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Current Research in Materials Chemistry

Conformational Polymorphism in Organic Crystals: Structural and Functional aspects - A Review

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Abstract

Polymorphism in organic crystals involves the formation of isomeric molecular identities. It is dependent on the structural arrangement due to inter-atomic interactions, as well as external stimuli, which include temperature, visible and UV radiation. Conformational polymorphism of organic crystalline molecules is often the result of isomerism due to the twisting and turning of angular bonds. The arrangement of the atoms supports different types of bonding mechanisms (which include hydrogen bonding) within the same compound. This, in turn, results in the formation of cis/trans configurational isomers or a proton transfer species (tautomer), having different functional properties. The conformers support the flexibility of bond angles in an attempt to reduce strains, thereby leading to the occurrence of different structural isomers resulting in polymorphism. The challenge of predicting a crystalline structure from chemical formula (connectivity of atoms in the molecule) is overcome by the recent advances in molecular mechanics simulations. The useful applications of this methodology in the field of pharmaceutical development has played a vital role in understanding the function and dynamics of the thermodynamically most stable organic crystal polymorph landscape.

Introduction

Organic crystal polymorphs are compounds which exhibit more than one crystalline form of the same molecule, depending on the conformation of their constituent molecules. Polymorphism is the result of different types of bonds and packing existing in the conformers of the same compound which, interestingly, can result in chromatic fragments. This mechanism follows the self-assembly pathway of the organic compound during synthesis and is often referred to as crystal nucleation [1,2]. The growth of the crystal to macroscopic visualization level is dependent on the inter- and intra-molecular interactions in the compound. This, in turn, results in the most stable arrangement of atoms which is dependent on the position of each individual atom or molecule and their packing mode. The

occurrence of specific structural rearrangements results in various crystalline polymorphs.

Representative examples of structural polymorphs in organic crystals: molecular conformation, packing mode and related aspects

First we refer to the interesting case of 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile which exists as six solvent-free polymorphs [3]. Figure 1 presents such compounds where differences in bond arrangements and molecular interactions lead to differences in the overall crystal morphologies. The structural differences among the polymorphs is dependent on the mode of packing and conformation. Yu et al. [3] discovered that the different conformers are dependent on the torsional strain existing between thiophene and the o-nitroaniline fragment which results in different crystal colors (yellow, orange, and red). Further studies have shown that the most thermodynamically stable conformer is favored. For instance, formation of the polymorphs of bicifadine hydrochloride is dependent on molecular conformation as well as mode of packing. Interestingly, upon heating, a second polymorph is formed, slightly below the melting point [4]. The thermodynamic stability introduces external factors such as temperature-controlled movements resulting in locomotion (walking, rolling and jumping) in the crystals [5]. Also, the structure-property relationship is vital in predicting the different forms a single compound can exhibit. In this context Amplified Spontaneous Emission (ASE) has come into much recent prominence as a powerful technique for characterizing individual crystalline forms of organic compounds [6]. This method is especially effective in predicting conformational polymorphs (isomers). Remarkably, it provides evidence indicating that manipulating the polymorphic structure of organic compounds can reveal their functional properties, and developing structures of polymorphs are solely dependent on the atomic arrangements.

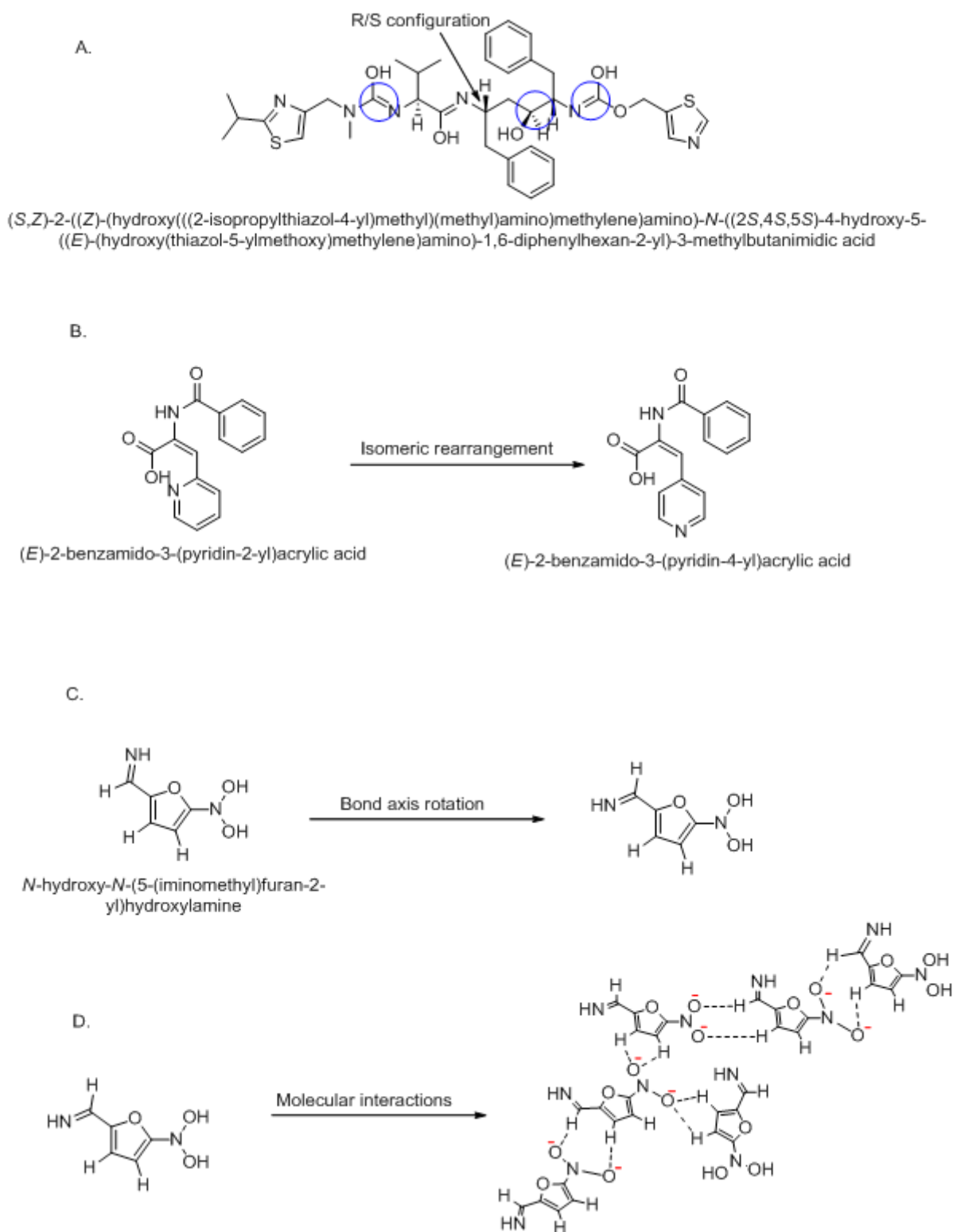


Figure 1. A. The chemical structure of Ritonavir [7]; blue circles denote torsion angles. B. The chemical structure of (*E*)-2-benzamido-3-(pyridin-2-yl)acrylic acid [8]. C and D shows the structure of *N*-hydroxy-*N*-(5-(iminomethyl)furan-2-yl)hydroxylamine [9].

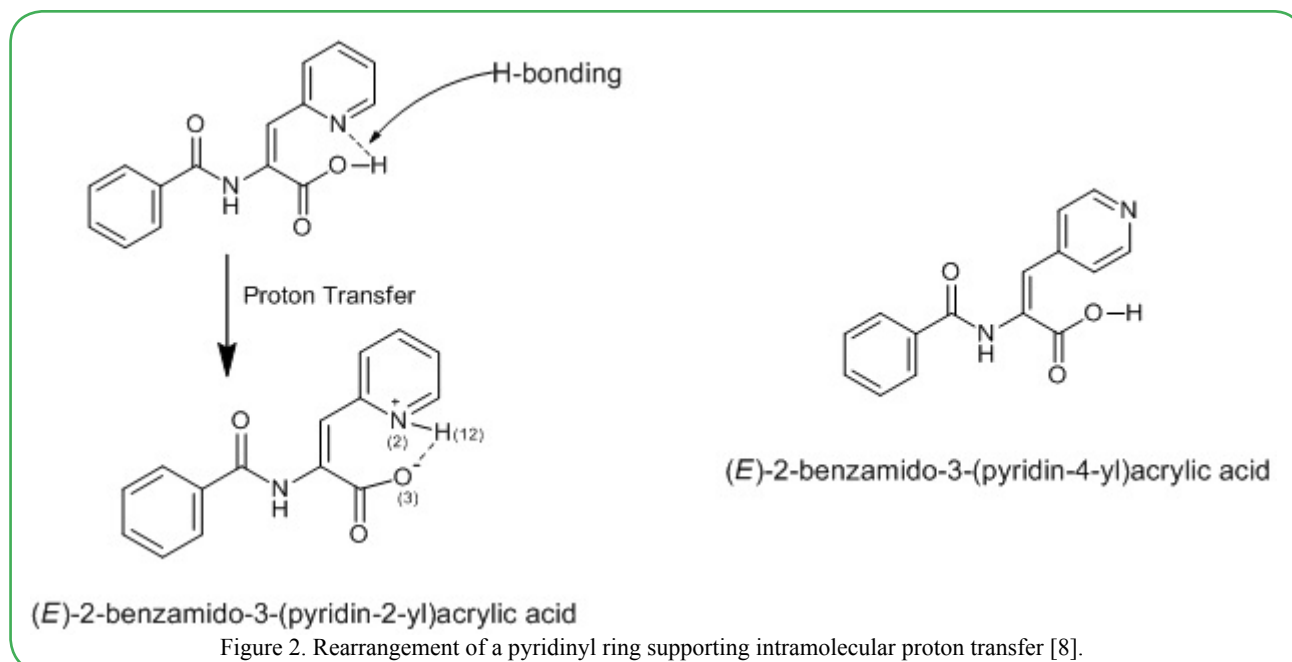
Role of hydrogen bonds on crystal structure and related physicochemical properties

Inter- as well as intra molecular hydrogen bonds in organic compounds have a crucial role on their crystal structure and physicochemical properties [8]. This is exemplified by the isomers (*E*)-2-benzamido-3-(pyridine-2-yl) acrylic acid and (*E*)-2-benzamido-3-(pyridine-4-yl) acrylic acid (shown in Figure 2), where the isomerization process

involves a rearrangement of a pyridinyl ring supporting hydrogen bonding. These two molecules contain a planar benzene ring and are chemically stable. The presence of the intramolecular H-bonding (IHB) in the first molecule, and its absence in the latter, causes remarkable differences in their physicochemical behaviors including solubility, pKa, and optical properties. The crystal structure of the first isomer (see Figure 2, left) shows a seven-membered ring intra-molecular hydrogen bond, which is absent in the other

isomer (Figure 2, right). These two isomers show distinctly different physicochemical properties, such as solubility and pKa. The π -conjugation between the pyridinyl and acrylate moieties is extended by IHB, leading to a strong electronic absorption maximum at ca. 340 nm. The O-H...N IHB facilitates occurrence of a photoinduced

excited state intramolecular proton transfer (ESIPT), which is a fundamental and extensively studied reaction in organic photochemistry [10,11]. Here, the ESIPT reaction results in 'two color' fluorescence with emission peaks at ca. 420 nm and 490 nm in the polar aprotic solvent acetonitrile, and furthermore, the IHB supports the strength of the organic crystals [8].

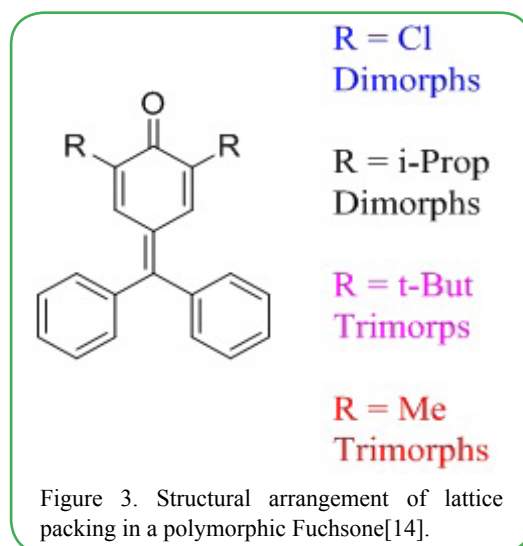


Intramolecular H-bonding in organic crystals in a donor-acceptor relationship usually ranges between $2.50 \leq d(\text{O} \cdots \text{O}) \leq 2.65$ and bonds shorter than 2.50 \AA ($d(\text{O} \cdots \text{O}) \leq 2.50$) exhibits very strong H-bonding [12]. Additional bonding in compounds can also affect the angular arrangements of atoms in the compound. These arrangements due to intramolecular forces of attraction and repulsion can also lead to additional bonding or bonding between the same atoms at different angles. This is demonstrated in Figure 2 where it is seen that hydrogen can be directly attached to the nitrogen of the pyridinyl ring. This results in a positive charge on the nitrogen (Figure 2) as it becomes protonated by the dissociated hydrogen from the acrylate part of the molecule. The hydrogen atom, in turn, is partially attracted to the negatively charged oxygen resulting in a different angular shape of the molecule ($\text{O}(3)\text{-H}(12)\text{-N}(2)$ angle is 171.3°).

X-ray diffraction is a common technique used for determining space between atoms in a molecule. X-ray diffraction studies on the compound shown in Figure 2 revealed the distance between $\text{O}(3)\text{-H}(12)$ to be 1.345 \AA , which is 0.425 \AA greater than the

theoretical length for hydroxyl (OH) in carboxylic acids. This length is also longer than the usual length of $\text{N}(2)\text{-H}(12)$ (1.145 \AA) indicating that $\text{H}(12)$ is bonded closer to $\text{N}(2)$ of the pyridine than $\text{O}(3)$ of the acrylate [8]. The tautomer in Figure 2 is stabilized by the delocalization of the electrons across $\text{O}(2)$, and -C=O making it to mainly exist as the proton transferred species (tautomer).

In a study on the analysis of the structure of conformational polymorph, Nangia et. al. [13, 14] indicated that X-Ray diffracted distance-angle scatter plots of $\text{O-H} \cdots \text{O}$ and $\text{C-H} \cdots \text{O}$ based on the data collected from Cambridge Structural Database implies that polymorphs with larger number of symmetry-independent molecules usually have better interactions than compounds with lower number of symmetry-dependent molecules. This study was done using crystal packing software to demonstrate the overlay of the rings in a molecule supporting the claim that bonding angle and length may result in a fully different crystal. A representation of the polymorphs is provided in Figure 3.



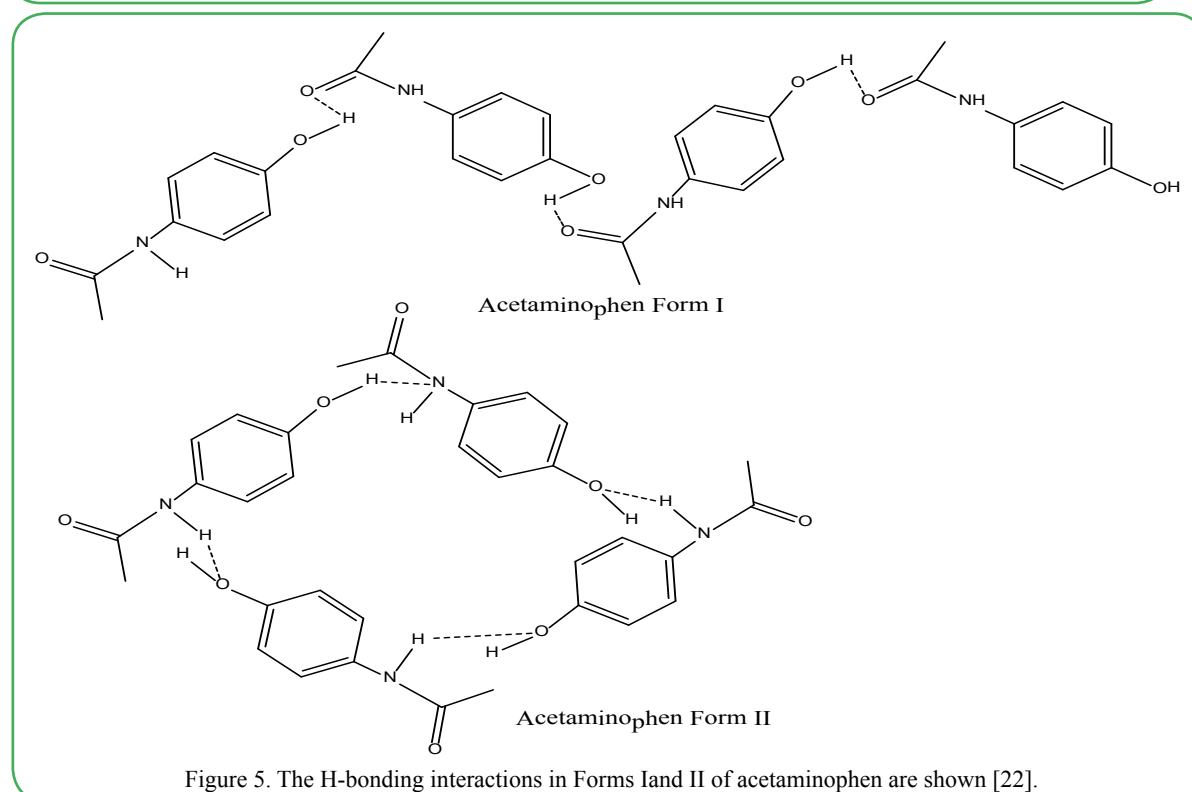
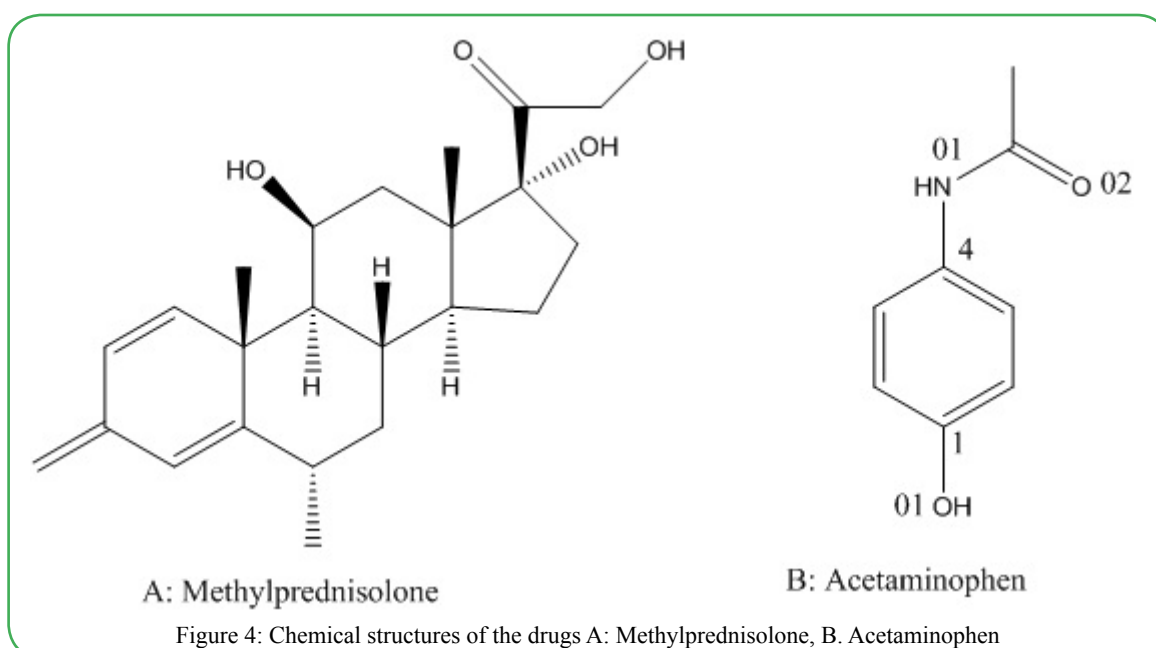
Polymorphism in pharmaceutically relevant compounds

Polymorphs of pharmaceutical drugs are particularly important due to the changes in their characteristics that may occur from one morph to the next. It is predicted that more than 50% of pharmaceuticals have multiple polymorphic forms [15,16]. Some potential drug characteristics that may be affected by polymorphic forms include efficacy, bioavailability, and toxicity [17].

Bioavailability is a major component of drug effectiveness; polymorphs of a drug may affect the solubility of the active ingredient, leading to an increase or decrease in the physiological concentration. The corticosteroid Methylprednisolone is typically used in therapeutic applications for its anti-inflammatory capabilities. Methylprednisolone (Figure 4) has two crystalline polymorphic forms, each of which exhibit different dissolution rates. During *in vivo* testing it was determined that Form II of methylprednisolone has a 1.2 times greater dissolution rate than the more stable Form I

of the drug [18]. A higher dissolution rate can be advantageous when considering the speed at which a drug will start taking effect and the levels to which it will be present.

Another common drug that shows polymorphic forms is acetaminophen (Paracetamol in Europe) (Figure 4). Acetaminophen has three known forms I, II, III [19]. Its unique structure makes it useful in conjugating with caffeine, morphine, phenatanyl and many other opioids of various strengths and delivering to the target [20]. Crystal structure prediction methodology (CSP) [21] is in high prominence for predicting the forms, and stability of many organic crystals and their polymorphs from known organic formulas. This will allow to determine the thermodynamically favorable polymorphs and their ability to bond to a specific substrate (e.g. opioid drugs) for a particular physiological target, and utilize more polymorphs in the pharmaceutical and medical field.



The most common and stable form I [22,23] (Figure 5) of acetaminophen is a sheet of acetaminophen with a herringbone packing Form I forming zig-zag shapes via (01)O–H----(02)O=C hydrogen bonds. Form II takes a flatter, plate-like morphology that is more organized than form I due to (01)N–H----O (02) and (01)O–H----O (2) intermolecular hydrogen bonds. The resulting structure has better tableting property. Form III is produced as needles organized into distinctive islands bonded much like form II, only orientated vertically [22]. Figure 5 shows the intermolecular hydrogen bonding in forms I and II.

Complex molecules that can form metal-ligand interaction are also affected by modification due to the docking of the metal ion [24]. Isonicotinic acid, for example, can stack together with different divalent metal ions which in turn changes the dimension of the molecular structure of the compound and also results in conformational polymorphism with different neutral layered arrays [24]. The new contorted molecule is now strengthened by additional hydrogen bonding interactions which stabilizes the structure of the compound. Another interesting example of polymorphism include the influence of a chlorine substituent in an aromatic system, such

as that in the potential anticancer drug, 4-chloro-2-phenylanthranilic acid (CPAA) (Figure 6). Three polymorphs of CPAA have been discovered. The highly electronegative chlorine can participate in hydrogen bonding, halogen bonding [25] and London dispersion forces [26]. This facilitates the rotation of the benzene ring making the interactions more accessible which thereby tightly pack the structure to global minima [27,28]. The hydrogen bond existing between the acidic portion of the compound 2-((3-chloro-2-methylphenyl)amino) benzoic acid) is shown in Figure 6. Due to twisting and turning of the aniline (Figure 6), H-bond strength varies. The resulting crystal will, therefore, be stronger though it may cause bending in the overall structure. Bending can result in mechanical stress which can be used to predict the mechanical response.

The aliphatic calorie-free sweetener acesulfame (6-methyl-1,2,3-oxathiazin-4(3H)-one 2,2-dioxide) is commonly used in food products, beverages, and in pharmaceutical formulations. Velaga and colleagues [29] discovered that acesulfame exist in two crystalline forms. One of the forms shows mechanical stress bending in crystalline studies. This form is more stable in ambient conditions

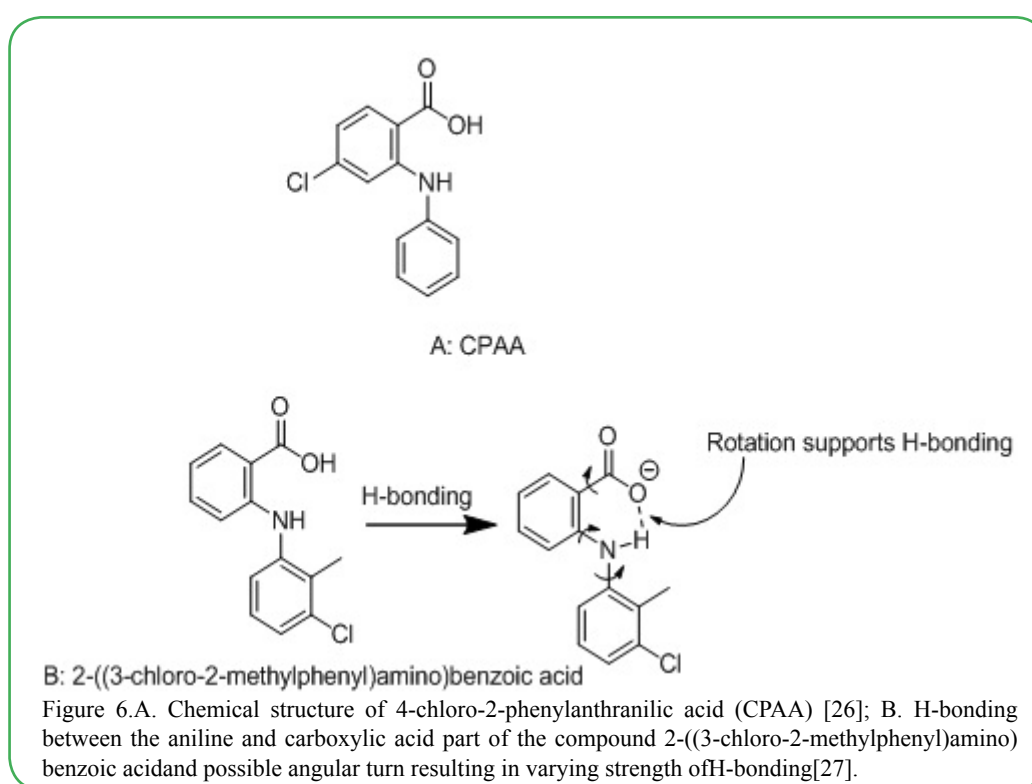


Figure 6.A. Chemical structure of 4-chloro-2-phenylanthranilic acid (CPAA) [26]; B. H-bonding between the aniline and carboxylic acid part of the compound 2-((3-chloro-2-methylphenyl)amino) benzoic acid and possible angular turn resulting in varying strength of H-bonding [27].

making acesulfame the first aliphatic organic compound to exhibit stabilized bending phenomenon. Additionally, bond bending and twisting can occur simultaneously, according to Bond, A. *et. al.*, as in the case of aspirin [30]. This may result in particles growing into each other. The crystalline arrangements are very similar such that aspirin crystals intergrow within itself forming inter growth structures [30].

Polymorphism can also occur in engineered cocrystals that may result from intergrowth [31]. In such case, calculated X-Ray powder diffractometric data for single crystal shows a valid relationship between the position of the peak and reflections. Error in measured data arises, however, when the intensity is increased. The difference in the structure of polymorphic organic crystals is determined by several different computational and analytical method including X-ray crystallography [32], Neutron Diffraction [33], BIOVIA Materials Studio Polymorph Predictor [34], and Cambridge Structural Database [35] for retrieving compounds.

Experimental Tools for determining crystal structures X-ray Crystallography and powder diffraction techniques

Diffraction of X-rays and neutrons provide powerful and complementary tools for determining the structures of organic crystals. X-ray crystallography [32] is a highly reliable method for determining the atomic and molecular structure of organic crystals. This is possible because the atoms can diffract X-ray beams in different directions, generating a pattern which reveals the arrangement of atoms within a crystal structure, thus providing precise information on 3-dimensional structure, including accurate data on bond lengths and bond angles. However, very often, if the crystals are not large enough to permit single crystal diffraction studies, the sample can be analyzed by an alternative (though less informative) technique, namely X-ray powder diffraction (XRPD) [32,36]. A beam of X-rays striking a sample containing randomly oriented micro-crystals (powders) produces a pattern of rings, which is useful for establishing the identity of the solid substance, and as a fingerprint for a particular crystalline phase.

Neutron Diffraction

In view of wave/particle duality, neutrons can be diffracted like X-rays. Unlike X-rays, neutrons do not interact with electron shells, and instead, they interact with the atomic nuclei. Therefore, using neutron diffraction, specific and accurate data can be collected on hydrogen bonds because of the depth of the penetrability of the radiation and its interaction with the atomic nuclei [33]. The quantum interactions and emanation of diffracted particles are measured in small units (Å, or even 10-15m.) making it suitable to measure the interactions of H-bonding and, thus, detecting the hardness of the crystal [33,38]. Use of the neutron diffraction technique increases the likelihood of validating conformational polymorphism. Thus X-ray and neutron diffraction serve as complementary techniques for in depth structural studies on organic crystals.

Solid state NMR and Electron Diffraction techniques

For pharmaceuticals, where samples are frequently available in powder form with micro to submicrometer sized grains, detailed

structural analysis is limited by X-ray crystallography and neutron diffraction. Solid state NMR along with electron diffraction (ED) appear to be promising tools with emerging potential in these cases. In a recent study, Oikawa et al. [39] demonstrated the combined use of multidimensional ssNMR and ED to discriminate (in finger print patterns) three crystalline polymorphs of L-histidine namely orthorhombic (form A) and monoclinic (form B) samples of L-histidine (shown in Figure 7), and L-histidine •HCl•H₂O. Since intense electron beam induces degradation in organic molecules, very mild level of irradiation was used, to avoid such degradation effects.

BIOVIA Materials Studio Polymorph Predictor

BIOVIA Material studio [34,42] is a computer simulation and modeling software that is useful for predicting potential polymorphs of a compound directly from its molecular structure. Users have a visual image to fully understand and compare polymorphic structures. Analyzing the simulation requires understanding of surface interactions, intra-molecular bonding and bond rotations.

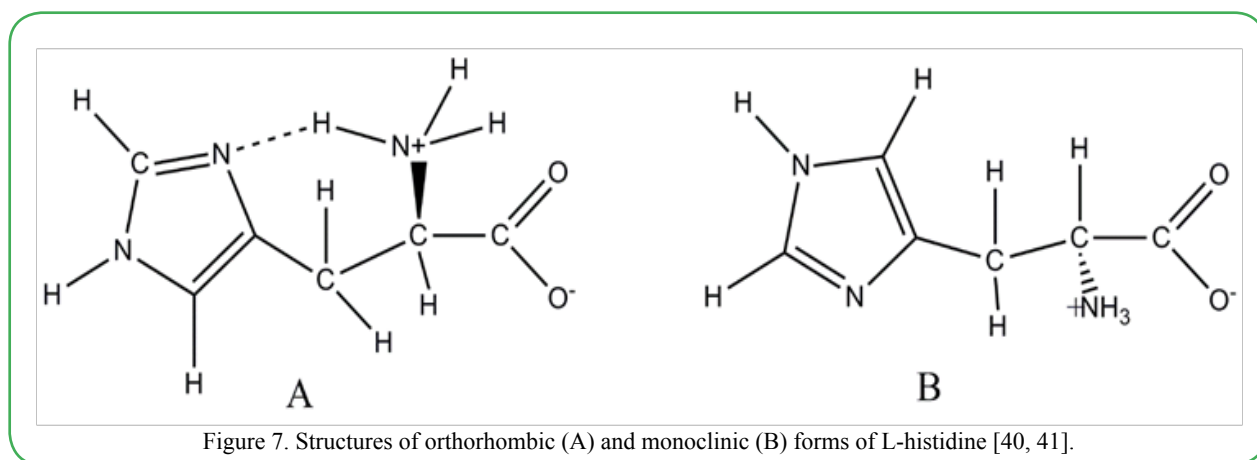


Figure 7. Structures of orthorhombic (A) and monoclinic (B) forms of L-histidine [40, 41].

This method of polymorph prediction is applicable to pigments, drug candidates, scale inhibition, and explosives. This is one of the easiest methods of analyzing the polymorphic structures and can be used by almost anyone. The user would simply select the molecule needed and the computer simulates the possible structure arrangement based on the bonding arrangement, reactivity and conformity making it an easy way to detect the varying structure of the crystal. The software also uses molecular packing arrangement space of low-lying minima in lattice energy of the organic crystal [43].

Cambridge Structural Database

The Cambridge Structural Database (CSD) is a large repository of experimentally determined organic and metal-organic crystal structures, based on X-ray and neutron diffraction studies. These data are readily accessible for chemists mainly for experimental purposes in computational chemistry. It is also the most widely used resource for conformational polymorphs of organic crystals. Originally created in 1965, the CSD is being continuously updated by new entries which are constantly been uploaded in the system. The structures are processed computationally by expert structural chemists prior to including in the database [44-46]. Scientists world wide use this system to view three-dimensional structures of conformational polymorphs of organic crystals.

Polymorphic structures are retrievable and attainable in molecular data management systems. These data are validated by numerous experts in computational chemistry to ensure accuracy for other users. Polymorphs can further be validated using X-ray crystallography and neutron diffraction.

Role of external stimuli, and self-healing properties

In response to external stimuli crystal structure rearranges in different forms exhibiting characteristics such as walking, bending,

rolling, etc. This characteristic also allows molecular interaction to undergo reverse phase transition: the same locomotion on the opposite form or direction [5,42]. Size of crystals can also affect the movement: Thicker crystals exhibit slow bending and straightening while thinner crystals are able to exhibit these changes at a faster rate. The symmetry of the crystal can also affect mobility of unsymmetrical crystals, and are more capable to promote rolling due to a slanted structure resulting in easier tilting to one side than the other. Thus, the crystal is more probable to roll to the tilted side when the crystal is exposed to temperature changes [5,42]. Furthermore, adjusting the temperature can result in crawling crystals. These crystals are capable of undergoing repeated recrystallization and melting under temperature fluctuations. Fluctuations in temperature may results in different atomic and molecular rearrangements. This results in different polymorphic structures. Moreover, thermodynamic manipulation can weaken or strengthen atomic and molecular interaction in the crystal. The shape of the crystal may deform when heated and reform when cooled. The change in shape and direct position of the temperature change result in overall mobility [5,42].

Recently, Gupta et al. [47] have presented a novel example of smart crystalline material (namely, the 2:1 cocrystal of probenecid and 4,4'-azopyridine) which exhibit reversible response to a variety of external stimuli (UV light, heat, and mechanical pressure), by bending, twisting and elastic deformation. The materials are capable of self-healing on thermal manipulation, involving heating and cooling. These properties are based on reversible trans-cis isomerization and crystal to crystal phase transitions. The importance of self-healing in determining polymorphic structures in a single crystal is receiving increasing attention. Soft crystals also have specific molecular packing. It is, therefore, crucial to find a polymer that can keep its integrity (via intermolecular interactions such as

hydrogen bonding, hydrophobic interaction, or interactions between aromatic rings during heating/cooling transitions [47]. The ability to self-heal allows the structure to regain and alter the shape during both heating and cooling periods or even at room temperature. This is opening the door to manufacturing micro-robotics [5,42,47-49], simulating natural organisms in the biosphere, many of which possess self-healing properties [50]. The mobility of organic crystals under heating or cooling is called inchworm walking or bending. The recorded temperature for bending and twisting in organic crystals ranges between 140 °C and -140 °C. Though there is a correlation between the shape of the crystal and the direction in which it moves, the reason for this relation is not yet established. Latest studies by Taniguchi et al. [42] on “photo-triggered phase transition” is rather interesting and worthy of note. These authors examined photochromic, chiral salicylideneamine crystals. The material exhibits temperature induced single crystal-single crystal phase transition which shows reversibility on heating and cooling. Interestingly, it transforms to the identical phase upon photo-irradiation at temperatures below the thermal transition temperature. The phototriggered phase transition has been attributed to the strain resulting from enol-keto photoisomerization which is facilitated by the small energy barrier associated with alterations in the crystal structures. Taniguchi et al. further reports that the photo-triggered phase is metastable and reverts back to the original stable phase, by a step involving back isomerization from the trans-keto to enol form [42].

Summary

Literature data suggests that one-third of organic compounds and about 80% of marketed pharmaceuticals show some kind of polymorphism where the initial species converts to subsequent crystal polymorphs depending on the crystallization conditions. Thus crystal structure prediction (CSP) plays a vital role in understanding the crystal energy landscape and screening polymorphs. X-Ray diffraction and neutron diffraction can be used to verify the conformational characteristics of the organic polymorphic crystals. The more accurate of the two experimental methods is neutron diffraction due to the in-depth penetrability of radiation in the molecular structure detecting specific bond angles and length especially in hydrogen exchange (H/D). The ability to predict possible polymorphs, as well as anticipate its stability, opens the possibility of conceptualizing the feasible application of the hypothetical polymorphs. Thermodynamics has subtle interplay between the molecular conformations and crystal packing, to transition organic crystals into more than one sister polymorphs. Polymorphic forms of therapeutic drugs may lead to increased performance in some applications. Future research into drug crystalline polymorphs has the potential to unlock hidden characteristics of common pharmaceuticals.

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