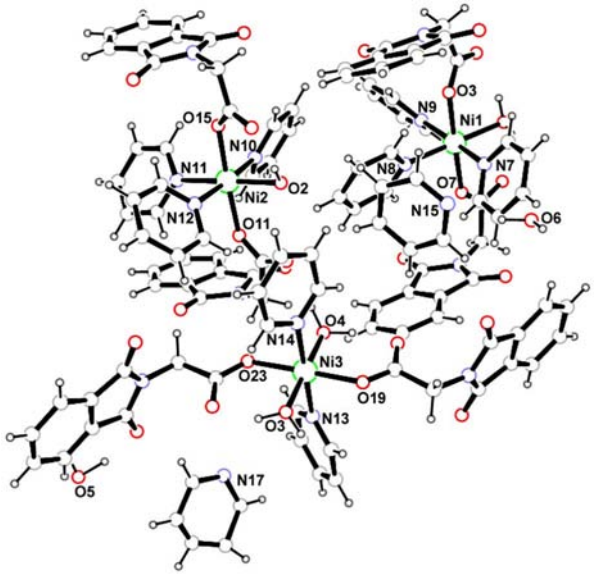
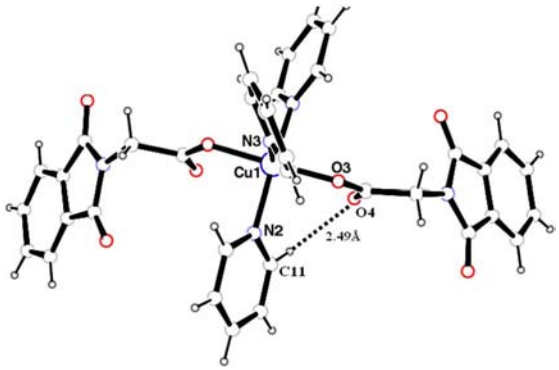


Fig. (21). Crystal structure of $[Ni(L)_2(py)_3(H_2O)].[Ni(L)_2(py)_2(H_2O)_2].2py.2H_2O$.

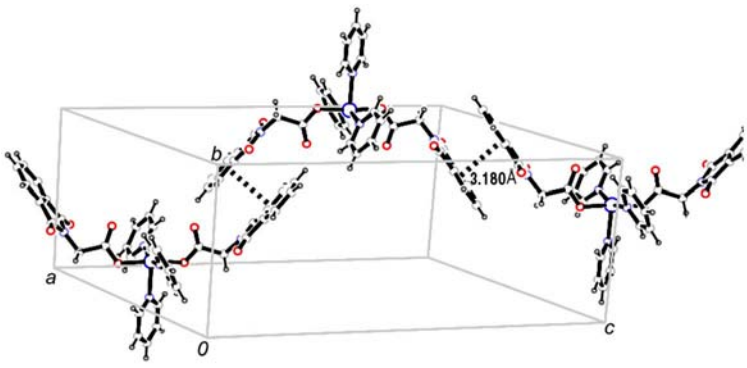
From reaction of nickel(II)acetate with *N*-phthaloyl-glycine, a water insoluble complex was obtained [52], structural studies revealed it to be a co-crystal of two molecules of $[Ni(L)_2(py)_3(H_2O)]$ with one molecule of $[Ni(L)_2(py)_2(H_2O)_2]$ where L= **18**, along with two molecules each of pyridine and water. The structure is shown in Fig. (**21**). One of the water molecules of crystallization is disordered: positions O(5W) and H(51W) have occupancies of 2/3, O(5W') and H(53W) of 1/3, H(52W) position is the same in both cases. One of the pyridine molecules of crystallization is intensely disordered. It was approximated by two orientations, (i) N(16) and C(106) to C(110) and (ii) N(17) and C(111) to C(115) [with their hydrogen atoms], having occupancies of 1/2 and restrained bond distances. This complex is interesting for two reasons. Firstly it is a co-crystal containing two independent inorganic complexes having difference in the composition but derived from same set of ligands. Secondly the self-assembly formed has some uncoordinated ligands suggesting it to be an intermediate meta-stable compound. Metastable nature of the compound is revealed from the ESI mass spectra of the compound in DMF solution has the highest mass at 483.0; corresponds to a $Ni(L)_2(H_2O)$ cation. The observation of the molecular peak of monomeric species shows that the complex remains as discrete unit in solution and during crystallization the assembly of the meta-stable product is formed.

Looking at the projection of the un-coordinated disordered pyridine one can project this as a species involved in nucleation process, where the pyridines are yet to be uniformly distributed among different nickel(II) ions.

The Cu(II) complex of *N*-phthaloylglycine, $[Cu(py)_3(Nphgly)_2]$ (**40**) is structurally characterized [50]. The crystal structure represented in Fig. (**22**) shows that this copper

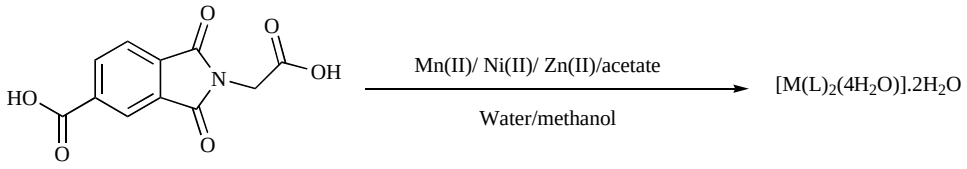


a)



b)

Fig. (22). a) Crystal structure of **40**, b) Self-assembly of **40** through aromatic π-stacking interactions.



LH2

41

42 M= Mn(II)
43 M= Ni(II)
44 M= Zn(II)
LH2 = 41

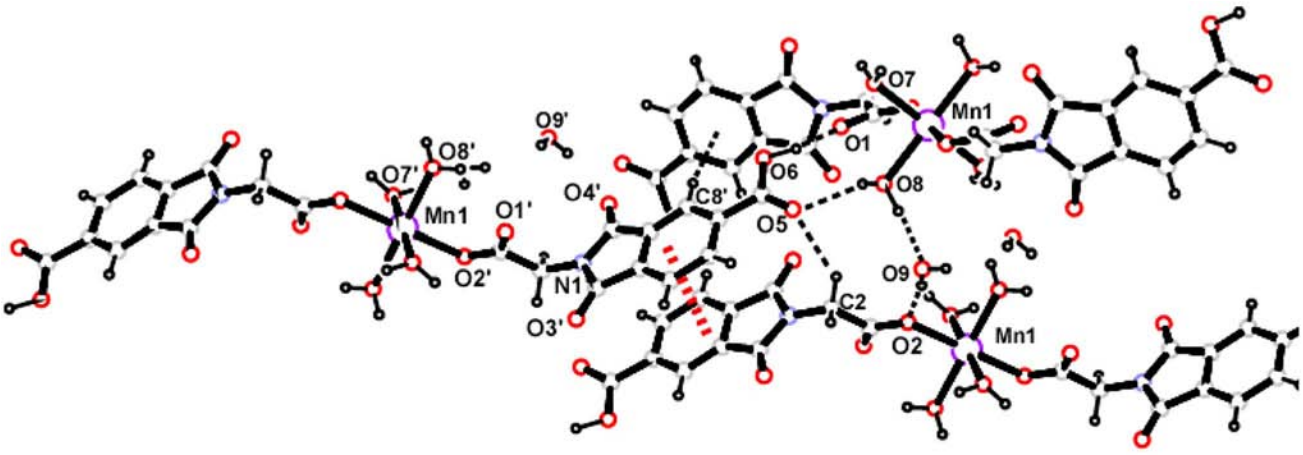
Scheme 5. Few first-row transition metal complexes of 4-carboxy *N*-phthaloylglycine.

complex has a square pyramidal geometry around the copper atom. In this complex also the *N*-phthalolylglycinate ligand coordinates to the copper in a monodentate fashion. Two of the pyridine ligands and two monodentate carboxylate ligands occupy the basal plane of a square pyramid and the other pyridine occupies the axial position.

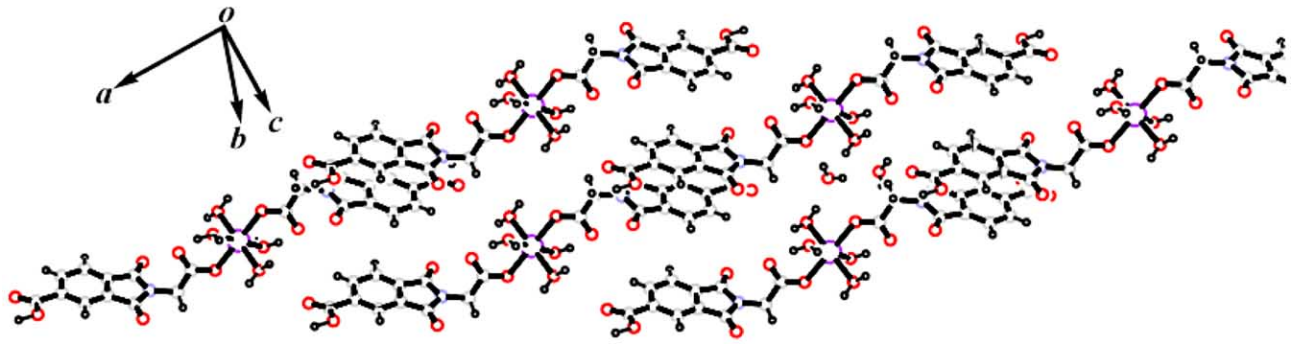
By using 1:1 metal acetate salt to ligand molar ratio the corresponding Mn(II), Ni(II) and Zn(II) complexes of 4-carboxy *N*-phthaloylglycine (**41)** were prepared according to Scheme **5**. In all the cases, single crystals of the complexes are reported [53].

One representative case of Mn(II) complex is shown in Fig. (**23**). In these complexes the carboxylic acid group attached to the aromatic phthalimide unit remains neutral. Moreover two water molecules are present as water of crystallization, which are held in the lattice through intermolecular hydrogen bonding with the coordinated water molecules and the carboxylate/carboxylic acid groups of the ligand.

Crystal structure of the complex **42** shows that the individual units self assembles through aromatic π-stacking interactions among the 4-carboxyphthalimide units of the ligand **41**. The interplanar distance of separation is 3.37Å indicating strong aromatic π-stacking between two such phthalimide units. One such 4-carboxyphthalimide unit interacts with another such unit which is orthogonal to the other, through aromatic C8–H··· π [dC8···π 3.71Å] interaction) [53].



a)



b)

Fig. (23). a) Self-assembly of the complex **42** in solid state b) Packing diagram showing the aromatic π-stacking interactions among the 4-carboxyphthalimide units (lattice water molecules are omitted for clarity).

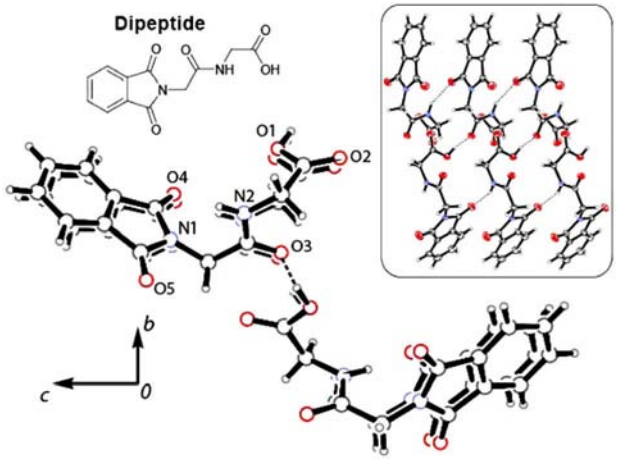
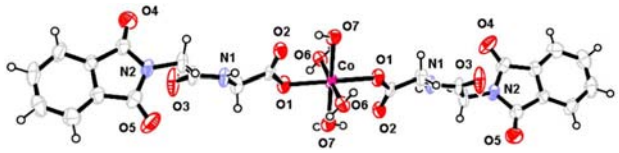
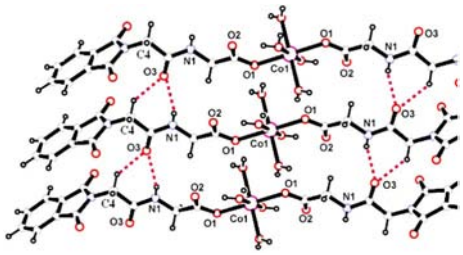


Fig. (24). 2D-molecular sheets arising from intermolecular hydrogen bonding in **45**; (Inset) The hydrogen bonded molecular sheets viewed parallel to bc-plane.

Glycylglycine is known to coordinate with divalent copper ions by means of its amino group, the deprotonated amido group and the carboxylate group [54]. Crystal structure shows that the self-assembly of the *N*-phthalimide protected glycylglycine in the solid-state is governed by intermolecular hydrogen-bonding interactions; instead of forming a β-sheet type of two dimensional assembly, the molecule adopts a puckered conformation [55] as shown in Fig. (**24**).



a)



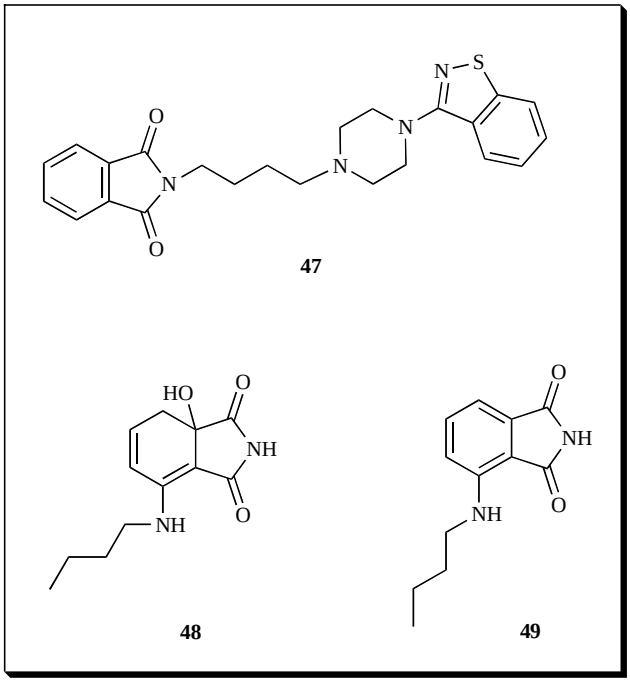
b)

Fig. (25). The ORTEP diagram (drawn with 30% ellipsoid probability) of a) *tetra*-aqua *bis*-*N*-phthaloylglycylglycinato cobalt(II) (**46**) b) Self assembly of **46** through the N-H···O and C-H···O interaction leading to β sheet structure in solid state.

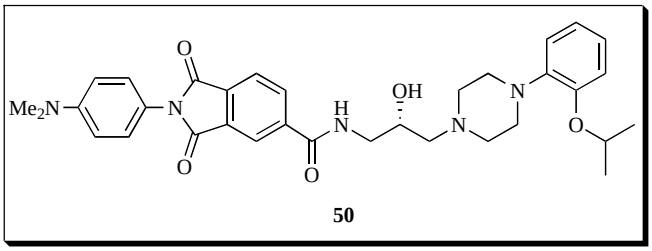
The templating effect of Co(II), Cu(II) and Zn(II) ions, three of the biologically important metal ions, on the self-assembly of the dipeptide (L) has been studied by preparing the corresponding $[ML_2(H_2O)_4]$ where M= Co(II) and Zn(II) and LH= **45** complexes and $[Cu_2L_4(H_2O)_4].2H_2O$ complex [55]. All these complexes have β-sheet structure in solid state despite having variation in coordination geometry around the metal ions (Fig. **25**).

Pharmaceutical and Material Applications of Phthalimide Derivatives

Phthalimide derivatives are also studied for their therapeutic uses. For example, 1-*N*-phthalamidobutane-3-one has a dose dependent hypolipidermic action with high therapeutic index, [56] which is free of estrogenic side effects and also with no apparent deposition of cholesterol in organs. *N*-phenyl phthalimide were shown to have anticonvulsant activities and neurotoxic properties [57]. 2-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl]-1-phthalimide (**47**) is a prominent therapeutic agent and it is active *in-vivo* antipsychotic agent [58]. Phthalimide derivatives such as 1-hydroxy butylphthalimidines (**48**) and butylaminophthalimide (**49**), exhibit anesthetic activity, the activities are comparable to that of novicine [59].



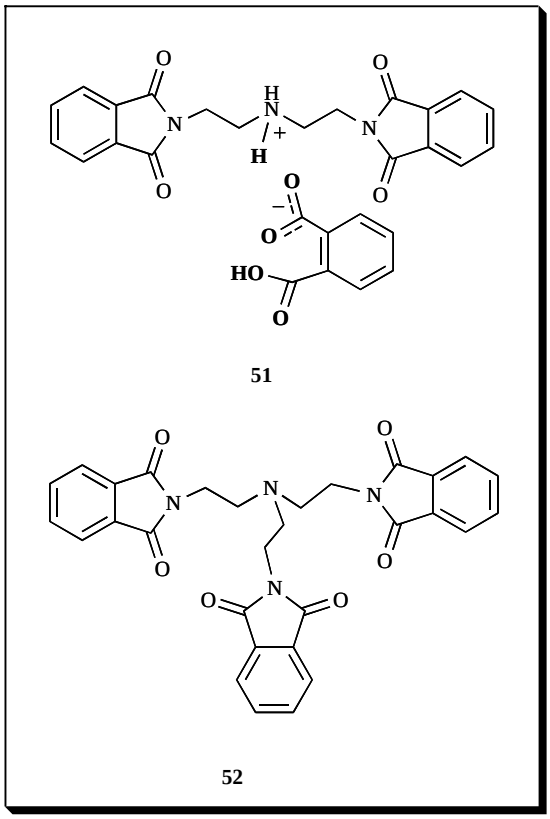
S-hydroxyphthalimide-phenylpiperazine derivative (**50**) is potential drug for treatment of prostatic hyperplasia in men [60].



Scope of the Phthalimide Derivatives

Foregoing discussion has shown that the phthalimide derivatives are useful materials for supramolecular chemistry and the host guest chemistry may have prospect for molecular recognition. The solid state structures of the phthalimide derivatives of diethylene triamine (**51**) and *N,N´*-triethylene tetraamine (**52**) as salts with corresponding phthalic acid showed the presence of offset π-π stacking interactions phthalimide units and they were held together by

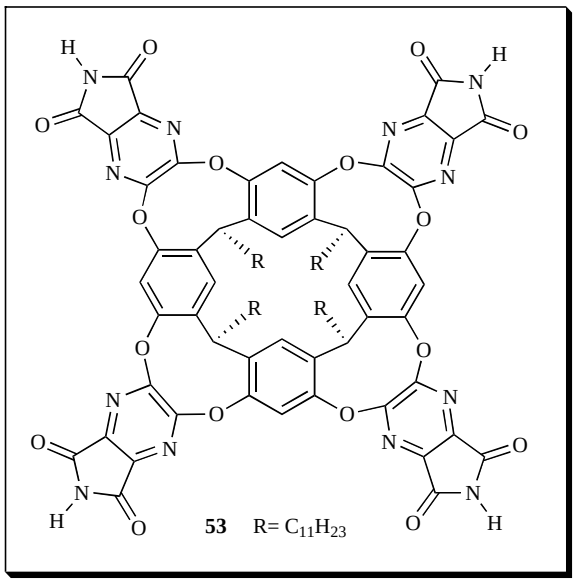
C−H···O and N−H···O hydrogen bonds. This result is an indicative of constructing interesting carboxylic acid salts having structural importance. These compounds show temperature dependence ^{1}H NMR spectra due to the possibility of different conformations that the phthalimide unit may adopt with respect to the intervening N-atoms in the linker.



51

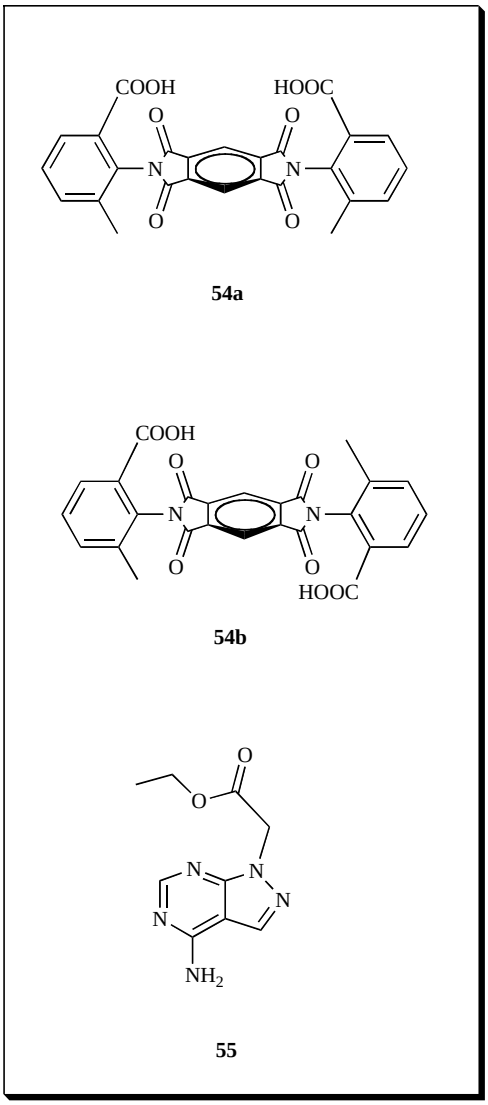
52

Resorcarene derivative (**53**) functionalized with phthalimide unit, self-assembles through complementary N−H••N and N−H••O hydrogen bond and reversibly encapsulates different *N*-protected amino acid esters, giving a method for enantio separation technique [61].



53 R= $C_{11}H_{23}$

The *syn*-isomer (**54a**) prepared from condensation of 2-amino-3-methylbenzoic acid with pyromellitic dianhydride have conformationally flexible and such molecules recognizes ethyl adenine-9-acetate (**55**) in acetonitrile [62]. The recognition process could be achieved by thermal isomerisation of the *anti*-isomer (**54b**) to the *syn*-isomer in presence of the guest. The *syn*-isomer retains its conformation even after the guest removal and thermal isomerisation leads to the *anti*-form. The recognition process is based on the fact that the rotation of the C_{aryl}–N_{imide} bond is restricted at room temperature and this conformationally imprintable atropisomeric system may be considered to be model to study complex dynamic recognition processes which can be turned on and off and also modified without any additional covalent syntheses. Thus, the study on such dynamic phenomenon would be of great value.

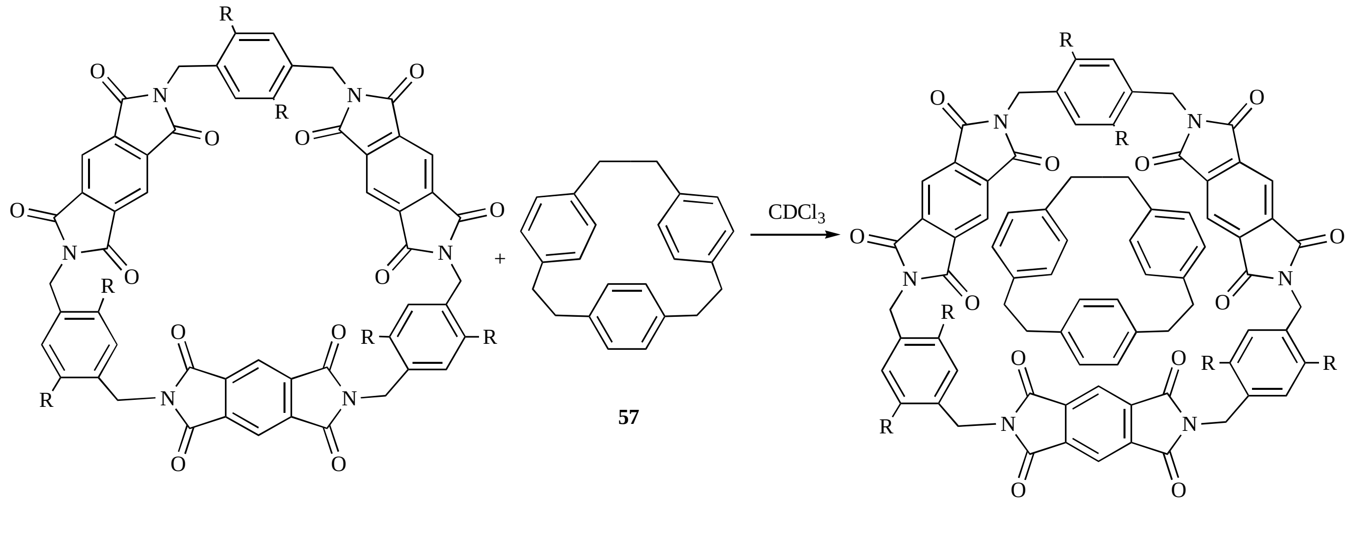


54a

54b

55

The *N,N´-bis*(2-tert-butylphenyl)pyromellitic diimide with guests such as phenols and indoles has sandwich structures [63]. Recently it has been demonstrated that the pyromellitic diimide based cyclophane (**56**) have rigid structure (Scheme **6**) and forms inclusion compound (**58**) with [64] paracyclophane (**57**) and solvents such as *p*-xylene and toluene. In this class of guest-host complex the inclusion



56, R= OMe

57

59

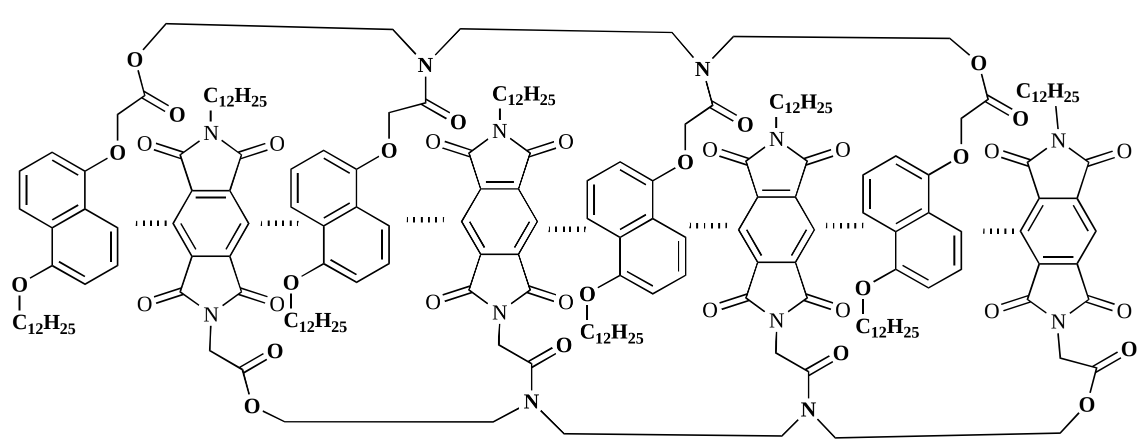
Scheme 6. Guest inclusion by a pyromellitic diimide based cyclophane.

of the guest molecules occurs due to donor-acceptor type π-stacking interactions [65].

The co-operativity of donor-acceptor interaction between electron rich 1,5-dihydroxynaphthalene or 1,4-dihydroxybenzene with electron deficient pyromellitic diimide is studied by ^{1}HNMR spectroscopy. Such studies show the formation of zipper type artificial duplex [66] (**59**).

Synthetic macromolecules (**60**) designed by connecting electron poor pyromellitic diimide with polyether bridge undergoes folding [67] in presence of ammonium salts of dialkoxy naphthalene derivatives (**61**). Such polymer folding is induced by the cooperative effects of the charge transfer interaction and also by the ammonium cation recognition.

Owing to the fact that phthalimide and pyromellitic diimide units are electron poor, these units can behave as π-acceptor; they form inclusion complexes with planar electron rich aromatic substrates [68]. Finally, metal ion coordination to such *N*-phthalimide derivatives leads to new self-assembled [69]. Systematic investigations on the weak interactions in the metal directed assemblies with ligands derived from phthalimide are still in infancy [69]. It is evident that from photochemical, photophysical properties of



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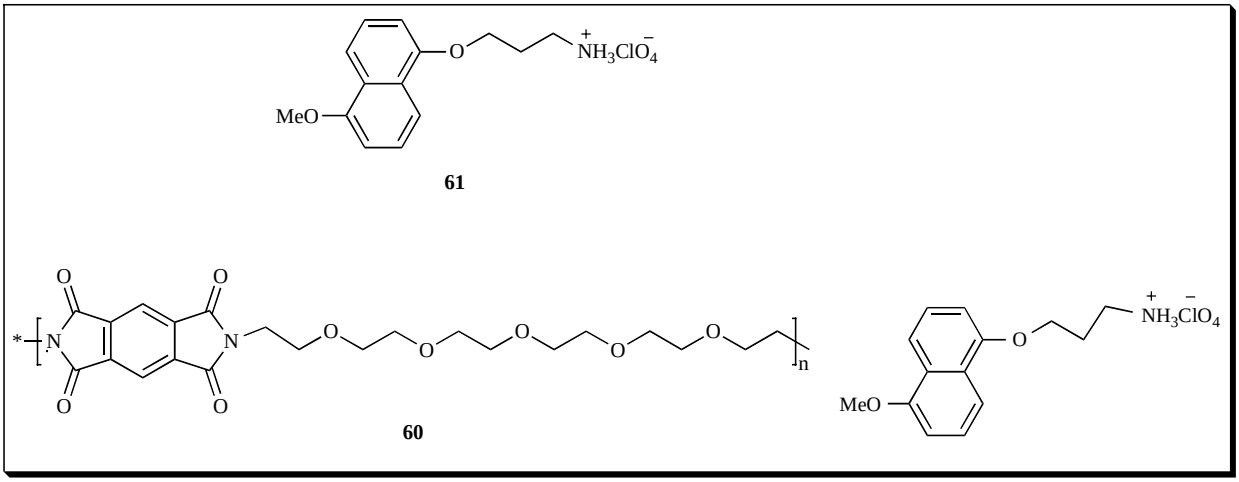

61

60

phthalimide derivatives have different facets and needs further understanding and definite goal can be obtained only taking up systematic study along with their properties. The nano-dimensional assemblies as well as selective guest host binding may be guiding factor for separation techniques and for obtaining novel electronic properties.

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