A Structural Systematic Study of Three Families of Salicylic Acid Derivatives

by

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Crystal structure assembly is a subtle compromise between geometrical features, a natural tendency to minimize the free, empty, volume, linked to the involvement of classical van der Waals forces, and the ability of particular complementary functional groups to form additional cohesive directional interactions. Depending on the system considered, each of these factors can have a more pronounced influence in determining the crystal packing. In order to develop a successful strategy to design new solid forms by a crystal engineering approach a complete understanding of crystal structure is required. It involves the so called “retrosynthetic” approach which allows the identification of robust assemblies. However, this procedure is worthless without a systematic approach able to define the structural consequences deriving from small changes in the molecular skeleton of a given target molecule.

In this thesis three families of substituted salicylic acid derivatives have been prepared and separately studied in order to compare the crystal structures and determine whether the substitution and the associated changes in shape and electrostatic of the parent molecule introduce alternative intermolecular interactions or molecular patterns. The first family is based on acetylsalicylic acid derivatives (aspirins) and contains 15 novel structures together with some substituted derivatives already present on the CSD. The second family contains 13 new structures of substituted salicylic acid and, as for aspirin derivatives, some already reported in CSD. The last family contains 13 new crystal structures of molecular salts based on the pair 4-aminopyridine-salicylic acid derivatives. The families of compounds are those in which the parent molecules are substituted with small groups (Cl, Br, I, Me, NO\textsubscript{2}, MeO etc.) and in different positions. The only exception is given by the acetylamino derivatives, which were included in the analysis in order to verify if they can compete with the carboxylic group in forming particular intermolecular interactions and consequently different supramolecular synthons.

The results in this work clearly showed that the substituent groups have an important role in generating similarities but, also, differences within the family under study. Furthermore the analysis has shown the significant involvement of both weak intermolecular interactions and shape-related packing features in the crystal structure assembly. In the other hand, the analysis showed the importance of particular functional group in defining robust supramolecular synthons. The three families studied showed, apart from a small number of exceptions, predictable synthons (carboxylic dimers for the aspirins and the salicylic acids and the well known pyridine-carboxylate synthon for the salts) observed in the majority of the structures.
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DECLARATION OF AUTHORSHIP

I, Riccardo Montis, declare that the thesis entitled:

A Structural Systematic Study of Three Families of Salicylic Acid Derivatives

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
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- parts of this work have been published as:


Signed: ........................................................................................................

Date: ........................................................................................................
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<table>
<thead>
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<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>CA</td>
<td>Cocrystallizing Agent</td>
</tr>
<tr>
<td>SC, SCs</td>
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<tr>
<td>3-D, 2-D, 1-D, 0-D</td>
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CHAPTER 1: CRystalline organic solid state.

In this chapter the crystalline organic solid state, intermolecular interactions and related topics such as polymorphism, supramolecular chemistry, crystal engineering are discussed.

1.1. Introduction.

Organic crystals consist of discrete molecules or molecular ions held together in a periodic arrangement by medium and long-range non-covalent interactions, to form a highly ordered macroscopic product, which has determined physical properties. Crystal packing is a compromise between “the necessity to fill the empty spaces”, the influence of geometrical features and the tendency of particular pairs of atoms or functional groups to form stable interactions. The forces involved in a crystal include directional hydrogen bonds and dipole-dipole and isotropic van der Waals interactions. In the last two decades, hydrogen bonds have received the most attention as descriptors for intermolecular interactions in crystal structure analysis. Hydrogen bonds are often involved in promoting recurrent molecular arrangements (e.g. homomeric motifs such as carboxylic dimers or catemers, heteromeric motifs like pyridine-carboxylic acid, etc.), defined in crystal engineering as supramolecular synthons. However the observation of similar geometrical arrangements (chains, tapes, columns, etc.) involving structures with different associations, suggests that isotropic van der Waals interactions and weak interactions in general could have a role as well in defining crystal packing geometry. This thesis is concerned with the identification of such assemblies for different families of compounds, which include single- and multi-component systems, by taking a systematic approach to gain a detailed assessment of the overall crystal packing features. Before discussing these, however, it is important to describe the main phenomena and the nature of the interactions involved, that characterize organic solid forms.

1.2. Intermolecular Forces and Interactions.

Intermolecular interactions are generally classified in two main types: short range forces and long range forces. The criteria for their classification are the distance dependence and the directionality. Intermolecular forces can be attractive or repulsive and their energy is proportional to $r^{-n}$, where $r$ is the distance between the atoms involved and $n$ is
usually considered as a positive integer, different for the types of interaction (see below).

The potential energy of a structure is given by the sum of these two contributions (attractive forces and repulsive forces) and a crystal structure is a result of the equilibrium between these forces.

Short range forces are generally repulsive and the energy associated decreases exponentially with the distance. At short intermolecular distances the electrons tend to avoid the overlap region and the nuclear charge is no longer screened so effectively, determining an effective Coulombic repulsion between the nuclei of two adjacent molecules. Repulsive forces are responsible for the shape and conformations of molecules and for phenomena such as steric hindrance. The energy associated with these forces increases rapidly at shorter intermolecular separations, varying approximately as $r^{-12}$.

Long range forces are attractive and may be classified into electrostatic, induction and dispersion forces. Depending on the differences in electronegativities of the atoms in a molecule, the permanent charge distribution of molecules are often not uniform and this non-homogeneous charge distribution can be described as a series of multipole moments.

The electrostatic or Coulomb energy can be expressed in terms of a series of different components with a different distance dependency: charge-charge ($r^{-1}$), charge-dipole ($r^{-2}$), dipole-dipole ($r^{-3}$), quadrupole-quadrupole ($r^{-5}$) etc.

A permanent dipole can also interact with a polarizable atom or group of atoms, inducing a charge separation (induced dipole). Induction energies have a distance dependency proportional to $r^{-6}$.

Even if molecules are not polar, weak forces exist between them. In fact interactions between dipoles and charges are not sufficient to explain the stabilization energies of crystals of non-polar molecules. The first explanation of dispersion forces was suggested by London\textsuperscript{1} describing them as forces of electrical nature. The movement of the valence electrons create, at any given instant, a fluctuating multipole moments which can induce dipole moments in adjacent molecules. The interaction between the transient multipole moment and the induced multipole results in a weak, short-range attractive force defined as London dispersion force. The dispersion energy drops off with the distance, decreasing as a function of $r^{-6}$. 


**Hydrogen Bonding.**

Among the directional intermolecular interactions, the hydrogen bond is surely the most important, not only for its key role in many aspects of the liquid and solid state chemistry but also for the uniqueness of the phenomenon. Its classical description derives from Pauling’s work \(^2\) which defines a hydrogen bond as a stable interaction between two electronegative atoms, X (the donor) and A (the acceptor), where the hydrogen atom is attracted to both atoms and thus acts as a bridge or a bond X-H···A between them (where X and A are atoms such as N, O, S and N, O, F, Cl, Br and I). Because of the electronegativity of the X atom, the electron of the H atom is located between X and H, generating a charge separation Xδ⁻-Hδ⁺. It can interact with the lone-pair on the electronegative acceptor A, forming an interaction with energies in the range 15-40 kJ mol⁻¹. The H···A interatomic distance of conventional hydrogen bonds is generally shorter than the sum of the van der Waals radii (2.6 Å). Conventionally this hydrogen bond model relates only to very electronegative atoms and does not take in account all those intermolecular interactions such as C-H···X (X = O, F, π, etc) or O-H···π, recently defined as weak hydrogen bonds \(^3\) (interaction energies in the range 2-4 kJ mol⁻¹), recognised to make decisive contributions to the cohesion in the structure. \(^4\)

As stated by Desiraju and Steiner \(^3\) there is no experimental evidence that at a critical distance the nature of X-H···A interactions is switched from hydrogen bonding to van der Waals type.

A broader definition \(^5\) describes the hydrogen bond as any cohesive interaction X-H···A where H carries a positive charge and A a partial or full negative charge and the charge on X is more negative than on H.

Jeffrey and Saenger have classified hydrogen bonds in two categories: weak and strong \(^6\). Further classifications \(^3\) divide hydrogen bonds into three types which depend on the strength of the interaction: weak (2-4 kcal mol⁻¹), strong (4-15 kcal mol⁻¹), and very strong (above 15 kcal mol⁻¹).

Hydrogen bonds have a strong electrostatic nature, however they can be considered as components of a more complex system. The total energy of the hydrogen bond can be subdivided into at least four component interaction types: electrostatic, charge transfer, dispersion, exchange repulsion and polarization. Apart from the dispersion term which is repulsive, the remaining components are attractive and can have more or less importance depending on the type of hydrogen bond considered: strong (most
electrostatic), weak (electrostatic) and very strong (most covalent). For example, very strong hydrogen bonds have a large charge transfer contribution and can be considered as quasi covalent interactions \cite{7} and very weak hydrogen bonds (in which the electrostatic contribution can be comparable to the dispersion term \cite{6,8} or even smaller) cannot be easily distinguished from van der Waals interactions.

Hydrogen bonds are often rationalised in terms of geometrical parameters \cite{9} such as bond angles and X-A or H-A distances (Figure 1.1). In a classical hydrogen bond the donor interacts with one acceptor forming a linear interaction (although experimentally, $\theta$ is normally smaller than $180^\circ$).

![Figure 1.1. Representation of hydrogen bond parameters d, D, $\theta$.](Image)

However a donor can interact simultaneously with two or three acceptors forming bifurcated (three-centre) \cite{6} and trifurcated (four centre) hydrogen bonds.

Hydrogen bonds are important tools in crystal engineering and have profound influences in crystal structures.

In 1984 Kennard \cite{9} recognised the necessity to rationalise, or even predict, hydrogen-bonding patterns in crystal structures, observing, for example, that it is unusual for an O-H or N-H group not to be hydrogen bonded if an acceptor atom is available in the crystal structure.

General rules were finally defined by Etter in 1990 \cite{10}. These rules apply equally to both strong donors and acceptors and correlate functional groups in neutral organic molecules with hydrogen bonded motifs in crystal structures. The rules can be summarized as follows:-

All good hydrogen bond donors and acceptors are used in forming this interaction.

Hydrogen bonds forming six-membered intramolecular rings are preferred to intermolecular hydrogen bonds.
The remaining donors and acceptors after intramolecular hydrogen bond formation will form intermolecular hydrogen bonds. Additional rules for specific classes of functional groups (e.g. nitroanilines, cocrystals between carboxylic acids and aminopyridines, etc.) are also given. However, though these rules are followed in the majority of the cases, it is worth noting that some exceptions may be observed.\[^{11}\]

**Other Interactions.**

In an analogous way, halogen bonds are directional D···X-Y intermolecular interactions with D = N or O or in general any Lewis base, X = Cl, Br and I and Y = carbon, halogen etc.\[^{12}\]. This type of interaction has recently been the focus of much interest in the area of organic solid state chemistry including crystal engineering and biomolecular engineering\[^{13}\]. Halogens Cl, Br, and I are also involved in forming short non-bonded interactions such as X···X and X···Y (where X and Y indicate two different halogens). The nature of these interactions is not completely clear and is still debated. An example is given by the crystal structure of chlorine (orthorhombic S.G. Cmca) which shows unusual short Cl···Cl contacts (3.271 Å). Some authors\[^{14}\] suggest that this is the result of a decreased repulsion in the direction of the short contact due to the elliptically shaped atoms (anisotropy), whilst others\[^{15}\] claim that there are specific attractive forces between halogen atoms in crystals.

π···π interaction is another important cohesive force responsible for directing the packing of aromatic molecules\[^{16}\]. These forces arise from the polarizable π-electron density that enhances the stabilizing dispersion interactions between the aromatic molecules. π···π interactions can adopt two different geometries: parallel stacked or parallel displaced (Figure 1.2)

![Figure 1.2. Aromatic-aromatic interactions: a) face-to-face parallel stacked; b) face-to-face parallel displaced; c) edge-to-face.](image-url)
However parallel stacked is a rare phenomenon and generally offset stacking is more common \cite{17}. The stability order of stacking interactions in polarized aromatic $\pi$-systems is $\pi$-deficient–$\pi$-deficient > $\pi$-deficient–$\pi$-rich > $\pi$-rich–$\pi$-rich \cite{18}. The concept of the $\pi$–$\pi$ interaction is often used erroneously to describe aromatic-aromatic interactions in which there is no substantial overlap of the aromatic rings. The resulting geometry is a T-shaped arrangement defined as edge-to-face motif (Figure 1.2 c). Phenyl rings generally prefer this geometry which is enthalpically favorable \cite{19}. This can be explained on the basis of the quadrupole-quadrupole interactions, in which the energy term is repulsive for the parallel stacked arrangements and attractive for the T-shaped arrangement \cite{20}.
1.3. Organic Solid Forms.

Organic crystalline materials play a central role in fine chemicals as well as in many area of industry such as pigments, explosives, food and, above all, in the pharmaceutical industry \[^{21}\]. Because of their direct relevance to products of commerce, which necessitate regulatory controls \[^{22}\], interests in the solid state properties has grown exponentially in the last few decades.

Depending on their features (e.g. conformational flexibility, hydrogen bonding sites, etc.), organic molecules can often exist in more than one solid form, each characterized by different molecular arrangements and, consequently different inter- or intramolecular interactions which lead to different physical and chemical properties such as melting point, solubility, chemical stability etc.

Particularly in the last two decades the attention has been focused on molecules of pharmaceutical importance. The development of a particular formulation is a complex process involving the production of the active ingredient and its conversion into a product suitable for administration. Properties such as solubility, rate of dissolution have a high importance in contributing on the bioavailability of particular drug substances. The stability of a given crystalline form is another crucial property that should be investigated during the manufacturing processes of an Active Pharmaceutical Ingredient (API).

The ultimate goal of solid form screening is to identify and to select or design the optimal solid form for the intended use in order to ensure a reliable and a robust process, avoiding problems such as tablet failure (e.g. tablets cracking, polymorphic transitions under mechanical treatment) \[^{23}\] precipitation from solutions, chemical production problems like filterability \[^{24}\].

In relation to these concepts, topics such as polymorphism, co-crystals and in general multiple component systems have in recent years gained in importance \[^{25}\].

The approaches to enhance solubility, dissolution rate and, generally, physical properties of solids involve altering the molecular networks follow two main routes:

- By producing different polymorphs
- By designing multi-component systems (e.g. co-crystals, solvates, salts).
Polymorphism is generally defined as the ability of a given compound to exist in different molecular arrangements and/or different conformations \[^{26}\].

API’s, which typically exhibit hydrogen bonding sites and conformational flexibility, are ideal candidates to crystallize in different polymorphic forms.

Multi-component systems are generally prepared by means of hydrogen bonded assemblies between API’s and other components such as solvent or other molecules.

Salt and hydrate formation are often used in pharmaceutical industry to improve properties such as hygroscopicity, toxicity, solubility and stability of many drug compounds \[^{27}\].

Cocrystals are currently studied as potentially useful tools in pharmaceutical field. Figure 1.3 reports a schematic representation of the solid state phenomena described in this chapter.

**Figure 1.3.** Schematic representation of solid state phenomena. a) Polymorphism: crystallization of metastable form (2) which converts in the stable form (1). b) Cocrystal formation. c) Salt formation. d) Solvate formation.
Polymorphism.

Although its first modern definition was given by McCrone in 1965 [24], polymorphism is a concept known since 1821, when Mitscherlich coined this term to describe the tendency of some inorganic compounds to crystallise in more than one form. Polymorphism is currently defined as “a phenomenon that involves different packing arrangements of the same molecule in the solid state” [21].

It is in recent years that polymorphism has been subject of a growing interest, especially for its implications in many areas of the industry, particularly in the pharmaceutical field. However, although a large number of works on this topic is available (about the frequency of its occurrence, its rational control, nomenclature and other aspects concerning this phenomenon) [21] it remains poorly understood and still difficult to control.

Many factors influence crystallization of different polymorphs such as chemical features of the organic molecule (hydrogen bond sites, conformational flexibility), solvents, concentrations, thermodynamic and kinetic factors, impurities etc. Because the complexity of this phenomenon, the experiments reported in the literature for crystallization of polymorphs are frequently unrepeatable [28].

Kuhnert-Brandstaetter stated that “probably every substance is potentially polymorphous. The only question is, whether it is possible to adjust the external conditions in such a way that polymorphism can be realised or not” [29].

Sarma and Desiraju [30] demonstrated that the frequency of occurrence of polymorphism is not uniform in all categories of compounds but it is probably more common with molecules with hydrogen bonds donor or acceptor and/or molecules with conformational flexibility.

As emphasised in some works [31], the solvent can have significant role in promoting the crystallization of a particular polymorphic form rather than another, however it is not the unique determinant of the polymorphic outcome [28].

Crystallization (from solutions, melts etc.) is a complex process governed by a combination of thermodynamic and kinetic factors. At a given temperature and pressure, only one polymorphic form of a given compound is thermodynamically stable, all other forms under these conditions are defined as metastable. A metastable form is a thermodynamically unstable form which may have a finite existence as a result of a slow rate of transformation.
From a thermodynamic point of view, at a given temperature and pressure, the crystallization determines a decrease of the free energy of the system and the resulting crystal structure it is assumed to have the greater negative free lattice energy. However, kinetic factors also play an important role in the crystallization process and can promote the crystallization of a metastable form.

Nucleation is a crucial process in the development and growth of the macroscopic crystal from a melt, solution or vapour. The nucleation rate depends to the supersaturation, the Gibbs free energy of activation, and the surface energy, which can be different for polymorphs of the same substance. Under specific experimental conditions nuclei of all possible polymorphs can exist and the metastable form can nucleate at a faster rate than the stable form. This is summarised in the well known Ostwald’s Rule of Stages \[32\].

If the rate of transformation of metastable polymorphs to the stable one is slow, it is possible to isolate more than one polymorphic form of a single compound under particular set of conditions. As stated by some authors, the very existence of a metastable polymorph is due to the “triumph of kinetics over thermodynamics” \[33\].

For two polymorphic forms of a given compound at constant pressure, two behaviours generally can be observed: monotropism and enantiotropism \[34\].

\[Figure 1.4.\] Schematic Energy-Temperature diagrams for a dimorphic system. a) Monotropism; b) Enantiotropism.

Two forms are monotropically related if one polymorph is always more stable below the melting points of both polymorphs. The transition is not reversible because the free energy of one form is always lower with respect to that of the other form (Figure 1.4 a).
Two polymorphs of the same compound are enantiotropically related if there is a transition temperature ($T_t$), at which the Gibbs energy of both forms is equal and transformation can, in principle, occur if the compound is heated above or cooled below such temperature (Figure 1.4 b). The presence of extraneous molecules such as additives or impurities can promote polymorphism.\(^{[35]}\) The first identification of elusive form II of aspirin was obtained in the presence of either levetiracetam or acetamide\(^{[36]}\). Bond et al.\(^{[37]}\) claimed that the presence of additives is not an important factor for the outcome of the polymorph II of aspirin, but a recent paper from some of these authors describes the isolation of pure polymorph II by crystallization in the presence of aspirin anhydride\(^{[38]}\).

**Solvates, Cocrystals and Salts.**

Multi-component systems are generally realized by means of hydrogen bonded assemblies between a given molecule and other components such as solvent, excipients or other molecules. Solvates are a common example of multi-component systems in which solvent molecules are incorporated in the lattice. “Pseudopolymorphism” is often used to define solvate forms of a given compound although it is going out of favor. Hydrate is used to define solvate forms in which the solvent is water. The ability of a given compound to form solvate forms is related to the molecular structure and in particular to the ability of the solvent molecules to give strong and weak hydrogen bonds with the solute molecules\(^{[39]}\). As suggested by Desiraju\(^{[40]}\), solvents can be incorporated into crystal structures to balance an eventual disproportion in the number of hydrogen bond donors and acceptor in the solute molecules.

Cocrystals are generally obtained by interaction between a given compound and a secondary molecule defined as cocrystallizing agent (CA). The field of crystal engineering uses these concepts to design new solid state forms with predictable stoichiometry and architecture and with desired chemical and physical properties\(^{[41]}\). The assembly of crystalline materials that contains both an API and a biologically passive component by cocrystallization may permit an adjustment of fundamental physical properties such as solubility, melting point or crystal stability, maintaining intact the activity of the drug molecule\(^{[42]}\). The choice of a cocrystallizing agents is critical. In effect, the probability to have intermolecular interactions API-CA should be
more favorable than the interactions between API-API and CA-CA [43]. CA should also be biologically and environmentally passive. In terms of both directionality and strength, hydrogen bonds often play a central role in cocrystal design. In general, it is observed that the best hydrogen bond donor tends to interact with the best hydrogen bond acceptor [10a].

Salts formation is a widely used strategy to modify physical properties such as solubility, bioavailability and stability of a given drug compound. The protonation/deprotonation of a basic/acidic site of a given organic compound results in a new solid form with a different crystalline structure and, as consequence, different physical properties. Many drugs compounds are marketed as salts. Mineral acids such as HCl are often used to prepare stable salt of pharmaceutical bases. Salt formation is strongly dependent on the pK\textsubscript{a} differences between the acid/base pair. To form a stable salt the pK\textsubscript{a} difference should differ approximately by more than three units. Molecular salt is, currently, used to distinguish salts in which both ionic components are neutral organic molecules prior to proton or electron transfer to salts in which one or both components are simple counterions (e.g. Cl\textsuperscript{−} or Na\textsuperscript{+}) [44]. If the pK\textsubscript{a} difference is less than zero, the acid-base pair can interact without proton transfer and the resulting solid form is defined as a cocrystal [45]. However when the pK\textsubscript{a} difference is between 0 and 3, the occurrence of salts or cocrystals is not predictable. As suggested by Stahly [46], for acid-base complexes in the range 0< ΔpK\textsubscript{a} <3 there exists a continuum between the two categories, in which the crystalline environment determines the location of the proton. From a structural point of view these two classes of compounds differ only in the proton location. For this reason molecular salts are often described using tools and definition normally applied for cocrystals. The same confusion can be extended to solvate forms (the distinction between pyridine solvate forms of carboxylic acids and pyridine-carboxylic acid cocrystals can be ambiguous).

A universal accordance of what actually constitutes a cocrystal (or co-crystal) is still unavailable and recently many authors proposed various definitions [25a, 47].

Dunitz, [47g] argues that the term cocrystal (co-crystal) should include molecular compounds, molecular complexes, solvates, inclusion compounds and other types of multi-component crystals or, in other words [47f], should be used as synonym for multi-component crystal.
1.4. Supramolecular Synthon.

Since the initial definition given by Lehn, supramolecular chemistry (“a chemistry beyond the molecule”) has influenced enormously different fields of chemistry. To summarize, a supramolecule is a highly organized system, obtained as result of molecular recognition events within polymolecular systems, held together by non-covalent interactions. In this context crystals might be considered in a supramolecular sense as examples of supramolecular assemblies, “supermolecule(s) par excellence”.

As stated by Lehn “supermolecules are to molecules and the intermolecular bond as molecules are to atoms and the covalent bond”. From this sentence the analogy between crystal formation and organic synthesis is a natural consequence (e.g. polymorphs can be regarded as supramolecular equivalents of structural isomers, phase transitions as molecular isomerization).

Intimately related to this analogy is the term crystal engineering, appeared for the first time in a paper written by Schmidt titled “Photodimerization in the solid state”. This concept was subsequently described by Desiraju, which define the crystal engineering as the rational design of functional molecular solids. Going back to the analogy between crystals and supermolecules, crystal engineering can be considered as a proper synthetic discipline (in a supramolecular sense) which uses intermolecular interactions as main tools to design and isolate solid forms with desired properties exactly in the same way as synthetic chemists design and functionalizes molecules.

However, crystals are more complex systems than molecules. As described in the next section, crystals are the result of a complex balance between forces, which possess different strength, distance dependence and directionality, and geometrical factors. A directed synthetic approach requires a complete control of these factors in order to create predetermined 3-D architectures.

The simplification of crystal structures into smaller units, in a so called “retrosynthetic process” permits the identification of particular recurrent interactions which may be robust enough to be predicted and used in a synthetic approach.

In this scenario, the “supramolecular synthon philosophy” has undergone a rapid growth in the last years.

The term Synthon was introduced in synthetic chemistry by Corey in 1967 to define “structural units within molecules which can be formed and/or assembled by known or conceivable synthetic operations”. This definition fell in disuse but it has been
recently introduced in a supramolecular sense by Desiraju [50]. Supramolecular synthons are structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations or conceivable synthetic operations involving intermolecular interactions”. A supramolecular synthon is “a structural unit which ideally expresses the kernel of a crystal structure” [51b].

Figure 1.5 reports some of the most common synthons identified.

![Synthons](image)

**Figure 1.5.** Selection of representative synthons.

A supramolecular synthon derives from designed combination of interactions that can involve one (e.g 1-3 in Figure 1.5) or more functional groups (4 or 6 in Figure 1.5). Supramolecular synthons can be divided in two distinct categories: supramolecular homosynthons (1-3 in Figure 1.5): composed of the same functional groups (e.g. same functional group behaving as hydrogen bond donor and acceptor in a self-assembly process to form the supramolecular motif); the supramolecular heterosynthon (4-7 in Figure 1.5): composed of different but complementary functional groups.

In case of heterosynthons formed between acid and base functionalities, if the donor and the acceptor are strong enough and the $\Delta pK_a$ is reasonable [54], a proton transfer can occur forming an organic salt and the resulting motifs can be defined as “ionic supramolecular synthons”. These synthons are generally more robust and more easily predicted than those in neutral systems [55].

Although the definition of synthon includes all types of molecular recognition [51b] (in particular Desiraju also include non-directional interactions such as phenyl···phenyl
herringbone and alkyl···alkyl stacking) \cite{50}, those involving hydrogen bonds are the most common \cite{56}.

Among the various functional groups often involved in hydrogen bonds formation, carboxylic acid is one of the most studied. It can self-associate generating a centrosymmetric dimer or catemers (or even both in the same structure) \cite{57} forming supramolecular homosynthons and, in presence of alternative functional groups, they can also form heterosynthons.

Although the synthon is intimately related to the chemical feature of the molecules (functional groups), it also takes in account the resulting geometry of the object deriving from the intermolecular interaction. 1 and 3 in figure 5, which involve different functionalities and are defined as different synthons, adopt an analogous geometry which can generate similar crystal packing. From this follows the concept of “Synthon Interchangeability” \cite{58}, used to describe similarity between structures of molecules with widely differing functionalities.

Supramolecular Synthon is a widely accepted concept not only because it is an elegant way to simplify crystal structures into smaller units but also because, in cases of synthon involving strong interactions, it could be considered a sort of “trait d’union” between the liquid state and the solid state during a crystallization experiment. A crystallization from solvent, for example, can be regarded as a process which begins with solvated molecules which interacts by molecular recognition events (e.g. supramolecular synthon formation) and through molecular assembly processes and nucleation leading to the crystal formation \cite{59}. This is supported by the fact that recurrent 0-D molecular arrangements promoted by hydrogen bonds (e.g. carboxylic dimers) can be observed in solution prior to the nucleation process \cite{60}.

1.5. Rationalizing Crystal Packing: Crystal Structure Analysis.

As described in section 1.1 crystal structure assembly is a subtle compromise between geometrical features of the contributing components \cite{16, 61}, a natural tendency to minimize the free, empty, volume \cite{62}, linked to the involvement of classical van der Waals forces, and the ability of particular complementary functional groups to form additional cohesive interactions, which can vary considerably in strength. Each of these factors can have a more pronounced influence in determining the crystal packing depending on the system considered. This description is the result of the seminal work
of Kitaigorodskii (which is mainly based on geometry) and Etter (which defined the rules on hydrogen bonding)\textsuperscript{10a}.

In his book\textsuperscript{62}, Kitaigorodskii defines an isotropic model, in which the possible interactions between molecules are weak and lacking in directionality with the consequence that the driving force for the crystal structure formation is the close packing. Desiraju describes this principle as a natural consequence of the atom-atom potential method, in which the molecules in a crystal tend to assume equilibrium positions in order to minimize the potential energy of the system\textsuperscript{51a}.

The need to achieve a close packed arrangement determines a maximization of favourable isotropic van der Waals interactions. Kitaigorodskii also observes that some space groups permit close packing much more readily than others. Although many structures deviate from this model, it is not uncommon in organic crystals to observe recurrent 1-D or 2-D periodic fragments, which may or not involve directional interactions. This behaviour is an evidence of the tendency of certain molecules to pack choosing particular arrangements over alternative motifs\textsuperscript{63} and it may be an indication that there are structures in which geometrical features rather than specific interactions seems to be the critical determinant\textsuperscript{11, 64}.

A good example is the structure of alloxan\textsuperscript{11} which shows a close structural similarity to fluorobenzene; interestingly the two molecules have a similar shape but different functionalities (Figure 1.6).

\textbf{Figure 1.6.} Isostructurality of a) alloxane, b) fluorobenzene.

The second model is based on directional forces such as hydrogen bonding and derives from Etter’s rules described in section 1.2.2. The donor and acceptor pairs interact with each other following a particular hierarchy based on the strength of the interaction and a crystal structure can be explained on this basis. However, hydrogen bond is not the only interaction available for crystal packing. In Etter’s model other intermolecular
interactions may also be employed for “intermolecular synthesis” when they are sufficiently strong and directional to give rise reproducible and recurrent molecular assemblies. As observed by Burgi and Dunitz [65], very weak electrostatic interactions sometimes give predictable molecular patterns and van der Waals interactions [66], charge-transfer interactions [67], and halogen-halogen [68] interactions can also be used.

Since the introduction of the concept that a crystal is a “supermolecule” among the various non-covalent interactions involved in a crystal structure, directional forces and in particular hydrogen bonds have been considered as of prime importance.

This is reflected, as described above, in the current tendency to associate the term “supramolecular synthon” [50] specifically with such interactions, although the original intention implied a more general approach [51b].

Supramolecular synthon contains both geometrical and chemical recognition concepts and in this regard can be considered as a good compromise between the two approaches described above [51b].

Following the considerations reported above it is clear that in order to develop a successful strategy to design new solid forms by a crystal engineering approach a complete understanding of crystal structure is required. It involves a retro-synthetic approach able to identify robust assemblies. However, this procedure is worthless without a systematic approach able to define the structural consequences deriving from small changes in the molecular skeleton of a given target molecule.

This is the driving force for the study being undertaken in our Group.

The Supramolecular Construct (SC) [69] represents an alternative approach to rationalize a crystal structure. This term defines any geometrically similar assemblies of molecules occurring in two or more structures and invites identification, not only of directed interactions but also of components that may reflect the influence of the more diffuse interactions, assemblies that are mainly the result of close packing or even directional interactions.

SCs may have different dimensionalities: 0-D (discrete molecular assemblies), 1-D (similar stacks or rows of molecules bundled differently), 2-D (similar sheets, packed differently and 3-D (isostructurality, isomorphism and pseudo-isostructurality) [70]. The approach, based on molecular shape which characterises SCs, permits comparison of structures with different functionalities such as single or multiple component systems.
1.6. Aims of the Research.

The identification of recurrent SCs in a given set of structures may represent an indication of particular preferences in the processes of both nucleation and crystal growth. A systematic search of SCs for given set of structures can be a useful approach aimed to gain more information on the assembly of molecules in the solid state. This idea is part of the strategy adopted in our laboratory for the systematic search of similarity in crystal structures. The XPac software[^69], has been developed to enable the search for SCs in molecular crystals (Chapter 2, Section 2.4).

In this vein three families of substituted salicylic acid derivatives were prepared and studied in order to compare the crystal structures and determine whether the substitution and the associated changes in shape and electrostatic of the parent molecule introduce alternative intermolecular interactions or molecular patterns. The families of compounds are those in which the parent molecules are substituted with small groups (Cl, Br, I, Me, NO$_2$, MeO etc.) and in different positions. The only exception is given by the acetylamino derivatives, which were included in the analysis in order to verify if they can compete with the carboxylic group in forming particular intermolecular interactions and consequently different supramolecular synthons.

The first set of compounds is based on acetylsalicylic acid (aspirin), which recently has been object of growing interest following the identification of a polymorph[^36-37, 71]. This is discussed in Chapter 3, in which the common molecular arrangements within the various substituted derivatives and, consequently, the importance of particular functionality in defining the similarities will be described.

The second set is based on 2-hydroxobenzoic acids derivatives (salicylic acids) and is described in Chapter 4. In this analysis the role of the rigid molecular conformation and the effect of the various substituents are discussed in detail.

The last set of compound is described in Chapter 5. For this analysis a set of molecular salts based on 4-aminopyridine and 2-hydroxobenzoic acid derivatives is chosen in order to study the effect on the crystal packing deriving from the introduction of a cocrystallizing agent.

Figure 1.7 a, b and c the three families under study are shown.
**Figure 1.7.** Family of salicylic acid derivatives chosen for this study.
Chapter 1

Crystalline Organic Solid State

References.


There are a large number of studies mainly focussed on directional interactions. This might arise from the fact that strong directional interactions are more easily predicted.


CHAPTER 2: GENERAL PROCEDURES.

In this chapter the analytical techniques and the general procedures are described. Particular attention is given to the single crystal X-Ray diffraction technique and the XPac procedure.

2.1. Introduction.

As described in the previous chapter (Chapter 1, Section 1.6) the work presented in this thesis focuses on the structural analysis of three families of salicylic derivatives. The experimental results are divided into three separate chapters, each dedicated to a particular family of compounds: acetylsalicylic acid derivatives (Chapter 3), salicylic acid derivatives (Chapter 4) and multiple component crystals based on 4-aminopyridine-salicylic acid derivatives (Chapter 5). The analyses, mainly based on the single crystal X-ray diffraction technique, can be divided into three steps: crystal growing (which in case of acetylsalicylic acid derivatives follows the synthesis starting from the salicylic acid precursors), structure determination and structural comparison. This last step is carried out following the XPac procedure [1] developed in our group. In the case of identification of possible polymorphic forms (see Chapter 3, Section 3.4) the analysis also involves solvent screening, and analytical techniques such as Fourier Transform Infrared Spectroscopy (FT-IR) and thermal analysis by Differential Scanning Calorimetry (DSC) and Hot-Stage Microscopy (HSM).

This chapter reports a brief summary of the basic knowledge for the techniques applied in the analysis such as crystallization methods, single crystal X-ray diffraction and, also, a description of the XPac procedure. Furthermore, starting materials and a description of the instrumentation is provided. Details such as synthesis, crystallization experiments, thermal analysis conditions are given in each chapter in specific experimental sections.

2.2. Crystallization Techniques.

Crystallization is a very popular technique, often used as a separation and purification procedure in many field of both research and industry. This process also represents a critical step in a single crystal X-ray diffraction experiment since the quality of the crystal might significantly affect the resulting quality of the diffraction data.
Within the various method of crystallization, those from solution are the most popular. However, crystallizations by sublimation and from melts are useful alternative ways to produce crystals. Crystallization can be regarded as a phenomenon which consists of two critical steps: nucleation and crystal growth.

Nucleation is generally defined as the starting point of the formation of a new phase in another\(^2\). In the case of crystallization processes, nucleation describes the initial formation of nanoscopic clusters of the new crystalline phase into another phase (such as liquid, gas and melt) which, under particular conditions, can spontaneously grow to form a macroscopic crystal. This is achieved under supersaturation conditions which is one of the most significant requirements for the crystallization process.

A solution is defined as supersaturated when the concentration of the solute exceeds the saturation value. Figure 2.1 shows a typical solubility diagram.

![Figure 2.1. Typical solubility diagram for a given solute reported as a function of an arbitrary crystallization variable.](image)

When the concentration values are in the region above the solubility curve (supersaturated conditions \([C] > [C_s]\)), thermodynamics states that the system must return to equilibrium by precipitating a solid phase until the equilibrium is achieved \(([C] = [C_s])\) \(^3\). However, a solution may be supersaturated over a concentration range (metastable zone) for a certain period without forming any new phase. This can be explained considering that the nucleation is an activated process and the free energy barrier depends on the size of the cluster formed \(^4\). When a number of molecules assemble forming a nucleus, there is a balance between the cohesion forces that hold the
molecules together and the solvent-solute interactions, which tend to pull apart the growth unit. For a given value of supersaturation there is a critical size of the nucleus below which the solvent-solute interactions are more important and determine the dissolution and above which the cohesion forces have a greater contribution and the nanocluster can grow spontaneously.

This description derives from the classical theory of homogeneous nucleation [5], described for the case of the condensation of a drop from its vapour phase and based on the Gibbs-Thompson expression (Equation 2.1, see also Figure 2.2).

\[ \Delta G = \frac{4}{3} \pi r^3 \frac{k T}{v} \ln S + 4 \pi r^2 \gamma \]  
Equation 2.1.

Where \( v \) is the molar volume occupied by a growth unit, \( S \) is the supersaturation and \( \gamma \) represent the surface energy.

![Figure 2.2](image)

**Figure 2.2.** Free energy of a nucleus as a function of the radius. The surface area and the volume contributions of the Equation 2.1 are indicated as grey curves.

This equation, applied to the ideal case of spherical nuclei, contains two terms both depending on the radius of the growth unit. The first term, which is related to the volume of the nucleus, takes into account the internal cohesion forces which hold together the molecules in the cluster; the second term, due to the surface area, is related to the surface forces such as solvent-solute interactions which tend to pull apart the growth units. When the radius of the assembly increases, the surface area term, which
increases with radius squared, become less important than the cubic term relative to the internal cohesion forces and the crystal grows spontaneously. Increasing the supersaturation the critical size and the activation barrier decrease and consequently more crystals will be formed. However, for very high values of supersaturation the new phase can result in oils or amorphous materials \[6\].

In order to grow crystal of suitable quality and size for single crystal X-ray diffraction analysis, the crystallization procedure must be developed carefully. Ideally all the factors which can affect the size and the quality of the crystal (e.g. mechanical stirring, impurities or dust in the vessel etc.) should be eliminated. In general a crystal should be grown slowly, in order to avoid phenomena such as twinning or disorder. The crystallization rate can be controlled with a correct choice of the solvent and the shape of the vessel. A high growth rate corresponds to less time for the molecules approaching the surface to the nucleus to orient themselves consistently to molecules already there. Impurities such as dust particles increase the number of sites of nucleation affecting the corresponding size of the crystals. The choice of the solvent is another crucial parameter which should be considered during a crystallization experiment. In general the solute should be moderately soluble in the solvent chosen. Depending on the crystallization experiment design the volatility of the solvent must also be considered carefully. As described above, the supersaturation plays a key role for a successful experiment and can be achieved following different routes corresponding to different crystallization techniques. Figure 2.3 shows three main cases used in this thesis work.

**Figure 2.3.** Typical solubility diagrams describing three different crystallization experiments: a) crystallization by slow evaporation, b) crystallization by slow cooling, c) Crystallization by using mixed solvent (drop-wise mixing of an anti-solvent, solvent diffusion, vapour diffusion).
Crystallization by Slow Evaporation.

This is the most common and intuitive procedure to grow crystals (Figure 2.3 a). It consists of the preparation of a saturated or nearly saturated solution and allowing the solvent to evaporate. In order to control the crystallization rate, a moderately volatile solvent can be used. Alternatively the vial can be covered by parafilm in which a desired number of holes are made.

Crystallization by Slow Cooling.

This method is carried out by preparing a saturated solution at one temperature and allows the solution to cool down slowly (Figure 2.3 b). In order to control the crystallization rate a water bath in an isolated vessel (e.g. a dewar) can be used. To avoid the evaporation of the solvent the system must be closed by covering the vessel with a cap or parafilm.

Crystallization by Mixture of Solvents.

This method involves two solvents, one in which the solute is moderately soluble (solvent 1) and the second, defined as anti-solvent, in which the solute is insoluble (solvent 2). The substance is dissolved in solvent 1 and the anti-solvent is slowly added drop-wise in order to decrease the solubility of the solute (Figure 3.2 c).

Strictly related to this method is the so called crystallization by solvent diffusion. This procedure is based on the fact that solvent with different densities mix slowly in absence of any mechanical stirring. Similarly to the previous case the solute is dissolved in the solvent 1 and a layer of the anti-solvent is added using a syringe fitted with a fine needle. This creates an interface between the two solvents in which the crystals grow.

An alternative method is the so called crystallization by vapour diffusion (also defined as isothermal distillation) which consists of a diffusion of vapours of the anti-solvent (which must be moderately volatile) into the solution with the solvent 1.

The mixed solvents method can also be used in conjunction with the method represented in Figure 2.3 a. After the solvent 1 and the anti-solvent are mixed, the system can be allowed to evaporate the solvent 1 (which should also be the most volatile). Referring to the diagram reported above, this case can be described imagining the arrow oriented along the diagonal of the two axes in Figure 2.3 c.
2.3. Structure Determination.

Crystal Structure.

The description of crystal structure given so far (in particular see section 1.5), was mainly based on concepts such as geometrical features and intermolecular interactions. However, in order to develop the basic concepts of crystallographic structure, a description based on symmetry must be given.

A crystal structure can be defined as an ordered arrangement of atoms, ions or molecules, repeated in all directions. This arrangement may comprise one, but usually more, chemical units (hereafter described as molecules, for convenience). In the case of such clusters of molecules, these are usually related by point symmetry elements such as rotation, reflection and inversion, plus relationships which contain elements of translation. Translation symmetry is a necessary requisite to generate a crystal structure and a convenient description of a crystal structure can be than made considering a representative repeat structural unit, which may contain a number of molecules in different, symmetry related, orientations, and defining how this composite unit is repeated in the three dimensions by translation symmetry. This can be made by considering the molecules in the repeated structural unit, selecting one molecule and its exact equivalent in all repeating units, and representing each molecule by an identical point (e.g. choosing one atom in each molecule). The translations of this point in the three non-coplanar directions result in an infinite three dimensional array of points. This collection of regular and infinite points, equivalent to each other by translation symmetry, is defined as a lattice. The lattice is independent to the choice of the point, choosing different points within the same representative molecule results in the same lattice. If an arbitrary lattice point is defined as the origin, the translation from any lattice point to another can be defined by a vector \( \mathbf{t} \) such that:

\[
\mathbf{t} = u\mathbf{a} + v\mathbf{b} + w\mathbf{c}
\]

Equation 2.2

where \( \mathbf{a}, \mathbf{b} \) and \( \mathbf{c} \) are the three unit vectors, connecting the origin with the three nearest, non-coplanar lattice points, and \( u, v \) and \( w \) are integers. Considering the length \( a, b \) and \( c \) of these vectors and the angle formed by each pair of them, \( \alpha, \beta \) and \( \gamma \) (where \( \alpha \) is the angle between \( b \) and \( c \), \( \beta \) the angle between \( a \) and \( c \) and \( \gamma \) the angle between \( a \) and \( b \) a parallelepiped defined by eight lattice points can be drawn (Figure 2.4). This is called
the unit cell and represents the smallest group of molecules, or other chemical components, which has the overall symmetry of a crystal structure. The three lengths and the three angles represent the unit cell parameters. Each of the lattice points at the corners of the unit cell is shared with other eight unit cells for a total of one lattice point per unit cell. This is by convention defined as the primitive cell \( (P)\). For a given lattice different unit cells can be defined simply choosing different vector lengths and different angles. However there are some conventions which rule this choice. In general, the conventional cell should have lengths that are as short as possible and angles close to \(90^\circ\).

Figure 2.4. Unit cell and unit cell parameters.

As described above, the unit cell should be the smallest representative repeat unit and some crystal structures might also contain other symmetry elements such as rotation, reflection which impose constraints on the shape of the representative unit cell. As consequence of these restrictions, seven types of unit cell, identifying the seven crystal systems can be defined. These are listed in Table 2.1. Note that the shape of trigonal and hexagonal unit cells are actually identical, with a rhombus base, but they generate fundamentally different crystal structure types as a result of the different symmetry. The angle for the hexagonal case is given as \(60^\circ\) to emphasise this point.

<table>
<thead>
<tr>
<th>Crystal System</th>
<th>Unit Cell Restrictions</th>
<th>Essential Symmetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triclinic</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Monoclinic</td>
<td>(\alpha = \gamma = 90^\circ)</td>
<td>One 2-fold axis and/or mirror plane</td>
</tr>
<tr>
<td>Orthorhombic</td>
<td>(\alpha = \beta = \gamma = 90^\circ)</td>
<td>Three 2-fold axes and/or mirror planes</td>
</tr>
<tr>
<td>Tetragonal</td>
<td>(\alpha = \beta = \gamma = 90^\circ, a = b)</td>
<td>One 4-fold axis</td>
</tr>
<tr>
<td>Trigonal</td>
<td>(\alpha = \beta = 90^\circ, \gamma = 120, a = b)</td>
<td>One 3-fold axis</td>
</tr>
<tr>
<td>Hexagonal</td>
<td>(\alpha = \beta = 90^\circ, \gamma = 60, a = b)</td>
<td>One 6-fold axis</td>
</tr>
<tr>
<td>Cubic</td>
<td>(\alpha = \gamma = \beta = 90^\circ, a = b = c)</td>
<td>Four 3-fold axes</td>
</tr>
</tbody>
</table>

Table 2.1. The seven crystal systems with their cell parameters and constraints.
In presence of some symmetry elements it is more convenient to increases the unit cell size to include more than one lattice point, in order to fully represent the full symmetry in the structure. This choice results in so called centred cells.

There are six different types of centred cells depending on the position of the lattice points. These can be located on the centre of opposite faces of the parallelepiped (type A, B or C consistent with which faces are centred), or at the body centre (type I), for a total of two lattice points; further types contain the lattice on the centre of all faces (type F) for a total of four lattice points or the special case of the trigonal rhombohedral centred unit cells (type R) which contain three lattice points.

The combination of the seven crystal systems with all the possible types of cell centring described above (P, A, B, C, I, F, R) allows fourteen unique crystal lattices (since the trigonal primitive and hexagonal are geometrically equivalent), which are defined as Bravais lattices. These are shown in Figure 2.5. The primitive trigonal lattice is included in this figure to highlight the fact that real structures can form with such a lattice.

Figure 2.5. The Bravais Lattices
A single molecule can show a degree of symmetry such that if a given symmetry operation (inversion, rotation or reflection) is applied through a symmetry element (point, line or plane), its appearance remains identical. The symmetry elements for a single molecule must pass through a common point and the collection of all symmetry operations constitute a group called point group. All the symmetry operations can be divided in two categories (Schoenflies convention) defined respectively as proper rotations (for example any rotation of a certain fraction of 360°) and improper rotations (the combination of a rotation and the reflection in a perpendicular plane through a point at the centre of the molecule). Crystallographers define improper rotation as a rotation followed by an inversion through a point at the centre of the molecule (Hermann-Maugin convention). This difference relates to the importance of the centre of inversion in crystallographic symmetry. Table 2.2 lists the symbols used in the two conventions for symmetry elements and operations relevant to crystallography.

<table>
<thead>
<tr>
<th>Hermann-Maugin</th>
<th>Proper Rotations</th>
<th>Improper Rotations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schoenflies</td>
<td>C₁ (or E)</td>
<td>C₂</td>
</tr>
<tr>
<td></td>
<td>C₃</td>
<td>C₄</td>
</tr>
<tr>
<td></td>
<td>C₆</td>
<td>C₂ (= i)</td>
</tr>
<tr>
<td></td>
<td>S₁ (= σ)</td>
<td>S₆</td>
</tr>
<tr>
<td></td>
<td>S₄</td>
<td>S₃</td>
</tr>
</tbody>
</table>

Table 2.2. Symmetry elements and operation notations in the Hermann-Maugin and Schoenflies conventions.

As mentioned above the translation symmetry is a necessary requisite to generate a crystal. For a molecule in a crystal not all types of symmetry are permitted. In fact the combination of the symmetry elements for a single molecule with the translation symmetry generates some restrictions due to the incompatibility of some order of rotation with the repeat nature of the lattice. The only orders possible are those reported in table 2.2. However the combination of the symmetry operations discussed so far with the translation generates other types of symmetry operations which can be divided in two types defined respectively screw axes (proper rotations followed by translation by a fraction of the unit cell vector) and glide planes (reflections followed by translation by a fraction of the unit cell vector). These symmetry operations are such that, similarly to the case of a single molecule (in which repeated operations leaves its appearance identical), a repeated application of the operation places the molecule in an equivalent position in the next unit cell along the translation vector. The possible types of screw axes and glide planes and the conventional symbols used to classify these symmetry operations are reported in Table 2.3.
Screw Axes | Glide Planes
--- | ---
**Order** | **Notation** | **Translation vector** | **Notation**
2-fold | 2<sub>1</sub> | Parallel to the cell axis | a b c
3-fold | 3, 3<sub>3</sub> | Parallel to diagonals | n
4-fold | 4, 4<sub>2</sub>, 4<sub>3</sub> | Between corner and centred lattice | d
6-fold | 6<sub>1</sub>, 6<sub>2</sub>, 6<sub>3</sub>, 6<sub>5</sub> | points |

Table 2.3. Possible types of screw axes and glide planes.

Similarly to the case of a single molecule, in which the symmetry operations are combined in a point group, in the case of a crystal the symmetry elements are arranged in space and constitute a group defined as space group. Each space group defines a particular combination of point and space symmetry elements compatible with the geometrical requirement of the lattice. There are 230 possible combinations and these are listed in the International Table for Crystallography [7].

**Single Crystal X-ray Diffraction.**

X-rays, discovered in 1895 by Wilhelm Röntgen [8], are a form of electromagnetic radiation with a wavelength (in the range 0.1-100Å) lying between the ultra violet and the gamma ray wavelengths in the electromagnetic spectrum. X-rays can be generated by bombarding a metal target, such as molybdenum or copper, with a beam of accelerated electrons. The electrons are produced by a tungsten filament (cathode) and accelerated toward the metal target (anode). The resulting collision of the photo-electrons and the target produces the emission of a continuous range of wavelengths known as Bremsstrahlung. The process also causes the emission of the characteristic radiation which consists of X-ray photons with specific wavelengths dependent on the metal target. The desired wavelength can be selected by passing the radiation through a monochromator such as a graphite crystal. In recent years, X-rays generated at a synchrotron source have also been used for diffraction experiments to very good effect.

Due the order of magnitude of their wavelengths, which is comparable to the inter-atomic distances in crystals, X-rays can be diffracted by crystals. This was recognised by Max von Laue in 1912 who derived three equations to describe the conditions for constructive interference of X-rays diffracted by crystals.

Following von Laue's work, in 1913 W. H and W. L Bragg developed an easier model to describe the diffraction of X-rays by crystals [9]. W. H. Bragg and his son showed that crystals may be regarded as a stack of lattice planes of separation \(d_{hkl}\) which acts as
a semi-transparent mirror (Figure 2.6) in which the angle formed between the incident X-ray beam and the reflected beam have the same value \( \theta \).

![Diagram of Bragg's Law](image)

**Figure 2.6.** Derivation of Bragg’s Law.

The Bragg equation (Equation 2.3) describes the conditions for constructive interference to occur between lattice planes.

\[
n\lambda = 2d_{hkl} \sin \theta \tag{Equation 2.3}
\]

Where \( n \) is an integer, \( \lambda \) the X-ray wavelength, \( d_{hkl} \) the lattice plane spacing, \( \theta \) the Bragg’s angle.

The equation can be simplified setting the value of \( n \) to one (Equation 2.4) because reflections of the \( n^{th} \) order from a set of planes \( d_{hkl} \) are geometrically equivalent to reflections with \( n = 1 \) from planes \( nh, nk, nl \) with spacing \( d_{hkl}/n \).

\[
\lambda = 2d_{hkl} \sin \theta \tag{Equation 2.4}
\]
**Structure Factors and Phase Problem.**

The scattering of X-rays by a crystal structure is due to the electron clouds of each atom and increases as the number of the electrons or, in general, the atomic number increases. For this reason X-ray are not very sensitive to atoms such as hydrogen. The individual contribution of the atoms to X-ray scattering is defined as atomic scattering factor \( f \) and depends on the electron density distribution of the atom and on the Bragg’s angle \( \theta \). When \( \theta = 0 \), all the electrons in an atom scatter in phase and the atomic scattering factor corresponds to the atomic number of the atom. For greater scattering angles, \( f \) decreases since the scattered waves from different regions of the electron cloud become out of phase with each other. In the case of the diffraction from a crystal, the scattering of all the atoms must be taken into account. Similarly to the case of a single atom, the scattering of a group of atoms for a reflection \( h, k, l \) is defined by the structure factor \( F_{hkl} \) and is a complex number with amplitude an phase:

\[
F_{hkl} = \sum_{j=1}^{N} f_j \exp\left[2\pi i (hx_j + ky_j + lz_j)\right]
\]

Equation 2.5.

where \( f_j \) is the atomic scattering factor for the \( j^{th} \) atom in the unit cell, with fractional coordinates \( x_j, y_j \) and \( z_j \). In other words the diffraction pattern is the Fourier transform of the crystal structure in which each reflection is a wave resulting from the sum of the waves scattered by each atom depending on its electron density distribution.

In a similar way the crystal structure (considered as the electron density distribution of the unit cell) is the Fourier transform of the diffraction pattern and can, in principle, be calculated as follow:

\[
\rho(xyz) = \frac{1}{v} \sum_{hkl} F_{hkl} \exp\left[-2\pi i (hx_j + ky_j + lz_j)\right]
\]

Equation 2.6.

where \( \rho(xyz) \) is the electron density at any point with coordinates \( x, y, z \) and \( V \) is the unit cell volume.

However, since the structure factors \( F(hkl) \) reported in Equation 2.6 are complex numbers, with an amplitude and a phase and only their magnitude is available, the crystal structure cannot be directly solved unless the lost phase information is recovered, at least to an approximation good enough to be applied in Equation 2.6. This
is known as the phase problem. The Equation 2.6 can be rearranged in order to isolate the phase angle from the electron density (Equation 2.7).

\[
\rho(xyz) = \frac{1}{v} \sum_{hkl} |F_{hkl}| \exp\left[-2\pi i \left(hx_j + ky_j + lz_j\right) - \varphi(hkl)\right]
\]

Two main techniques are used for this called respectively direct method and Patterson synthesis.

The direct method, mainly used for structures containing atoms of approximately equal atomic number (such as C, N, O), use mathematical relationships to estimate the structure factor phases directly from the observed intensities in the diffraction pattern.

The Patterson method is generally used for structures with few heavy atoms such as organo-metallic compounds.
Chapter 2

General Procedures

Refinements.

This is an iterative process aimed to improve the model generated from the structure solution. During the refinement process the parameter of the model are systematically varied in order to obtain the best least square fit between the observed \(|F(hkl)|\) values (\(|F_o|\)) and the calculated (\(|F_c|\)). Each atom is initially refined considering its three positional coordinates \(x, y, z\) and a displacement parameter \(U\). This last parameter is relative to the isotropic displacement due to the thermal vibrations. In the final step of the refinement process, \(U\) is modelled with six parameters and the thermal vibrations of the atoms are considered to vary by different amounts depending on the different directions. This is the anisotropic vibration and the atoms are considered as ellipsoids. This last step generally determines a consistent improvement on the fitting between \(|F_o|\) and \(|F_c|\). The quality of the refinement can be measured using the residual factor (R-factor) which is a measure of the difference between the calculated pattern and the observed one. This can be defined as follow:

\[
R = \frac{\sum|F_o| - |F_c|}{\sum|F_c|}
\]

Equation 2.8.

During the refinement the R-factor should decrease to values between 0.02-0.10 (in case of good quality data).

Experimental Procedure.

Single crystal diffraction data is nowadays recorded using a diffractometer. This instrument comprises a goniometer for moving the crystal in many orientations so that all possible Bragg “reflections” may be recorded by a photon capture device. Modern instruments now use area detectors which have a CCD detector situated behind a fluorescent screen. The orientation of the goniometer and the capture of all reflections are controlled by a computer, with relevant software modules. For the work reported in this thesis, the intensity data were recorded on a Nonius KappaCCD diffractometer situated at the window of a Bruker Nonius FR591 rotating anode generator equipped with a molybdenum target (\(\lambda\) Mo-\(\kappa\alpha = 0.71073\text{Å}\)) and driven by COLLECT\textsuperscript{10}, DirAx\textsuperscript{11} and DENZO software\textsuperscript{12}. Structures were determined using the direct methods procedure in SHELXS 97 and refined by full-matrix least squares on \(F^2\) using
SHELXL97\textsuperscript{[13]} Data were corrected for absorption effects by means of comparison of equivalent reflections using the program SADABS\textsuperscript{[14]}. Non-hydrogen atoms were refined anisotropically, whilst non-carboxylate hydrogen atoms, although located easily in difference maps, were fixed in idealised positions with their displacement parameters riding on the values of their parent atoms (1.2 $U_{ij}$). In most cases carboxylate, hydroxo and amine hydrogens which were also located in difference maps, were included in the refinement with isotropic $U_{iso}$ values depending on the quality of the data.
2.4. XPac Procedure.

The XPac procedure enables the structural systematic comparison of families of compounds deriving from a common target molecule. The analysis is carried out by using the XPac algorithm developed by Dr T. Gelbrich\(^1\). The software identifies any geometrically similar assemblies of molecules occurring in two or more structures. The recurrent arrangement, as described in Chapter 1, is defined as Supramolecular Construct (SC) and may have different dimensionalities: 0-D (discrete molecular assemblies), 1-D (similar stacks or rows of molecules), 2-D (similar sheets, packed differently) and 3-D (isostructurality, isomorphism and pseudo-isostructurality). Differently to the concept of the supramolecular synthon\(^{15}\), which focuses on intermolecular interactions (directional or non-directional), the SC is a pure geometrical arrangement and does not identify any form of connectivity, such as H-bonding or other commonly defined form of directed intermolecular interactions. If present, these are identified when the results of the calculation are analysed in detail. In this regard the SC encompasses the approach originally proposed by Desiraju.

The identification of the SCs is based on the comparison of non-conventional crystallographic descriptors. Each molecule in a crystal structure is considered as surrounded by closest neighbour molecules to form a cluster. The central molecule is the kernel and the surrounding group of molecules is the shell. This model is then independent of crystal structure descriptors such as space groups (symmetry operations), unit cell parameters and atomic coordinates. Each kernel molecule is typically surrounded by a shell of 14 molecules.

In order to directly compare crystal structures of different compounds, the basic geometrical features of any molecule must be parameterised by selecting a representative set of corresponding atoms defined as the corresponding ordered set of points (COSP). The consistency or similarity of the COSP from two or more structures is given by comparing sufficiently large lists of internal coordinates (distances, angles, torsion angle). If N single pairs of corresponding entries \(x_i\) and \(x_i'\) in two such lists, then the mean value \(\delta\) of all N absolute differences \(|x_i - x_i'\)| is an indicator for the consistency of the COSP:
\[ \delta = \frac{1}{N} \sum_{i=1}^{n} |x_i - x'_i| \]  
Equation 2.9.

For each structure the software generates the coordination sphere around the kernel from the symmetry operations of the space group of each structure. The kernel is paired with each of the 14 molecules (COSPs) in the shell leading to 14 sets of parameters based on angular, planar and distance relationships. Each of these sets of parameters is compared with each of the 14 sets deriving from the other structure (or structures) under study. Any matches (within the defined tolerances) of these sets correspond to matches in the position of the molecules in the cluster for each of the structures under study. Depending on the number of matches the dimension of the similarity can be derived.

Table 2.4 shows the dimensionalities of the various SCs related to the number of matches.

<table>
<thead>
<tr>
<th>Number of Matches</th>
<th>Dimensionality</th>
<th>Type of SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1-2</td>
<td>0-D</td>
<td>Discrete assembly (e.g. dimer)</td>
</tr>
<tr>
<td>3-5</td>
<td>1-D</td>
<td>Infinite chain or row of molecules</td>
</tr>
<tr>
<td>6-13</td>
<td>2-D</td>
<td>Layer of molecules</td>
</tr>
<tr>
<td>14</td>
<td>3-D</td>
<td>Isostructurality</td>
</tr>
</tbody>
</table>

Table 2.4. Number of matches/dimensionality relationships. The type of Supramolecular Constructs (SCs) are also reported.

A tolerance criteria consisting of filter parameters can be defined. The filter parameters differ depending on the version of the software. XPac1 set limits for intermolecular angles (ang), dihedrals (dhd) and torsion angles (tor) (all in degrees). XPac2 use a different set of filters which set the limits for angular deviation (a), interplanar angular deviation (p) (both in degrees) and corresponding molecular centroid distance deviation (d) (Angstroms). By default there are three different sets of filter parameters (low, medium and high) but if needed they can be adjusted to more appropriate values.

For each similarity identified a quantitative dissimilarity index \( X \) is provided \[^{16}\]. This is expressed as follow:

\[ X = \sum_{i=1}^{M} \left( \delta_{a,i}^2 + \delta_{p,i}^2 \right)^{1/2} \]  
Equation 2.10.
where $\delta_a$ and $\delta_p$ are the mean differences between the comprehensive sets of angles and interplanar angles, respectively, between a chosen group of atoms in the core molecule and the corresponding atoms in one shell molecule.

The results are generally represented in a relationship diagram based on Hasse Diagram which is a form of “family tree”, in which the SC’s are ordered in rows vertically in terms of dimensionality, and relationships are then indicated by connecting lines.

Whilst there is some degree of flexibility in creating this diagram, the convention generally adopted in our group is to attempt to order the structures at the head of the diagram so that the lines indicating the relationships have the least possible crossings.

The experimental procedures adopted for the three families of substituted salicylic acid derivatives are described in each chapter in a section dedicated to the XPac analysis. In these sections the choice of the COSP and the notation chosen to describe the relationship diagram are also reported.

2.5. Thermal Analysis.

Differential Scanning Calorimetry (DSC).

Differential Scanning Calorimetry (DSC) is a useful technique which has a wide range of applications. It measures thermodynamic properties such as melting point, boiling point, sublimation temperature, glass transition temperature, decomposition temperature\(^{[17]}\). Furthermore it is a valuable tool for polymorphism characterization often used to determine phase transitions and kinetics of polymorphs. DSC measures the amount of energy absorbed or released by a sample under heating, cooling or held at a constant temperature in a controlled atmosphere.

The DSC data are typically expressed as a curve of heat flux versus temperature or versus time (Figure 2.7).
Figure 2.7. Typical DSC curve. The extrapolated onset temperature and the peak melting temperature are also shown.

As shown in Figure 2.7, the melting point can be taken from different points of the curve: the temperature at which deviation from the base line begin ($T_b$), the extrapolated onset temperature ($T_m$) the peak temperature ($T_p$) and the temperature at which the trace returns to the base line ($T_e$)\(^{[18]}\). The extrapolated onset temperature is generally preferred since it is not affected by the heating rate. However in case of peak broadening (due to impurities) the peak temperature ($T_p$) should be chosen\(^{[19]}\).

The sample is generally prepared by placing approximately 2-5 mg of substance in a sample pan. For this thesis work Al pans hermetically sealed were used (see section 3.2).

The analysis can be performed at different heating rates. High heating rates (e.g. 20°C/min) result in increasing of the width of the melting peak and so affect resolution (for example the ability to discriminate between thermal events close together). However it also results in a decrease of experimental times. Low heating rates (e.g. 3-5°C/min) result in a better resolution but the experimental time is significantly high. A heating rate about 10°C/min is generally a reasonable compromise in term of resolution/experimental time for most DSC investigations.
Hot-Stage Microscopy (HSM).

Intimately related to the previous technique is the Hot-Stage Microscopy (HSM). This technique allows the observation of melting points and in particular phase transitions, since these are frequently accompanied by reorganizations of the structure visible as changes in optical properties. Furthermore it can be used to analyze cocrystals and in general multiple component systems\(^{[20]}\) and solvate forms.

The HSM is one of the oldest techniques for phase transition analysis. The first example of thermo-analysis using an hot-stage equipped with a microscope was performed by Otto Lehmann more than a century ago\(^{[21]}\). Afterwards Kofler developed a simple and successful hot-stage which still is used in many laboratories.

The procedure is quite simple and mainly consists of placing the sample on a suitable slide which is afterwards covered with a cover slip. The analysis is carried out by increasing the temperature of the system and observing the eventual phase transitions and melting processes by means the microscope.

The HSM also allows the observation of desolvation processes which normally determine a darkening of the surface of the crystals (pseudomorphosis). Alternatively solvate forms can be detected by adding during the sample preparation some silicon oil. The desolvation process then determines vigorous bubbles formation in the oil.

As mentioned above the HSM can also used to investigate two component systems by applying the contact preparation method.

The contact preparation method was first described by Lehmann\(^{[22]}\). This technique is a useful and effective tool to investigate two-component systems. The main advantage is the small amount of substance needed, usually less than 5 mg.

In the contact preparation method, two small portions of different component A and B are sequentially melted and recrystallized on a microscope slide so that a zone of mixing is created (Figure 2.8).

![Figure 2.8](image-url) Contact preparation method. Preparation of the two-component slide.
By slow heating of that preparation under crossed polar filters on a light microscope, two main behaviours can be observed. The two components form a eutectic. Under heating process the contact surface melts at lower temperature than the two components. When a single eutectic melt is observed, it indicates that A and B do not interact to form a molecular compound.

The two components form a molecular compound. Under heating process two eutectics are observed and the molecular compound (salt or cocrystal) resides between them. The observance of two melting zones separated by solid indicates that a cocrystal or a salt of A and B have formed.

Figure 2.9. a) Eutectic. b) Molecular compound (cocrystal, salt).

Details of the thermal analysis (DSC and HSM) carried out in this thesis work are described in Chapter 3 (section 3.2).
2.6. **Fourier Transform Infrared (FT-IR) Spectroscopy.**

Fourier Transform Infrared (FT-IR) Spectroscopy is a useful technique for both quantitative and qualitative analysis which provides information about the vibrational states of a molecule. It is often used as complementary technique with thermal analysis in characterization of polymorphs since it allows the identification of functional groups, hydrogen bonding and conformations.

When a sample is irradiated with infrared radiation the vibrational and rotational status of the molecules change and the frequency of the radiation adsorbed is characteristic of the particular molecular structure. The energies associated with the vibrational modes of organic solids lie in the mid-infrared region (400-5000 cm$^{-1}$).

2.7. **Materials.**

Salicylic acid derivatives (range of purity 96-99%) and 4-aminopyridine (98 % purity) where mainly purchased from Acros. 6-F, 6-MeO, 4-F and 3-NO$_2$ were purchased from Aldrich.

Aspirin derivatives were synthesized in our laboratory starting from the salicylic derivative precursor and acetic anhydride and purified directly by crystallization (for the procedure and crystallization methods see Chapter 3, Section 3.2).
References.


Chapter 3: Substituted Acetylsalicylic Acid Derivatives.

In this chapter the crystal structures of aspirin derivatives and their comparison with XPac are described and discussed. A further section is focused on the polymorphism of 5-chloro aspirin.

3.1. The Family of Substituted Aspirins.

o-Acetylsalicylic acid, also known as aspirin, has been a world bestselling drug since it was first synthesized in 1853 \[1\]. In 1964 Wheatley provided the first crystal structure determination of this compound \[2\]. Although until recently it was known in only one polymorphic form, studies on the polymorphism of this simple analgesic molecule were known since 1960s \[3\]. Only in 2005, following on from the projection of its possible existence via predictive work \[4\], a second polymorph of aspirin was accidentally isolated by Zaworotko and coworkers \[5\] during cocrystallizations with levetiracetam and acetamide. The two structures show identical layers containing carboxylic dimers, which arrange differently (Figure 3.1) through acetyl···acetyl interactions (arrangement A: centrosymmetric C-H···O dimers for form I and arrangement B: C-H···O catemers for form II).

![Different arrangements found in the two polymorphs of aspirin: a) acetyl dimer, b) acetyl catemer.](image)

Figure 3.1. Different arrangements found in the two polymorphs of aspirin: a) acetyl dimer, b) acetyl catemer.

However, as highlighted by Bond et al. in a paper entitled “On the polymorphism of Aspirin” \[6\], the structure as then determined clearly showed problems with the refinement. Furthermore, the very close metric similarity between the unit cells of the two forms, induced these authors to prompt the question whether the new polymorph “might be an experimental artefact originating from erroneous handling of diffraction data collected from a form I crystal” \[6-7\]. The issue was finally resolved in a second
paper by Bond et al. [7] which describes form II as an unusual intergrowth structure in which both arrangements A and B are present within the same crystal, with a variable distribution and ratio. As suggested by these authors [7] and thereafter by Desiraju [8] this also has consequences on the definition of polymorphism, and raises the question concerning how many polymorphs of aspirin exist. This year Bond et al. isolated the pure form II by a crystallization of aspirin in various solvents in presence of aspirin anhydride [9].

Following the considerations reported above, was decided to develop a family of some substituted aspirin derivatives [10] and apply the systematic approach developed in our laboratory [11] in order to see how robust are the packing features in the two phases of the parent molecule, which have 2D similarity. Of particular interest were the two types of weaker acyl···acyl interactions which play an important role in determining the differences of the two polymorphs, and whether the additional substituent groups, and the associated changes in shape and electrostatics in the aspirin derivatives chosen, would introduce additional or alternative intermolecular interactions and/or packing patterns.

The type of compounds chosen for this study are those in which the parent molecule is substituted in the phenyl ring by small groups (Cl, Br, I, Me, MeO, etc), and in different positions.

The CSD database showed three main entries corresponding to the desired compound type, the 3-methyl (ACMEBZ) [12], the 6-methyl (BEHWOA) [13] and the 4-trifluoromethyl (HIRCOB) [14].

New members of the target compound family, obtained by acylation of pre-substituted salicylic acid derivatives as described in the next section, are summarised in Figure 3.1.

![Figure 3.2. Set of aspirin derivatives chosen for this analysis.](image)
In this chapter are thus reported the new crystal structures of 4-methylaspirin (4-MeAsp), 5-methylaspirin (5-MeAsp), 5-fluoroaspirin (5-FAsp), polymorphs I and II of 5-chloroaspirin (5-ClAsp I and 5ClAsp II), 5-bromoaspirin (5-BrAsp), 5-iodoaspirin (5-IAsp), 5-nitroaspirin (5-NO$_2$Asp), 5-methoxyaspirin (5-MeOAsp), 4-methoxyaspirin (4-MeOAsp), 3-methoxyaspirin (3-MeOAsp), 4-fluoroaspirin (4-FAsp), 6-fluoroaspirin (6-FAsp). The new structures are compared with the previously reported 3-methyl and 6-methyl aspirins (3-MeAsp and 6-MeAsp) [12-13], the 4-CF$_3$Asp [13] and with the two forms of the parent aspirin aspirin I (Asp1 CSD code ACSALA14) [6] and aspirin II (Asp2 CSD code ACSALA15) [7]. Two slightly different derivatives are also described 5-acetamidoaspirin (5-ACMAsp), and 3-acetamido (3-ACMAsp) aspirin, obtained by acylation of the corresponding aminosalicylic acids.

A further section is focused on the polymorphism of 5-chloroaspirin [10a] which currently comprises two anhydrous forms (5-ClAsp I and II where I denotes the highest melting form), with a complete characterization by several techniques such as FT-IR, Hot-Stage Microscopy, Differential Scanning Calorimetry (DSC) and contains a brief discussion of the crystal packing features.

### 3.2. Experimental.

**Synthesis and Crystallization of Functionalized 2-acetylsalicylic acids.**

The functionalized salicylic acid (10.8 mmol) was mixed with acetic anhydride (2 mL, 21 mmol) and 1 drop of 85% phosphoric acid solution. The mixture was stirred under reflux for 2 hours at 80° C whereupon water (2 mL) was added. The reaction continued for 5 minutes and the mixture was cooled with an ice water bath. The precipitate formed was filtered off and washed with water.

Colourless single crystals suitable for X-ray study were variously grown by slow evaporation from several solvents Table 3.1.
### Table 3.1. Summary of the solvents used for crystallizations, crystal habits for the aspirin (ASP) derivatives analyzed. (* The solvent deriving from the synthesis is an aqueous solution of acetic acid).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Crystal Habit</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-F H₂O / MeOH</td>
<td>Block</td>
</tr>
<tr>
<td>5-F H₂O / MeOH</td>
<td>Plate</td>
</tr>
<tr>
<td>6-F From Synthesis*</td>
<td>Block</td>
</tr>
<tr>
<td>5-Cl (I) H₂O / CH₃CN</td>
<td>Lath</td>
</tr>
<tr>
<td>5-Cl (II) 2-propanol</td>
<td>Needle</td>
</tr>
<tr>
<td>5-Br CH₃CN</td>
<td>Needle</td>
</tr>
<tr>
<td>5-I H₂O / CH₃CN</td>
<td>Needle</td>
</tr>
<tr>
<td>5-NO₂ H₂O / CH₃CN</td>
<td>Rod</td>
</tr>
<tr>
<td>4-Me H₂O / CH₃CN</td>
<td>Prism</td>
</tr>
<tr>
<td>5-Me CH₃CN</td>
<td>Plate</td>
</tr>
<tr>
<td>3-MeO MeOH</td>
<td>Slab</td>
</tr>
<tr>
<td>4-MeO From Synthesis*</td>
<td>Plate</td>
</tr>
<tr>
<td>5-MeO MeOH</td>
<td>Lath</td>
</tr>
<tr>
<td>3-ACM MeOH</td>
<td>Needle</td>
</tr>
<tr>
<td>5-ACM MeOH</td>
<td>Block</td>
</tr>
</tbody>
</table>

For simplicity, in the remainder of this Chapter, the derivatives of aspirin are labelled omitting the extension Asp and are referred to using only the abbreviation of the substituent group (e.g. 5-Cl, 5-Me, 4-CF₃ etc.).
**Chapter 3**

**Substituted Acetylsalicylic Acid Derivatives**

**Thermal Analysis.**

DSC measurements on the two polymorphs of the 5-Cl derivative (5-Cl (I) and 5-Cl (II)) were performed on a Mettler Toledo DSC821e low temperature differential scanning calorimeter fitted with a 34 place autosampler. The instrument was calibrated for temperature accuracy using an indium standard. Approximately 1-5 mg of sample was encapsulated in Al-Pans which were hermetically sealed. Thermomicroscopic investigations were carried out on a Mettler Toledo FP90 and FP82HT Hot Stage Microscope.

**Fourier Transform Infrared (FT-IR) Spectroscopy.**

FT-IR spectra were recorded with a Nicolet FT-IR Golden Gate Spectrometer (4000-400 cm\(^{-1}\)), at an instrument resolution of 4 cm\(^{-1}\), 32 scans per spectrum).

**Crystal Structure Determination.**

A summary of the basic crystal data are given in Table 3.2, in which we have also included information on the five previously reported derivatives and the aspirin forms, for completeness. Full X-rays experimental data are provided as detailed cif files in the Appendix CD.

<table>
<thead>
<tr>
<th>Compound</th>
<th>SG</th>
<th>a /Å</th>
<th>b /Å</th>
<th>c /Å</th>
<th>α /º</th>
<th>β /º</th>
<th>γ /º</th>
<th>V /Å(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-F</td>
<td>P2(/h</td>
<td>4.90840(10)</td>
<td>10.0101(5)</td>
<td>17.4781(9)</td>
<td>90.00</td>
<td>96.917(3)</td>
<td>90.00</td>
<td>852.51(6)</td>
</tr>
<tr>
<td>5-F</td>
<td>P2(/h</td>
<td>9.7655(5)</td>
<td>4.8919(2)</td>
<td>18.3338(10)</td>
<td>90.00</td>
<td>104.739(3)</td>
<td>90.00</td>
<td>847.02(7)</td>
</tr>
<tr>
<td>6-F</td>
<td>P2(/c</td>
<td>7.3711(2)</td>
<td>7.09520(10)</td>
<td>16.7141(4)</td>
<td>90.00</td>
<td>100.9190(10)</td>
<td>90.00</td>
<td>858.31(3)</td>
</tr>
<tr>
<td>5-Cl (I)</td>
<td>P2(/h</td>
<td>10.1217(4)</td>
<td>4.7359(10)</td>
<td>19.4447(7)</td>
<td>90.00</td>
<td>96.219(2)</td>
<td>90.00</td>
<td>926.60(5)</td>
</tr>
<tr>
<td>5-Cl (II)</td>
<td>P2(/c</td>
<td>5.0853(2)</td>
<td>17.8953(10)</td>
<td>10.4472(6)</td>
<td>90.00</td>
<td>98.267(3)</td>
<td>90.00</td>
<td>940.85(8)</td>
</tr>
<tr>
<td>5-Br</td>
<td>P2(/h</td>
<td>10.3912(4)</td>
<td>4.72650(10)</td>
<td>19.5116(9)</td>
<td>90.00</td>
<td>96.383(2)</td>
<td>90.00</td>
<td>952.35(6)</td>
</tr>
<tr>
<td>5-I</td>
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<td>96.630(2)</td>
<td>90.00</td>
<td>987.77(7)</td>
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<td>5.04440(10)</td>
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<td>90.00</td>
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<td>4.88310(10)</td>
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<td>90.00</td>
<td>100.696(2)</td>
<td>90.00</td>
<td>921.98(5)</td>
</tr>
<tr>
<td>6-Me</td>
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<td>7.238(2)</td>
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<td>90.00</td>
<td>978.83(5)</td>
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<td>P2(/c</td>
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<td>Pca(_2)</td>
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<td>102.56(3)</td>
<td>90.00</td>
<td>2144.93(7)</td>
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</table>

**Table 3.2.** Summary of basic crystallographic data. (\(^a\)ACMEBZ \([12]\), \(^b\)BEHWOA \([13]\), \(^c\)ACSALA14 \([16]\), \(^d\)ACSALA15 \([17]\), \(^e\)HIRCOb \([14]\))

3.3 Results and Discussion.

Diagrams of the twenty structures are given in Figures 3.2. a-l.
Interestingly, the family of Asp derivatives do not show any tendency to crystallize as solvate forms within the set of solvents used.

4-F

- Monoclinic, P2/n
- a = 4.9084(10) Å, b = 10.010(1) Å, c = 17.478(1) Å
- α = 90.00°, β = 96.917(3)°, γ = 90.00°
- V = 852.51(6) Å³
- Z' = 1

5-F

- Monoclinic, P2/n
- a = 9.7655(5) Å, b = 4.8919(2) Å, c = 18.3338(10) Å
- α = 90.00°, β = 104.739(3)°, γ = 90.00°
- V = 847.02(7) Å³
- Z' = 1

6-F

- Monoclinic, P2/c
- a = 4.9629(2) Å, b = 11.0915(8) Å, c = 13.6559(9) Å
- α = 90.00°, β = 98.788(4)°, γ = 90.00°
- V = 742.88(8) Å³
- Z' = 1

5-Cl (I)

- Monoclinic, P2/n
- a = 10.1217(4) Å, b = 4.7359(10) Å, c = 19.4447(7) Å
- α = 90.00°, β = 96.219(2)°, γ = 90.00°
- V = 926.60(5) Å³
- Z' = 1

5-Cl (II)

- Monoclinic, P2/c
- a = 5.0853(2) Å, b = 17.8953(10) Å, c = 10.4472(6) Å
- α = 90.00°, β = 98.267(3)°, γ = 90.00°
- V = 940.85(8) Å³
- Z' = 1

5-Br

- Monoclinic, P2/n
- a = 10.3912(4) Å, b = 4.72650(10) Å, c = 19.5116(9) Å
- α = 90.00°, β = 96.383(2)°, γ = 90.00°
- V = 952.35(6) Å³
- Z' = 1
Substituted Acetylsalicylic Acid Derivatives

5-1
monoclinic  P₂₁/n
a = 10.7838(5)  b = 4.7168(2)  c = 19.5502(8)
α = 90.00  β = 96.630(2)  γ = 90.00
V = 987.77(7)
Z' = 1

5-NO₂
monoclinic  P₂₁/n
a = 9.9166(3)  b = 5.04440(10)  c = 18.6808(5)
α = 90.00  β = 99.6860(10)  γ = 90.00
V = 921.15(4)
Z' = 1

3-Me
monoclinic  P₂₁/c
a = 4.910(1)  b = 11.702(2)  c = 17.233(6)
α = 90.00  β = 98.36(2)  γ = 90.00
V = 979.632
Z' = 1

4-Me
monoclinic  P₂₁/n
a = 4.6363(3)  b = 10.3293(9)  c = 19.5855(16)
α = 90.00  β = 93.632(5)  γ = 90.00
V = 936.06(13)
Z' = 1

5-Me
monoclinic  P₂₁/n
a = 10.1301(3)  b = 4.88310(10)  c = 18.9682(7)
α = 90.00  β = 100.696(2)  γ = 90.00
V = 921.98(5)
Z' = 1

6-Me
monoclinic  P₂₁/n
a = 10.164(2)  b = 7.238(2)  c = 13.186(3)
α = 90.00  β = 96.74(2)  γ = 90.00
V = 963.351
Z' = 1
Chapter 3

Substituted Acetylsalicylic Acid Derivatives

Asp 1
monoclinic P2₁/c

a = 11.2776(2)  b = 6.5517(1)  c = 11.2741(2)

α = 90.00  β = 95.837(1)  γ = 90.00

V = 828.70(2)

Z' = 1

Asp 2
monoclinic P2₁/c

a = 12.1515(10)  b = 6.5064(5)  c = 11.3637(9)

α = 90.00  β = 111.574(3)  γ = 90.00

V = 835.79(12)

Z' = 1

3-MeO
monoclinic P2₁/c

a = 9.5451 (3)  b = 14.2427(5)  c = 7.3811(2)

α = 90.00  β = 102.716 (2)  γ = 90.00

V = 978.83 (5)

Z' = 1

4-MeO
monoclinic P2₁/n

a = 5.06880(10)  b = 9.4619(3)  c = 20.0281(6)

α = 90.00  β = 94.069(2)  γ = 90.00

V = 958.14(5)

Z' = 1

5-MeO
monoclinic P2₁/c

a = 5.03850(10)  b = 17.3609(5)  c = 10.8931(3)

α = 90.00  β = 95.402(2)  γ = 90.00

V = 948.62(4)

Z' = 1

3-ACM
orthorhombic Pca2₁

a = 18.379(4)  b = 4.3789(11)  c = 13.658(3)

α = 90.00  β = 90.00  γ = 90.00

V = 1099.24(4)

Z' = 1
Another interesting feature concerns the tendency of aspirin derivatives to crystallize as monoclinic, space group No 14, in the $P2_1/c$ or $P2_1/n$ setting. Exception to this trend are represented only by the acetamido derivatives, 3-ACM and 5-ACM, which crystallize respectively as orthorhombic ($Pca2_1$) and triclinic ($P-I$). Furthermore, the structures in the family predominantly crystallize with $Z' = 1$. Only the 4-CF$_3$ derivative shows two molecules in the asymmetric unit.

The most interesting result concerns the accidental identification of a polymorphic form of the 5-Cl derivative (5-Cl (II)). As mentioned above, the crystal packing features, which are briefly discussed in this section as part of the systematic analysis carried out, will be commented on in a further section focussed on the polymorphism screening of the 5-Cl derivative (see Chapter 3, Section 3.2).

**Conformational Analysis.**

The molecular conformations are very similar in the majority of the structure. Figure 3.3 shows a typical molecule in the dominant conformational form. Table 3.3 reports the conformational parameters for the derivatives analyzed.
Figure 3.4. Geometrical parameters: torsion angles \( \tau_1, \tau_2 \) and \( \tau_3 \) and O–O distance \( d \).

Table 3.3. Summary of the geometrical parameters as defined in Figure 3.3. \(^a\) ACMEBZ \(^{[12]}\), \(^b\) BEHWOA \(^{[13]}\), \(^c\) ACSALA14 \(^{[6]}\), \(^d\) ACSALA15 \(^{[7]}\), \(^e\) HIRCOB \(^{[14]}\). ESD’s for 3-Me and 6-Me derivatives are not available.

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<th>( \tau_2/{}^\circ )</th>
<th>( \tau_3/{}^\circ )</th>
<th>( d/\text{Å} )</th>
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<td>2.719(1)</td>
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<tr>
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<td>11.4(2)</td>
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<td>-6.3(9)</td>
<td>89.0(6)</td>
<td>-0.2(9)</td>
<td>2.701(6)</td>
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The ring-carboxylate torsion angle, \( \tau_1 \) is very close to zero (the majority of the values lie between \( 1^\circ \) and \( 14^\circ \)) but for the 6-fluoro and 6-methyl, where the close proximity of the 6-substituents generate a steric hindrance; the values for these molecules are respectively \( 46.29^\circ \) and \( 44.7^\circ \). An intermediate value is moreover observed for the 5-ACM derivative which shows a torsion angle \( \tau_1 \) of \( 20.06^\circ \).

In contrast to what is observed for the two 6-derivatives, it is interesting to note here that in the other structures, the proximity of the acyl oxygen in the ortho position does not have an equivalent effect, even though the approximate co-planarity of the carboxylate and phenyl groups require an O (carbox)···O (acyl) contact distance of \( \text{ca.} 2.7\text{Å} \) (Table 3.3).

Further analysis shows that the acyl group, itself planar (\( \tau_3 \) values lie between \( 0^\circ \) and \( 13^\circ \)), is very close to orthogonal (\( \tau_2 = 90^\circ +/- 11^\circ \) with respect to the aromatic ring) in all
structures, with a consistent orientation which places the carbonyl group back towards the benzene ring.

**Description of Structures.**

The most significant, but not unexpected, feature of the family of structures is that, as shown in Figure 3.2, the carboxylic centrosymmetric dimer is the most common supramolecular synthon\[^{10,15}\] adopted by the aspirin derivatives. This is not the case in the 6-fluoro derivative, however, which shows a carboxylate catemer, in which the carboxylate groups interact via single hydrogen bonds to form a zig-zag chain (Figure 3.4).

![Figure 3.5. Carboxylate catemer of 6-fluoroaspirin (6-F). One representative carboxylate···carboxylate catemer is coloured orange, O-H···O distances are indicated by dashed lines.](image)

This is the first example of a carboxylate catemer structure in the aspirin family, and is a major departure for this group of compounds. However this result is more surprising in view of the normal dimer present in the 6-Me structure which, as in the 6-F derivative shows a high value of the torsional angle \(\tau_1\) (Table 3.3). Close examination of the structure shows the presence of other relevant intermolecular interactions in addition to the carboxylate catemer link. Figure 3.5 shows C-H···F and acetyl C-H···O hydrogen bonds responsible for the linking of the catemers along the 100 direction (Figure 3.5 a), C-H···O hydrogen bonds (aromatic C···O acetyl) connecting two linked molecules in one catemer with three other catemers approximately along the 010 direction (Figure 3.5 b) and, finally a C-H···O hydrogen bond (acetyl Me···O acetyl) connecting the catemers approximately along the 001 direction (Figure 3.5c).
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Figure 3. 6. Supplementary weak interactions in the 6-fluoroaspirin (6-F). One representative carboxylate···carboxylate catemer is coloured orange, Y-H···X distances are indicated as dashed lines.

A second departure from the typical carboxylic dimer is found for the 4-CF₃ derivative [14], in which the two independent molecules in the asymmetric unit are connected to form a non-centrosymmetric carboxylic dimer (Figure 3.6), with approximate $C_s$ symmetry.

Figure 3. 7. Cis-carboxylate dimer in the 4-trifluoromethaspirin (4-CF₃).

The last departure from the norm is observed for the acetamido derivatives (3-ACM and 5-ACM), in which, as consequence of the competition between the substituent groups, a different synthon involving the carboxylic group and the acetylamino group is adopted. However the two structures adopt significantly different geometries. In 3-ACM (Figure 3.7 a) the two interacting molecules are oriented to form approximately an angle of 90° and are connected via O-H···O (O···O distance 2.600 Å) between the carboxylate oxygen and the C=O of the acetylamino group, forming an infinite chain which
develops along the 100 direction. In 5-ACM (Figure 3.7 b) the two molecules adopt a co-planar conformation and, as for the 3-ACM, interact via O-H⋯O (O⋯O distance 2.597 Å) supported by a C-H⋯O hydrogen bond between the methyl of the acetylamino group and the other carboxylate oxygen (C⋯O distance 3.381 Å).

Interestingly a check in the CSD database reveals that these kinds of synthon are common for 3- or 5- acetylaminobenzoic acids (e.g. VIDLUQ) \(^{[16]}\), conversely to the 4-acetylamino derivatives which mainly show the carboxylic dimer (e.g. DIXFAR, ZAYRIA) \(^{[17]}\). The different behaviour of meta-isomers with respect the para-isomers might arises from a more efficient packing or an energetically more favourable set of interactions.

The analysis of the unit cell parameters (Table 3.2) in conjunction with the similarities in the conformations discussed above suggests possible relationships between the structures of some of the 5-substituted derivatives, and links between these and some of the 4-substituted derivatives. Furthermore, a deep analysis of the crystal packing reveals four set of isostructures (set 1: 5-Cl, 5-Br and 5-I; set 2: 5-F, 5-NO\(_2\) and 5-Me; set 3: 4-Me, 4-MeO and 4-F; set 4: 5-MeO and 5-Cl (II)).

**XPac Analysis.**

In order to explore whether any other relationships exist outside the above 3-D similarities, the whole group of structures have been compared using the XPac program, developed in our laboratory \(^{[11d]}\). The XPac analysis of the twenty ASP derivatives was carried out using the Corresponding Ordered Set of Points (COSP) represented in
Figure 3.8. The general procedure for the calculations (see Chapter 2, Section 2.4) is to use low filter parameters for identification of similarities, but in selected cases, in order to explore possible broader similarities the analysis is carried out using more “generous” parameters (medium and high). These are highlighted in the relevant cases. The program generated a total of 190 comparisons between all possible pairs of structures within the whole family.

![Diagram](image)

**Figure 3.9.** Numbering scheme and Corresponding Ordered Set of Points (COSP) defined for the XPac analysis.

The results are displayed in the structural relationship diagram (see Chapter 2, Section 2.4) reported in Figure 3.9 (For more details see Appendix A1).

The following notation is used to describe the relationships reported in figure:

The diagram is divided into different regions, each indicating a given dimension (3-D, 2-D, 1-D, 0-D). Higher similarities are positioned on the top of the diagram and the dimensions decrease going downwards. The COSP is labeled as X.

The different crystal structures are positioned on the top of the diagram. Each structure is indicated by a grey circle. Structures in the same position define isostructurality.

The SCs are indicated by letter followed by numbers. The first number is used to indicate the dimensionality (e.g. 0, 1, etc.), the second indicates an arbitrary numbering scheme. The same letter means the same family of SCs (deriving from a common arrangement), this is also indicated using circles having the same colour. Mixed letters define SCs deriving from the contribution of different arrangements. This is also indicated by circles with more than one colour.

The relationships among the different structures and SCs are indicated by connecting lines.
Dashed lines indicate connections between COSP (X) and those SCs which directly derive from it (e.g. the carboxylic dimer A0 is built by two COSP related by inversion symmetry).

\[ \text{Figure 3. 10. Structural relationship diagram showing the relationships between supramolecular constructs (SCs) identified for the aspirin derivatives under study.} \]

The analysis, as expected, confirms the presence of four isostructural sets. Interestingly the 3-Me derivative shows 3-D similarity to the 4-substituted isostructural set: 4-Me, 4-MeO and 4-F (see below).

The analysis shows three 0-D SCs labeled respectively A0, B0 and C0. Interestingly all these arrangements are centrosymmetric dimers but involving different substituent groups. This is in agreement with the regular tendency of molecules to pack across inversion centres \[^{18}\] which, especially for hydrogen bond ring motifs, play a significant role \[^{19}\].
A0 is the carboxylic dimer and, as shown in Figure 3.9, it has a strong influence in the crystal packing of the aspirin derivatives since it is precursor of a large number of relationships with higher dimensions.

B0 is a motif present in the isostructural pair 5-Cl (II) and 5-MeO, the isostructural set of 5- haloderivatives (Cl (I), Br and I) and in the 5-ACM derivative (Figure 3.10). As mentioned above B0 is also a centrosymmetric dimer, in which two molecules in anti-parallel orientations are connected by interactions involving a carboxylic group oxygen and the substituent group in position 5, a halogen in the case of the Cl, Br, I set, a methyl hydrogen of the 5-methoxy group in the 5-MeO derivative and the methyl of the acetylamino in the 5-ACM structure. B0 in conjunction with the 0-D SC A0, contributes to a 1-D arrangement (SC AB1) which relates the halo derivatives and the 5-MeO structure (see below).

The third 0-D SC, labeled as C0, is the acetyl-acetyl centrosymmetric dimer which, as described above (see Section 3.1), plays a role in defining the differences between the two polymorphic forms of aspirin$^{[5-7]}$.

This is identified for the 6-F derivative and Asp1 using low filters (Figure 3.11 a and b). However increasing the filter parameters to high values it is also observed in the two sets of isostructures (5-F, 5-NO$_2$, 5-Me and 4-Me, 4-MeO, 4-F and 3-Me).
Figure 3.12. The acetyl···acetyl dimer (Supramolecular Construct (SC) C1) as found in: a) 6-fluoroaspirin (6-F) and b) aspirin 1 (Asp 1).

Table 3.4 reports the O···H and C···O distances for the structures involved in forming C0.

<table>
<thead>
<tr>
<th></th>
<th>O···H (Å)</th>
<th>C···O (Å)</th>
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<tbody>
<tr>
<td>5-F</td>
<td>2.616(2)</td>
<td>3.541(2)</td>
</tr>
<tr>
<td>5-NO₂</td>
<td>2.843(2)</td>
<td>3.747(2)</td>
</tr>
<tr>
<td>5-Me</td>
<td>2.793(2)</td>
<td>3.726(2)</td>
</tr>
<tr>
<td>4-Me</td>
<td>2.669(3)</td>
<td>3.614(3)</td>
</tr>
<tr>
<td>3-Me⁺</td>
<td>3.056(5)</td>
<td>4.072(5)</td>
</tr>
<tr>
<td>4-MeO</td>
<td>2.739(3)</td>
<td>3.653(3)</td>
</tr>
<tr>
<td>4-F</td>
<td>2.624(2)</td>
<td>3.561(2)</td>
</tr>
<tr>
<td>Asp1⁺</td>
<td>2.620(1)</td>
<td>3.574(1)</td>
</tr>
<tr>
<td>6-F</td>
<td>2.820(2)</td>
<td>3.670(2)</td>
</tr>
</tbody>
</table>

Table 3.4. Acetyl-Acetyl intermolecular distances for the set of structures adopting the 0-D Supramolecular Construct (SC) C1. (ACMEBZ [12], ACSALA14 [6]). ESD’s for 3-Me is estimated considering that C=O bond reported by the authors has value about 4 in the 3rd decimal place.

The acetyl dimer C0 is precursor of two 1-D SCs; the first, C1, relates the 6-F derivative and Asp 1; the second, which is in conjunction with A0, labelled as AC1 is common for the two sets of isostructures (5-F, 5-NO₂, 5-Me and 4-Me, 4-MeO, 4-F and 3-Me). The SC C1 consists of a row of acetyl dimers (Figure 3.12 a and b) developing along the shortest axis (010 in both structures). It is most interesting to note that the connections between adjacent instances (C1 and C1’) of the 1-D SC, then involve the two most significant synthons, the carboxylate catemer for the 6-F and the carboxylate dimer for Asp1, thus generating major differences in the resulting 2D arrangements.
Figure 3.13. Supramolecular Construct (SC) C1: a) 6-fluorospirin (6-F) viewed along the \(100\) direction; b) aspirin 1(Asp1) viewed approximately along the \(001\) direction. Instance of SC C1 (C1 and C1’) are indicated by different colours. Acetyl-Acetyl dimer is indicated by red dashed lines; the connectivity between different instances of C1 are indicated with green dashed lines.

Strictly related to the C1 is a second 1-D SC, E1 (Figure 3.13 a-c), which consists of a single row of molecules propagating along the \(010\) axis (i.e. one half of SC C1 in Figure 3.13 a and b). This is common for the two polymorphic forms of aspirin and for the 6-F derivative. Note that the two instances of the arrangement, E1 and E1’, in Asp1 and the 6-F derivative are related by a centre of inversion in the acetyl-acetyl dimer, but by \(2_1\) screw axis in Asp2 in the acetyl catemer.
Figure 3.14. Supramolecular Construct (SC) E1 viewed along the 010 direction: a) aspirin 1 (Asp 1); b) 6-fluoroaspirin (6-F); c) aspirin 2 (Asp 2). Instance of SC E1 (E1 and E1’) are according to the orientation of the ring-carboxylate vector: green pointing towards the viewer, blue pointing away from the viewer. The SC C1 is also indicated in a) and b).

As mentioned above, the C0 is precursor of another 1-D SC, AC1, obtained by the combination with the carboxylic dimer A0. This is a zig-zag row of molecules, present in the 5-F, 5-NO₂, 5-Me, 3-Me and 4-Me derivatives (Figure 3.14 a-c).

Figure 3.15. 1-D Supramolecular Construct (SC) AC1 in aspirin derivatives; a) Asp1, b) 3-Me, c) 5-F. SC AC1 is shown in red and hydrogen bonds between constituent molecules are shown in blue. All other hydrogen bonds are omitted for clarity. Each structure is orientated to best show the SC.
It is interesting to note that, a part the centrosymmetric acetyl dimer identified, the acetyl group might be precursor of other arrangements not identified since they do not represent common features within the family under study. In fact, since his approximate 90° orientation with respect the aromatic ring (see $\tau_2$ values in Table 3.3), it is available for possible participation in supplementary interactions, developing particular arrangements (e.g. carboxylic dimers or higher dimensional motifs) along directions approximately orthogonal to the aromatic ring (stacking arrangements or diagonal rows of molecules) similarly as seen for the dimer C0. An example of this is given by the 3-Me derivative, in which the acetyl dimer is a packing consequence (see Table 3.4) and the acetyl group is available for a closer acetyl···acetyl association, in the form of a new type of acetyl catemer, linking molecules in a translational stack, as shown in Figure 3.15.

![Figure 3.16. Acetyl···Acetyl translation catemer identified in 3-methylaspirin (3-Me) structure.](image)

The next 1-D SC, A11, consists in stacks of tilted carboxylate dimers which develop along the shortest axis (Figure 3.16 a and b) and is common for the three set of isostructures (5-Cl (I), 5-Br, 5-I; 5-F, 5-NO$_2$, 5-Me and 3-Me, 4Me, 4-F, 4-MeO).

![Figure 3.17. 1-D Supramolecular Construct (SC) A11: a) 5-I derivative; b) 4-Me derivative.](image)
Strictly linked to A11 is another 1-D SC, D11, which relates the 4-CF$_3$ and the 3-ACM derivatives; this is a stacking arrangement built from single molecules of the aspirin derivatives. D11 is, essentially, one half of the 1-D SC A11 which is common for the three sets of isostructural compounds discussed above (Figure 3.16). Note that the occurrence of different supramolecular synthons (in 3-ACM and 4-CF$_3$) does not affect their tendency to adopt similar molecular arrangements. In particular Figure 3.17 shows the comparison between the 4-CF$_3$ and 4-F derivatives in which the stacking similarity occurs between one half (with the disordered CF$_3$ group) of the cis-dimer in the trifluoro structure and each half of the centrosymmetric dimer of the 4-F derivative. This similarity was obtained using low filters for some structures but for a total characterization medium angle filters with an increase in the distance parameter (d = 2.0) were needed.

Interestingly, although the stacking of the two halves of the cis dimer appears from the diagram to be similar, the D1 similarity only applies to the molecule with the disordered CF$_3$. The non-equivalent packing of the two symmetry independent molecules is such that the two halves have arrangements which differ by parameters which are higher than the filter parameters available for the analysis.

The next 1-D SC deriving from the carboxylic dimer A0, SC A12, is formed by a row of tilted dimers (Figure 3.18) and relates the 5-halo isostructural set with the 6-Me derivative. There are no intermolecular contacts of any significance within this SC, other than the carboxylate dimer. However, it is interesting to note the small influence
of the different geometry of the dimer in 6-Me derivative, due to the twist of the ring-carboxylate bond.

Figure 3.19. 1-D Supramolecular Construct (SC) A12 in aspirin derivatives; a) 5-Cl, viewed approximately along the 110 direction, b) 6-Me, viewed approximately along the 100 direction. SC A12 is shown in green for each structure.

A further 1-D SC, A13, consists of a tilted stacking motif involving carboxylic dimers in the 3-MeO derivatives and 6-MeAspirin (Figure 3.19) found with medium filters.

Figure 3.20. Supramolecular Construct (SC) A13: a) 3-methoxyaspirin (3-MeO) viewed along the 001 direction; b) 6-methylaspirin (6-Me) viewed along the 010 direction.

As previously observed for the SC A12, it is worth noting that, in spite of the different shapes of the dimers, the two compounds adopt this similar motif. However this feature
reflects the fact that the main arrangement in the stack of tilted molecules places the
carboxylate groups in a region where there is enough space to accommodate the
different twist without affecting too much the arrangement. Furthermore this last feature
does not change the separations of the coplanar phenyl rings but only influences the
stacks, determining a shift of the relative position of the molecules along the two
directions at angles to the stacking (Figure 3.29 a and b below). This is also reflected in
the differences in the associations between the molecules in these constructs Figure 3.20
a and b). For 3-MeOAsp, SC A13 is built by carboxylic dimers which develop along the
001 direction, and which are linked by C-H···O hydrogen bonds involving the acetyl
carbonyl group and the methyl hydrogen H(10) in the methoxy group. In 6-MeAsp, SC
A13 is arranged along 010 without any hydrogen bond between two adjacent carboxylic
dimers (the shortest O···H distances between two adjacent molecules in the stacking
arrangement are approximately 5 Å with respect to the aromatic hydrogen H(1).

Figure 3.21. Intermolecular interactions involved in forming the Supramolecular Construct (SC) A13. a) 3-methoxyaspirin (3-MeO), b) 6-methylaspirin (6-Me). Short and long contacts distances are respectively indicated in blue and red.

A further 1-D SC identified is labelled as AB1. This construct consists of a double chain
combining A0 and B0, and it is common for the two isostructural sets 5-Cl (I), 5-Br and
5-I and 5-MeO and 5-Cl (II). The centrosymmetric carboxylic dimer A0 interacts with
neighbouring dimers across a further centre of symmetry, via SC B0 through
reciprocating pairs of X···carboxylate O halogen bonds in the halo structures, and via
methyl C-H···carboxylate O in the 5-MeO derivative, to form an infinite tape which
develops respectively along 100 for the isostructural set 5-Cl (I), 5-Br and 5-I, along -
10-1 for the 5-MeO derivative and along 101 for 5-Cl (II) (Figure 3.21). One subtle
point is that in the halo derivatives this secondary interaction involves the carboxylate
carbonyl oxygen and in the methoxy derivative the carboxylate hydroxyl oxygen.
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Figure 3.22. 1-D Supramolecular Construct (SC) AB1 viewed along the shortest axis in each case: a) 5-bromo aspirin (5-Br); b) 5-methoxy aspirin (5-MeO). Intermolecular interactions involved in the formation SC AB1 are indicated in blue. In 5-MeO C-H···O hydrogen bonds are indicated in red.

An XPac calculation with medium filter parameters actually suggests a higher 2-D similarity involving a stacking arrangement of AB1 constructs, along 010 for the isostructural set 5-Cl (I), 5-Br and 5-I and along 100 for the set 5-MeO and 5-Cl (II) (Figure 3.22).

![Figure 3.22](image)

**Figure 3.23.** Approximate 2-D similarity obtained using medium filter parameters: a) 5-bromo aspirin (5-Br); b) 5-methoxy aspirin (5-MeO). Differences in the corresponding lattice vectors and angles are also reported.

<table>
<thead>
<tr>
<th></th>
<th>Corresponding Lattice Vectors and Angles:</th>
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<tbody>
<tr>
<td>a)</td>
<td>0 1 0 = 4.727 Å</td>
</tr>
<tr>
<td></td>
<td>1 0 0 = 10.391 Å</td>
</tr>
<tr>
<td></td>
<td>90°</td>
</tr>
<tr>
<td>b)</td>
<td>1 0 0 = 5.038 Å</td>
</tr>
<tr>
<td></td>
<td>-1 0 -1 = 11.563 Å</td>
</tr>
<tr>
<td></td>
<td>110.31°</td>
</tr>
</tbody>
</table>

The comparison of the angle between the two directions of propagation (the base vectors reported in figure 3.22) of the 2-D SC for the two representative structures analyzed, reveals a difference of about 20°. This value in particular, but also the distance vectors, is indicative of the slipping of the molecules in the stacks. Further examination of the crystal structures reveals the major difference between the 3D structures to be the symmetry relationships and associated packing between neighbouring 2-D slabs. In the halo derivative the stacks are related by vertical 2_1 screw axes (Figure 3.23 a). In 5-MeO, they are related by c-glide operations (Figure 3.23 b).
This difference can also be responsible for the shift in the stacking arrangement previously described.

**Figure 3.24.** Packing arrangements of slabs of the Supramolecular Constructs (SCs) AB1: a) 5-bromoaspirin (5-Br); b) 5-methoxyaspirin (5-MeO). Vertical screw axis (green) and glide (red) relationships are also reported. The molecules are colour coded according to the orientation of the ring-carboxylate vector: orange pointing towards the viewer, blue pointing away from the viewer.

The SC B0 is also precursor of the last 1-D SC, B1, which is common for the isostructural halo derivatives 5-Cl (I), 5-Br, 5-I and the 5-ACM derivative. This is a chain of SCs B0 which develops diagonally along 110 for the halo isostructural set and 101 for the 5-ACM. This arrangement was indentified using medium filter parameters and increasing the distance parameter (d = 2.0). However, using less restricted filters (high with the distance parameter d = 2) the similarity is also extended to the isostructural set 5-Cl (II) and 5-MeO. This is a further confirmation of the differences in the stacking arrangement of the two isostructural sets discussed above (see Figure 3.22). Although this similarity was not included in the relationship diagram (Figure 3.9) the Figure 3.24 shows the 1-D SC for the 5-MeO (developing along 001) and the 5-ACM derivatives (developing along 101).
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Figure 3.25. Supramolecular Construct (SC) B1 in aspirin derivatives; a) 5-ACM, b) 5-MeO. SC B1 is shown in orange and the significant interactions between constituent molecules are shown in black. Each structure is orientated to best show the SC.

AE2 is the first of the three 2-D SCs identified within the family of aspirin derivatives. It derives from the combination of the carboxylic dimer A0 and the 1-D row of molecules E1 related by 2/1 screw axis to form a layer (Figure 3.25) which is common for the two polymorphs of aspirin (Asp 1 and Asp 2).

Figure 3.26. 2-D Supramolecular Construct (SC) AE2 in the aspirin polymorphs, viewed along the 010 direction: a) Asp 1; b) Asp 2. Each molecule represents the 1-D SC E1 extending into the page. The molecules are colour coded according to the orientation of the ring-carboxylate vector: blue = pointing towards the viewer, red = pointing away from the viewer. Individual instances of the SC, AE2 and AE2’, are separated by dashed lines. Symmetry operations are also included: 2/1 screw axis (green), inversion (yellow circles).
As previously discussed\textsuperscript{[5-7]} (see also Section 3.1), the two polymorphs of aspirin (Asp1 and Asp2) show differences mainly due to the shift in the relative position of the layers AE2 and AE2’ which is related to the formation of a C-H⋯O dimer (form I), across a centre of inversion (see Figure 3.11), or catemer (ideal form II), spiralling around a 2\textsubscript{1} screw axis, each involving the carbonyl and a methyl hydrogen of the acetyl groups.

The two set of isostructures 5-F, 5-NO\textsubscript{2}, 5-Me, and 3-Me, 4-Me, 4-F, 4-MeO, show a common 2-D SC labelled as AC2 (Figure 3.26). This is formed by stacks of tilted, parallel dimers, which themselves each constitute a 1D SC, but not identified separately since it only exists as part of the higher dimensional 2D SC (AC2), connected via weak C-H⋯O hydrogen bonds (see Table 3.4) between atoms of the acyl groups (cfr the SC AC1 in Figure 3.14). Interestingly the stack of dimers is analogous to the 1-D SC A11 discussed above (Figure 3.16), but differing in tilt and spacing. This results in significant differences in the cell dimensions related to the stacking directions (4 Å for the aspirin derivatives involved in forming A11 and 6 Å for aspirins).

\textbf{Figure 3. 27.} 2D Supramolecular Construct (SC) AC2 in the 5-F aspirin derivative. The colour scheme is analogous to that used for Figure 3.25: gold = pointing towards the viewer, black = pointing away from the viewer. Hydrogen bonds between acid and acetyl moieties are shown in blue. Instances of SCs AC2 and AC2’ are related by a 2\textsubscript{1} screw axis and are shown separated by dashed lines. The structure is viewed along the 010 axis.
The last 2-D SC, A2, relates the two isostructural set 5-Cl (I), 5-Br, 5-I and 5-F, 5-NO$_2$, 5-Me. This consists of a sheet of SCs A11 related by 2$_1$ screw axes and connected along the 101 direction by C-H···O involving the acyl carbonyl oxygen and aromatic hydrogen in position 4. This is shown in Figure 3.27 for the 5-NO$_2$ and 5-I derivatives (C···O distances are respectively 3.10 Å and 3.24 Å).

![Figure 3.27](image)

As shown in the figure, the two sets of isostructures show differences in the development of the instances of the SC A2, which, as consequence of this, are connected via different interactions. For the 5-Cl (I), 5-Br and 5-I structures, these are X···O$_{\text{carboxylate}}$ (where X= Cl, Br, I) short contacts which have values of 3.12Å, 3.20Å, 3.37Å for the Cl, Br and I derivatives, respectively. As described above, these contacts have a significant role in defining the 0-D SC B0 (see Figure 3.9). For the 5-F, 5-NO$_2$ and 5-Me structures, the contacts between the A21 sheets involve weak acyl···acyl dimers (see SC C0), which for the 5-F and 5-NO$_2$ derivatives are assisted by additional contacts involving the fluoro and nitro substituents. In particular 5-F shows F···O contact to the carboxylate hydroxyl oxygen (F···O distance 2.93 Å) and a C-H···F (C···F distance 3.24 Å) contact to the methyl of the acyl group; 5-NO$_2$ shows C-H···O hydrogen bonds (C···O distance 3.12Å) between the nitro group and the acyl methyl. Interestingly, as consequence of the isostructurality of the two derivatives, the 5-NO$_2$ structure shows a close approach, presumably non-bonding, between the nitro group and the carboxyl hydroxyl oxygen (O···O = 3.03Å).
As mentioned above, the analysis showed a 3-D relationship between the 3-Me derivative and the 4-substituted isostructural set 4-Me, 4-MeO and 4-F. This is a case of approximate isostructurality and derives from the choice of the COSP components (see Figure 3.8) which do not include the substituted groups. In fact, though atoms of the COSP, have a reasonably close isostructural relationship, the comparison of the two methyl structures (3-Me and 4-Me) reveals that the different position of the groups has a significant influence on the values of the a and b cell dimensions (see Table 3.2). This is also confirmed by the comparison of the “dissimilarity index” \(^{21}\) values calculated by the software, which also provides values for the other isostructural sets (see Table 3.5). This case can be considered part of the concept “quasi-isostructurality” \(^{22}\) proposed by Kalman, which then was changed to “main part isostructurality” \(^{23}\). In a recent paper we proposed the simple term “pseudo-isostructurality” \(^{10a}\) as suitable to cover all such cases.

<table>
<thead>
<tr>
<th>Structure 1</th>
<th>Structure 2</th>
<th>Dissimilarity Index ((\chi))</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Br</td>
<td>5-Cl (I)</td>
<td>1.1</td>
</tr>
<tr>
<td>5-Br</td>
<td>5-I</td>
<td>1.7</td>
</tr>
<tr>
<td>5-Cl (I)</td>
<td>5-I</td>
<td>2.7</td>
</tr>
<tr>
<td>5-F</td>
<td>5-Me</td>
<td>3.8</td>
</tr>
<tr>
<td>5-F</td>
<td>5-NO(_2)</td>
<td>5.1</td>
</tr>
<tr>
<td>5-Me</td>
<td>5-NO(_2)</td>
<td>4.7</td>
</tr>
<tr>
<td>3-Me</td>
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<td>3-Me</td>
<td>4-MeO</td>
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<td>4-F</td>
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</tr>
<tr>
<td>4-Me</td>
<td>4-MeO</td>
<td>7.4</td>
</tr>
<tr>
<td>4-Me</td>
<td>4-F</td>
<td>7.0</td>
</tr>
<tr>
<td>4-MeO</td>
<td>4-F</td>
<td>6.4</td>
</tr>
<tr>
<td>5-Cl (II)</td>
<td>5-MeO</td>
<td>4.4</td>
</tr>
</tbody>
</table>

**Table 3. 5.** Dissimilarity indices (\(\chi\)) for groups of structures exhibiting 3D similarity.

The data shows the small influence of changing the size of the substituent in the first two isostructural sets, and the greater effect in the 4-substituted isostructural set. This last result might be explained by considering that the position para to be more exposed to the neighbouring molecules and small variations of the substituent group can increase or decrease steric hindrance with the surrounding environment, generating differences in the crystal packing.

A similar effect can also be responsible for the small differences in the stacking arrangements observed in the family under study. Although the aspirin derivatives show stacking arrangement which can objectively be considered analogous, the structural similarity analysis reveals the presence of, at least, three different arrangements. The first is related to the 1-D SC D1, which is found in the three set of isostructures (5-Cl (I)
set, 5-F set and 4-Me set, where these three derivatives are considered as representative for each set) and the 4-CF₃ and 3-ACM derivatives, the second is related to the 1-D SC A13 and relates the 3-MeO and the 6-Me derivatives and the last is related the 1-D SC E1 which relates the two polymorphs of aspirin (Asp1 and Asp2).

Stacking arrangements are also observed in the other members of the family but not discussed so far since they do not show any significant similarity within the filter parameters adopted for the analysis. However, since this is a recurring feature for this family of compounds, it is interesting analyze the differences for all member of the family. The analysis is carried out using three main parameters (Figure 3.28) [24]: a) the distances between the molecular planes of two adjacent molecules 1 and 2 (P1 and P2), b) the distance between the centroids of 1 and 2 (Cen1 and Cen2) and c) the offset angle, defined as the angle formed between the Cen1-Cen2 vector and the perpendicular vector to the plane of molecule 2 (ϕ). This last parameter defines the shifts occurring between adjacent molecules along the stacking direction. The angle between the molecular planes of molecule 1 and 2 is not reported since is observed to be approximately 0 for all the structures.

**Figure 3.29.** Geometrical parameters used to describe the stacking arrangement occurring in aspirins. Cen = centroid, P = molecular plane, ϕ = offset angle formed between Cen1-Cen2 vector and ring normal of molecule 2.
Table 3.6. Geometrical parameters defining stacking arrangements observed in aspirin structures as described in Figure 28. Rows with same colour indicate isostructurality. Structures not involved in any 3-D similarity are indicated by colourless rows. (a) ACMEBZ [12], (b) BEHWOA [13], (c) ACSALA14 [6], (d) ACSALA15 [7], (e) HIRCOB [14]). ESD’s for these parameters are estimated as <0.01 for distances and 0.1 for angles, based on values for molecular parameters.

The values reported in Table 3.6 confirm that the aspirin derivatives show a quite extensive and varied slippage. This is clearly demonstrated in Figure 3.29 (a-k), in which the structures are viewed perpendicular to the planes of the molecules in the stacks.
Figure 3.30. Comparison of the stacking arrangements identified in the representative aspirin derivative structures viewed along the shortest axis (left) and their orthogonal projections: a) 3-methoxyaspirin (3-MeO), b) 6-methylaspirin (6-Me), c) 5-methoxyaspirin (5-MeO), d) 5-chloroaspirin form I (5-Cl (I)), e) 5-fluoroaspirin (5-F), f) 4-fluoroaspirin (4-F), g) aspirin 1 (Asp1), h) aspirin 2 (Asp2), i) 4-trifluoromethylaspirin (4-CF₃), j) 6-fluoroaspirin (6-F), k) 3-actylaminoaspirin (3-ACM).

In particular it is worth noting that for the 6-F and 6-Me derivatives the values reported in Table 3.6 are higher with respect to the other derivatives. As previously discussed for
the stacking arrangement identified as the 1-D SC A13, the 6-Me and, for the same reason, 6-F derivatives require space in order to accommodate the different twist of the carboxylic group due to the steric hindrance of the substituent in position 6. This results in an arrangement which can be described as an averaged motif in between the typical slipped stacks and a row of molecules. Interestingly a similar behaviour is also observed for the 3-MeO derivative which showed a common arrangement with the 6-Me derivative (see SC A13) even though the torsion angle value is close to 0. This might arise from a steric hindrance involving the methoxy group. However the analysis of the Cen1-Cen2 and, in particular, of the $\phi$ angles reveals that this behaviour is also observed in the two polymorphs of aspirin (Asp 1 and Asp 2) in which there are no substituent groups at all.

Interestingly the 5-ACM derivative shows a significant departure from the other structures under study. In fact, the stacking arrangement develops with an anti-parallel reciprocal orientation of the carboxylate group of adjacent molecules along the 010 direction (Figure 3.30).

![Figure 3.31. Stacking arrangement of 5-ACM along the 010 direction.](image)

### 3.4. Polymorphism of 5-chloro aspirin.

As previously mentioned (see section 3.3), 5-Cl derivative is the only compound within the family of aspirin derivatives which showed polymorphism [10a]. The structures of two forms (5-Cl (I) and 5-Cl (II) where I denotes the highest melting polymorph) have been analyzed as part of the structural systematic analysis reported in Section 3.3. In this section, both, similarities and differences of the crystal packing of the two polymorphs are discussed in more detail. The two forms are also characterized by means several techniques such as thermal analysis using differential scanning calorimetry (DSC) and Hot-Stage Microscopy (HSM) and FT-IR. Furthermore, as part
of a collaboration with Dr. John Kendrick and Dr. Frank Leusen from University of Bradford, results of solid state density function (DFT) calculations of lattice energies are also provided\[15\].

The two forms of 5-ClAsp were initially obtained respectively by slow evaporation from, MeCN/H\textsubscript{2}O 1:1 and 2-propanol. However, a proper screening with different solvent revealed that both forms grow from several solvents and adopt different habits, such as needles, laths and prisms (Figure 3.31 a-d).

Table 3.7 shows the occurrence of the two polymorphs in various solvents.

<table>
<thead>
<tr>
<th>Solvents</th>
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<th>5-Cl (II)</th>
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<tr>
<td>MeOH</td>
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<td></td>
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<tr>
<td>EtOH</td>
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<td>√</td>
</tr>
<tr>
<td>MeCN</td>
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</tr>
<tr>
<td>MeNO\textsubscript{2}</td>
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<td>√</td>
</tr>
<tr>
<td>acetone</td>
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<td>√</td>
</tr>
<tr>
<td>2-propanol</td>
<td>-</td>
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<tr>
<td>acetone/ H\textsubscript{2}O 1:1</td>
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<td></td>
</tr>
<tr>
<td>acetone/ MeCN 1:1</td>
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</tr>
<tr>
<td>Toluene</td>
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</tr>
<tr>
<td>CHCl\textsubscript{3}</td>
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</tr>
</tbody>
</table>

Table 3.7. Occurrence (√) of 5-Cl (I) and 5-Cl (II) in various solvents.

Crystals of both 5-Cl (I) and 5-Cl (II) grow from pure MeOH, EtOH, MeCN and MeNO\textsubscript{2}. 5-Cl (I) grows selectively from pure toluene, CHCl\textsubscript{3} and mixed solvents (with the exception of MeCN/H\textsubscript{2}O 1:1) such as MeOH/H\textsubscript{2}O, EtOH/H\textsubscript{2}O, acetone/H\textsubscript{2}O and acetone/MeCN; on the other hand, 2-propanol is shown to be selective for 5-Cl (II).

Figure 3.32. Various crystal habits for 5-Cl (I) and 5-Cl (II).

The FT-IR spectra show differences mainly in the region 400-1800 cm\textsuperscript{-1} (Figure 3.32). The IR frequencies of some of the characteristic bands of 5-chloroaspirin are reported in Table 3.8.
In the region of the aromatic C-H stretch vibrations (3100-3000 cm\(^{-1}\)) a small difference is observed between the two forms (3093 cm\(^{-1}\) in form I and 3102 cm\(^{-1}\) in form II). At about 1700 cm\(^{-1}\) the two forms show the carboxylic carbonyl (C=O \text{carb.}) stretch (1686 cm\(^{-1}\) and 1693 cm\(^{-1}\) respectively for 5-Cl (I) and 5-Cl (II). The shift at higher values observed in 5-Cl (II) suggests that the carbonyl group of this form is involved in weaker interactions.

Small differences are also found in the C-O (ester) stretching which is found respectively at 1196 cm\(^{-1}\) in 5-Cl (I) and 1200 cm\(^{-1}\) in 5-Cl (II).

![Figure 3.33. FT-IR of 5-chloroaspirin form I and II.](image)

<table>
<thead>
<tr>
<th>Band Type</th>
<th>Form I</th>
<th>Form II</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\nu_{\text{CH arom.}})</td>
<td>3093</td>
<td>3102</td>
</tr>
<tr>
<td>(\nu_{\text{C=O carb.}})</td>
<td>1686</td>
<td>1693</td>
</tr>
<tr>
<td>(\delta_{\text{CH}_3})</td>
<td>1412</td>
<td>1419</td>
</tr>
<tr>
<td>(\nu_{\text{C-O-C est.}})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1196</td>
<td>1200</td>
</tr>
</tbody>
</table>

Table 3.8. Characteristic IR bands for 5-chloro-2-acetoxybenzoic acid form I and II.

The thermal properties were investigated by Differential Scanning Calorimetry (DSC) and Hot-Stage Microscopy (HSM).

Problems with the reproducibility were initially noticed in some DSC curves, in which a broadening of the peaks and various melting temperatures were observed. In particular some samples showed the presence of an extra peak at approximately 130 °C. This behavior was observed for both 5-Cl (I) and 5-Cl (II) and may arise from impurities of 5-chlorosalicylic acid in the samples.

A new set of sample was then produced and the thermal analysis shows a good degree of purity. The DSC curves were obtained at different heating rates (5, 10 and 20 °C / min) and display a single endothermic signal for both polymorphs (Figure 3.33). At
heating rate 10 °C / min, 5-Cl (I) and 5-Cl (II) melt with an onset temperature of respectively 146.4 ± 0.8 °C (ΔH_{fus} = 30.97 ± 0.26 kJ mol\(^{-1}\)) and 141.3 ± 0.3 °C (ΔH_{fus} = 28.98 ± 0.47 kJ mol\(^{-1}\)) (Table 3.9). On the basis of the DSC data and the density values of the two forms (1.538 g/cm\(^3\) for 5-Cl (I) and 1.515 g/cm\(^3\) for 5-Cl (II)) and applying the heat of fusion rule and the density rule by Burger and Ramberger\(^{[25]}\) it follows that the two forms are monotypically related. In fact 5-Cl (I) which is the highest melting form show the highest enthalpy of fusion (ΔH_{fus} = 30.97 ± 0.26 kJ mol\(^{-1}\) for form I and ΔH_{fus} = 28.98 ± 0.47 kJ mol\(^{-1}\) for 5-Cl (II)) and the highest density value as well (1.538 g/cm\(^3\) for 5-Cl (I) and 1.515 g/cm\(^3\) for 5-Cl (II)). However the differences between the two forms are small and this fact suggests a high degree of similarity between the two structures.

<table>
<thead>
<tr>
<th></th>
<th>Form I</th>
<th>Form II</th>
</tr>
</thead>
<tbody>
<tr>
<td>TM (°C)</td>
<td>144-152</td>
<td>139-147</td>
</tr>
<tr>
<td>DSC_{Onset}(°C)</td>
<td>146.4 ± 0.8</td>
<td>141.3 ± 0.3</td>
</tr>
<tr>
<td>DSC_{Peak}(°C)</td>
<td>151.6 ± 0.8</td>
<td>147.0 ± 0.2</td>
</tr>
<tr>
<td>ΔH_{fus}</td>
<td>30.97 ± 0.26</td>
<td>28.98 ± 0.47</td>
</tr>
</tbody>
</table>

Table 3.9. Physicochemical data for the two polymorphs of 5-chloroaspirin (the average of at least three measurements at heating rate 10 °C / min is given): TM, thermomicroscopy; ΔH_{fus}, enthalpy of fusion.

This is also confirmed by DFT calculations (see Table 3.10) which show 5-Cl (I) to have a higher stability, with calculated lattice energy 2 kcal mol\(^{-1}\) of molecule greater than that for 5-Cl (II) (-38.8 kcal mol\(^{-1}\) for 5-Cl (I) and -36.8 kcal mol\(^{-1}\) for 5-Cl (II)).
Chapter 3

Substituted Acetylsalicylic Acid Derivatives

Table 3.10. The lattice energies and its components for 5-Cl (I) and 5-Cl (II).

<table>
<thead>
<tr>
<th>Energies (kcal mol⁻¹ of molecule)</th>
<th>5-Cl (I)</th>
<th>5-Cl (II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔE_{conformation} lattice</td>
<td>4.5</td>
<td>3.9</td>
</tr>
<tr>
<td>ΔE_{vdw} lattice</td>
<td>-22.2</td>
<td>-22.3</td>
</tr>
<tr>
<td>ΔE_{electrostatic} lattice</td>
<td>-21.10</td>
<td>-18.4</td>
</tr>
<tr>
<td>E_{lattice}</td>
<td>-38.8</td>
<td>-36.8</td>
</tr>
</tbody>
</table>

This mainly arises from differences in electrostatic interactions (1.6 kcal mol⁻¹). However, the data also show small differences in the contribution coming from the conformational changes in the molecule and no changes deriving from the van der Waals contributions to the lattice energies.

The monotropic relationship between the two forms is also confirmed by HSM analysis (heating rate: 10 °C/min) which shows melting process in the range 144-152 °C for 5-Cl (I) and 139-147 °C for 5-Cl (II) (Figure 3.34). No solid-solid transitions are observed under polarized light (generally recognized by changes in the interference colours of the crystals).

Figure 3.35. Photomicrographs of the Hot-Stage analysis (heating rate: 10 °C/min).

The presence of the impurities in the samples of both polymorphic forms was also investigated. In particular, a comparison of the FT-IR of some samples of 5-Cl (I) and 5-Cl (II) and pure 5-chlorosalicylic acid (5-ClSA) revealed that the salicylic acid impurities are present in some of them and might derive from decomposition process or directly from the synthesis (Figure 3.35).
Figure 3.36. Comparison of the FT-IR spectra of 5-chlorosalicylic acid (5-CISA) and pure and impure samples of the two polymorphs. Green circles indicate the peaks deriving from the impurities of 5-CISA.

This is also confirmed by a HSM analysis using the “contact method” (see Section 2.5) procedure aimed to ascertain if 5-ClAsp in presence of 5-CISA (M.P. = 170°C) forms an eutectic mixture which melts at approximately 130°C as observed in some DSC curves. Figure 3.36 shows the two components, 5-ClAsp (on the left side) and 5-CISA (on the right side), separated by the contact surface. At 129-130°C in correspondence of the contact surface a melting process occurs indicating that the melting point of the eutectic mixture lies in this range of temperatures.

Figure 3.37. HSM analysis on the eutectic mixture obtained recrystallizing from the melt 5-ClAsp (left side of each image) and 5-CISA (right side of each image).

The small differences observed in the thermal analysis and in the DFT calculations reflect the structural analogies between the two polymorphs. As shown in Table 3.2, 5-
Cl (I) and 5-Cl (II), crystallize in the monoclinic system with conventionally chosen space groups \( P2_1/n \) (5-Cl (I)) and \( P2_1/c \) (5-Cl (II)), each with one independent molecule in the asymmetric unit. The two polymorphs, which, as shown in Figure 3.9, are each part of two isostructural sets (5-Cl (I), 5-Br, 5-I and 5-Cl (II), 5-MeO), showing a 1-D similarity consisting of a chain of centrosymmetric carboxylic dimers connected via Cl···O interactions (see Figure 3.21 in Section 3.3). However, a deeper analysis revealed that the two types of structure also adopt a very close stacking arrangement which only differs by a shift of the adjacent molecules propagating along the stacking direction. This also generates small differences in the interactions assisting the stacking arrangement. In fact, though the stacking arrangement of both polymorphs involves weak C-H···O hydrogen bonds, a deeper analysis reveal that in 5-Cl (I) these are formed between the acetyl carbonyl group and the acetyl methyl group and in 5-Cl (II) these involve the acetyl carbonyl group and the aromatic hydrogen in position 3 with respect to the carboxylate group (Figure 3.37).

![Figure 3.38](image)

**Figure 3.38.** Comparison of the interactions involved in the stacking motif; a) 5-chloroaspirin (I) (5-Cl (I)); b) 5-chloroaspirin (II) (5-Cl (II)). Shorter intermolecular distances are indicated as black dashed lines, longer as red dashed lines.

The apparent 2-D stacks of molecules, then, develop differently in the two polymorphs. In 5-Cl (I) neighbouring 2D stacks are related by rows of vertical \( 2_1 \) screw axes and are connected via C-H···O hydrogen bonds between the acetyl carbonyl oxygen and the aromatic hydrogen in position 3. In 5-Cl (II), the neighbouring stacks are related by \( c \)-glide operations and connected, by the same C-H···O interactions as observed in 5-Cl (I).

The comparison of the main intermolecular interactions, involved in forming the crystal structure of the two polymorphs, also provides a further confirmation of the close similarity between them (Table 3.11).
Table 3.11. Distances and angles for the main interactions of the two forms.

<table>
<thead>
<tr>
<th>Interactions</th>
<th>X-H···Y /Å</th>
<th>X···Y /Å</th>
<th>θ /°</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Cl (I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O-H···O</td>
<td>1.785 (2)</td>
<td>2.623 (2)</td>
<td>176.3 (1)</td>
</tr>
<tr>
<td>C-H(4)···O(4)</td>
<td>2.352 (2)</td>
<td>3.118 (2)</td>
<td>137.4 (1)</td>
</tr>
<tr>
<td>C-H(9)···O(4)</td>
<td>2.641 (2)</td>
<td>3.538 (2)</td>
<td>152.3 (1)</td>
</tr>
<tr>
<td>Cl···O(2)</td>
<td>-</td>
<td>3.121 (1)</td>
<td>-</td>
</tr>
<tr>
<td>5-Cl (II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O-H···O</td>
<td>1.829 (2)</td>
<td>2.668 (2)</td>
<td>176.9 (1)</td>
</tr>
<tr>
<td>C-H(4)···O(4)</td>
<td>2.389 (3)</td>
<td>3.306 (3)</td>
<td>162.3 (1)</td>
</tr>
<tr>
<td>C-H(3)···O(4)</td>
<td>2.655 (2)</td>
<td>3.519 (3)</td>
<td>151.5 (1)</td>
</tr>
<tr>
<td>Cl···O(1)</td>
<td>-</td>
<td>3.261 (1)</td>
<td>-</td>
</tr>
</tbody>
</table>

As shown in the table, the two structures adopt the same type of interactions but in general 5-Cl (I) shows shorter interactions compared to 5-Cl (II) and this is in agreement with the calculated density values for the two forms (1.538 g/cm³ for 5-Cl (I) and 1.515 g/cm³ for 5-Cl (II)).
3.5. **Conclusions.**

The family of aspirin derivatives developed for this analysis adopts a range of crystal structures types, which show both varying levels of similarity and some differences. In most cases these can be related to features which derive from the shape of the target molecules, resulting from the different substituents and their positions of attachment, and the behaviour of the functional substituents themselves. The most significant example of this compromise between shape and interactions in directing packing modes is given by the set of structures 5-Cl (I), 5-Br and 5-I in which similar shape and substituent groups able to form similar interactions result in isostructures. Furthermore, significantly different substituents can also generate very similar crystal packing as occur in the other three isostructural sets identified: the first containing 5-NO₂, 5-F and 5-Me, the second 5-Cl (II) and 5-MeO and the last containing 4-F, 4-Me, 4-MeO and 3-Me. The last set and in particular the 3-Me and 4-Me derivatives demonstrate how close, but different, substitutions can be accommodated within a common structure determined by other associations, including packing, which may be dominated by a particular part of the molecule. In this respect it is also worth noting the recurring stacking arrangement observed in aspirin derivatives, which may show different shifts of adjacent molecules and constitutes different arrangements.

On the other hand, the analysis showed how important are some functional groups in forming robust synthons which may have a significant role in determining particular molecular arrangement. Of significant importance is the carboxylate groups which showed preference for the well known centrosymmetric carboxylic dimer. However some exceptions are observed; first of all, the carboxylic catemer adopted by the 6-F derivative which is the only example of catemer found on aspirin derivatives. Molecular shape showed in some cases to have a crucial importance in generating some particular interactions. An example is given by the acetylamino derivatives 3-ACM and 5-ACM which instead of forming the typical carboxylic dimer adopt a synthon consisting of interactions between the carboxylate group and the acetylamino group. However a search in the CSD database showed some preference for the centrosymmetric dimer to be adopted if the acetylamino is substituted in the para position.

The acetyl group, which is one of the recurring features in aspirin derivatives, is shown in some cases to be very important in defining similar arrangements. In particular the
acetyl-acetyl centrosymmetric dimer is a robust feature which may derive from both directional interactions or simply by packing features.

Of particular relevance is, also, the identification of a polymorphic form of the 5-Cl derivative (5-Cl (II)) which is isostructural with 5-MeO. As shown in the discussion the small differences in the crystal packing between the two 5-Cl polymorphs are, as expected, confirmed by similar thermal behaviour. Although this is the only case of polymorphism within the family chosen, it does not exclude the possibility of isolate polymorphic forms for some of the other aspirin derivatives. In this regard, the relationships diagram can be, in principle, useful to develop seeding experiments involving species with high degree of structural similarity (by using the 5-MeO to seed 5-I or 5-Br). Further work will be devoted to start a proper polymorphism screening.
References.


[21] The 3-Me derivative shows a large C···O distance (4 Å) and the dimer arrangement was identified using a high filter XPac calculation. This is a clear indication that this arrangement, differently to the other derivatives (C···O distances in the range 3.5 3.7Å) is a consequence of the crystal packing.


CHAPTER 4: SUBSTITUTED SALICYLIC ACID DERIVATIVES.

In this chapter the crystal structures of salicylic acid derivatives and their comparison with XPac program are described and discussed.

4.1. Introduction.

o-hydroxybenzoic acid, better known as salicylic acid (SA) is derived from the metabolism of salicin. Salicylic acid was originally used as drug for its anti-inflammatory properties, before being replaced by acetylsalicylic acid (aspirin) \([1]\).

SA has been subject to various structural studies, mainly focused on the ability of this compound to form an intramolecular hydrogen bond between the beta-hydroxyl group and the carboxylic oxygen \([2]\). This interaction, described as a six-membered ring formation stabilized by resonance effect \([2i]\), is defined as resonance-assisted hydrogen bonding (RAHB) \([3]\). This phenomenon, also known as π-bond cooperativity \([4]\), occurs with strong hydrogen bonds and involves a significant covalent component (i.e. exchange).

As consequence of this intramolecular interaction, SA has an increased acidity when compared to other hydroxybenzoic acids \([5]\) and also adopts a co-planar conformation between the carboxylic functionality and the aromatic ring.

As previously described (Chapter 3), this kind of hydrogen bond does not occur in aspirin derivatives \([6]\) which, however, show a co-planar conformation with torsional angles \(τ_1\) close to zero degrees (values in the range 0-10 in the majority of the structures). However, depending on the steric hindrance of substituted groups, the total absence of any intramolecular interaction involving the carboxylic group allows aspirin derivatives to adopt different conformations. As described in the previous chapter, 6-substituted derivatives, in fact, showed higher values of torsional parameter, differences in the synthon choice and, consequently, subtle differences in the crystal packing.

The availability of a series of substituted salicylic acid derivatives, accumulated in order to develop the set of aspirin derivatives previously discussed (Chapter 3), provided the opportunity for a related investigation. The new family of compounds, based on SA, shows a fixed planar conformation throughout. Compared to the aspirin derivatives previously discussed (Chapter 3), this new family of compounds shows a reduced conformational flexibility and, consequently, higher similarity in molecular shape. As for the aspirin derivatives, the choice of members of the family is based on those in
which the parent SA molecule is substituted with small groups (Cl, Br, I, Me, MeO, etc) and in different positions. In this way the only differences within the family of compounds defined arise from the substituent groups and these should have some influence in the crystal packing features.

As for Asp derivatives (see Chapter 3), the derivatives of salicylic acid (SA) are labelled omitting the extension SA and are referred to using only the abbreviation of the substituent group (e.g. 5-Cl, 5-Me, 4-ACM, etc.).

![Salicylic Acid Derivatives Diagram](image)

**Figure 4.1.** Set of salicylic acid derivatives chosen for this analysis.

Although the CSD database reports many crystal structures of salicylic substituted derivatives, no structural systematic analysis of these compounds has been previously reported.

For this purpose a series of different salicylic acid derivatives (Figure 4.1) have been crystallized from various solvents in order to obtain suitable crystals for X-Ray determination. Some of the crystal structures determined for this study have been previously reported by other authors (3-MeO (PIDJES) [7], 3-MeO h (DIWNON) [8], 4-NH₂ (AMSALA and AMSALA01) [9], 5-Me (BESKEP) [10], 5-NO₂ (GUTNIS) [11] derivatives and SA (SALIAC, 01, 03, 12-16)) [2b, 12]. In order to define a family which is consistent with the analysis previously reported (chapter 3) we included in the study some entries from CSD (5-F (ABENEB) [13], 5-Br (IYAWIO) [14], 5-NO (NTSALA)) [15]. As for the aspirin analysis (chapter 3) the objective is to identify structural similarities in the family, and to see how robust are the packing features and which role the different substituted groups have in defining differences in the crystal packing.
4.2. *Experimental*.

**Crystallisation of functionalized 2-hydroxybenzoic acids.**

Single crystals suitable for X-ray analysis were grown by slow evaporation from several solvents (Table 4.1).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Crystal Habit</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-MeO h</td>
<td>2-propanol</td>
</tr>
<tr>
<td>3-MeO</td>
<td>pyridine</td>
</tr>
<tr>
<td>4-MeO</td>
<td>CH₃CN</td>
</tr>
<tr>
<td>5-MeO</td>
<td>CH₃OH</td>
</tr>
<tr>
<td>6-MeO</td>
<td>CH₃OH</td>
</tr>
<tr>
<td>3-NO₂h</td>
<td>CH₃CH₂OH</td>
</tr>
<tr>
<td>5-NO₂</td>
<td>H₂O / CH₃OH</td>
</tr>
<tr>
<td>4-ACM</td>
<td>2-propanol</td>
</tr>
<tr>
<td>5-ACM h</td>
<td>acetone</td>
</tr>
<tr>
<td>4-NH₂</td>
<td>CH₃OH</td>
</tr>
<tr>
<td>5-NH₂</td>
<td>DMSO</td>
</tr>
<tr>
<td>4-Cl</td>
<td>pyridine</td>
</tr>
<tr>
<td>5-Cl h</td>
<td>H₂O / CH₃CH₂OH</td>
</tr>
<tr>
<td>5-Cl</td>
<td>acetone</td>
</tr>
<tr>
<td>5-I</td>
<td>CH₃OH</td>
</tr>
<tr>
<td>SA</td>
<td>pyridine</td>
</tr>
<tr>
<td>6-F</td>
<td>pyridine</td>
</tr>
<tr>
<td>4-Me</td>
<td>H₂O / CH₃OH</td>
</tr>
<tr>
<td>5-Me</td>
<td>H₂O / CH₃OH</td>
</tr>
</tbody>
</table>

*Table 4.1.* Summary of the solvents used for crystallizations, crystal habits for the salicylic acid (SA) derivatives under study.

**Crystal Structure Determination.**

A summary of the basic crystal data are given in Table 4.2, which also includes information on the three previously reported derivatives (ABENE[13], IYWIO[14], NTSALA[15]). Full X-rays experimental data are provided as detailed cif files in the Appendix CD.
<table>
<thead>
<tr>
<th>SG</th>
<th>a /Å</th>
<th>b /Å</th>
<th>c /Å</th>
<th>α /º</th>
<th>β /º</th>
<th>γ /º</th>
<th>V /Å³</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-MeO h</td>
<td>P2₁/c</td>
<td>17.9971(3)</td>
<td>14.3789(2)</td>
<td>6.7373(10)</td>
<td>90.00</td>
<td>91.1210(10)</td>
<td>90.00</td>
</tr>
<tr>
<td>3-MeO</td>
<td>P2₁/n</td>
<td>3.7935(2)</td>
<td>27.8954(16)</td>
<td>7.0172(4)</td>
<td>90.00</td>
<td>94.891(3)</td>
<td>90.00</td>
</tr>
<tr>
<td>4-MeO</td>
<td>P2₁/c</td>
<td>4.9629(2)</td>
<td>11.0915(8)</td>
<td>13.6559(9)</td>
<td>90.00</td>
<td>98.788(4)</td>
<td>90.00</td>
</tr>
<tr>
<td>5-MeO</td>
<td>P2₁/c</td>
<td>3.97840(10)</td>
<td>16.1049(4)</td>
<td>11.5198(3)</td>
<td>90.00</td>
<td>90.261(2)</td>
<td>90.00</td>
</tr>
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<td>6-MeO</td>
<td>P2₁/n</td>
<td>6.6697(2)</td>
<td>9.3476(4)</td>
<td>12.2016(5)</td>
<td>90.00</td>
<td>104.305(2)</td>
<td>90.00</td>
</tr>
<tr>
<td>3-NO₂ h</td>
<td>P2₁/c</td>
<td>3.5943(2)</td>
<td>21.115(2)</td>
<td>10.7227(10)</td>
<td>90.00</td>
<td>98.950(6)</td>
<td>90.00</td>
</tr>
<tr>
<td>5-NO₂</td>
<td>P-1</td>
<td>5.1246(5)</td>
<td>8.7762(8)</td>
<td>9.2647(9)</td>
<td>62.252(6)</td>
<td>75.292(6)</td>
<td>82.654(7)</td>
</tr>
<tr>
<td>4-ACM</td>
<td>Pna2₁</td>
<td>3.7472(4)</td>
<td>11.509(17)</td>
<td>21.979(3)</td>
<td>90.00</td>
<td>90.00</td>
<td>90.00</td>
</tr>
<tr>
<td>5-ACM h</td>
<td>P₂₁/z₁</td>
<td>7.1371(3)</td>
<td>3.7278(2)</td>
<td>24.445(12)</td>
<td>90.00</td>
<td>94.386(2)</td>
<td>90.00</td>
</tr>
<tr>
<td>5-NH₂</td>
<td>P₂₁/n</td>
<td>3.7239(2)</td>
<td>7.3696(4)</td>
<td>23.3107(11)</td>
<td>90.00</td>
<td>91.806(3)</td>
<td>90.00</td>
</tr>
<tr>
<td>4-Cl</td>
<td>P₂₁/c</td>
<td>3.7241(2)</td>
<td>14.4178(8)</td>
<td>12.9156(6)</td>
<td>90.00</td>
<td>97.933(3)</td>
<td>90.00</td>
</tr>
<tr>
<td>5-Cl h</td>
<td>P-1</td>
<td>3.72890(10)</td>
<td>8.2430(4)</td>
<td>13.0565(7)</td>
<td>80.768(2)</td>
<td>87.719(3)</td>
<td>83.755(3)</td>
</tr>
<tr>
<td>5-Cl</td>
<td>P₂₁/c</td>
<td>23.3708(10)</td>
<td>3.70890(10)</td>
<td>16.5722(7)</td>
<td>90.00</td>
<td>104.853(2)</td>
<td>90.00</td>
</tr>
<tr>
<td>5-I</td>
<td>C₂/c</td>
<td>38.4671(15)</td>
<td>4.5765(2)</td>
<td>19.9300(7)</td>
<td>90.00</td>
<td>118.789(2)</td>
<td>90.00</td>
</tr>
<tr>
<td>5-NO₂</td>
<td>P₂₁/c</td>
<td>4.8894(3)</td>
<td>11.2411(13)</td>
<td>11.3347(13)</td>
<td>90.00</td>
<td>91.919(7)</td>
<td>90.00</td>
</tr>
<tr>
<td>5-F</td>
<td>P₂₁/c</td>
<td>8.1854(18)</td>
<td>21.219(4)</td>
<td>8.2107(17)</td>
<td>90.00</td>
<td>101.172(4)</td>
<td>90.00</td>
</tr>
<tr>
<td>5- Br</td>
<td>P₂₁/c</td>
<td>5.3146(2)</td>
<td>5.2118(2)</td>
<td>22.5378(10)</td>
<td>90.00</td>
<td>91.907(3)</td>
<td>90.00</td>
</tr>
<tr>
<td>5-F</td>
<td>P-1</td>
<td>4.805(1)</td>
<td>12.047(2)</td>
<td>14.666(3)</td>
<td>114.06(3)</td>
<td>90.00</td>
<td>90.40(3)</td>
</tr>
<tr>
<td>4-Cl</td>
<td>P-1</td>
<td>3.8685(3)</td>
<td>7.2380(9)</td>
<td>13.2142(15)</td>
<td>100.756(5)</td>
<td>93.271(7)</td>
<td>90.788(7)</td>
</tr>
<tr>
<td>5-Br</td>
<td>P₂₁/c</td>
<td>7.2810(3)</td>
<td>5.0146(2)</td>
<td>20.2789(7)</td>
<td>90.00</td>
<td>95.498(2)</td>
<td>90.00</td>
</tr>
</tbody>
</table>

Table 4.2. Summary of basic crystallographic data. (a: ABENEB[13], b: IYAWIO[14], c: NTSALA[15])
4.3. Results and Discussion.

The crystal structures of the SA substituted derivatives studied, and the unit cell parameters are reported in figure 4.2. in contrast to what has been observed for aspirin derivatives \[^6\] (Chapter 3, Section 3.2 and 3.3), as shown in Table 4.2 and Figure 4.2, some SA derivatives have shown the tendency to crystallize as hydrate forms. 3-MeO, 3-NO\(_2\), 5-ACM and 5-Cl, indeed, include water molecules in the crystal packing. For 3-MeO and 5-Cl, however, the anhydrous structures have also been isolated. The majority of the structures crystallize with \(Z' = 1\); exceptions are observed for 3-MeO h, 5-Cl, 5-I and 5-Br which show \(Z' = 2\). As observed in aspirin derivatives \[^6\] (Chapter 3), the carboxylic centrosymmetric dimer occurs in the majority of the structures. However the 6-MeO derivative and the hydrate forms adopt different choices (see below). Surprisingly no isostructures are identified in this family of compounds, in contrast to what was found for the Asp derivatives, which showed three different set of isostructures.
Chapter 4  

Substituted Salicylic Acid Derivatives

3-MeO h
monoclinic P2₁/c
\[a = 17.9971(3) \quad b = 14.3789(2) \quad c = 6.7337(10)\]
\[\alpha = 90.00 \quad \beta = 91.1210(10) \quad \gamma = 90.00\]
\[V = 1742.20 (5)\]
\[Z' = 2\]

3-MeO
monoclinic P2₁/n
\[a = 3.7935(2) \quad b = 27.8954(16) \quad c = 7.0172(4)\]
\[\alpha = 90.00 \quad \beta = 94.891(3) \quad \gamma = 90.00\]
\[V = 739.86(7)\]
\[Z' = 1\]

4-MeO
monoclinic P2₁/c
\[a = 4.9629(2) \quad b = 11.0915(8) \quad c = 13.6559(9)\]
\[\alpha = 90.00 \quad \beta = 98.788(4) \quad \gamma = 90.00\]
\[V = 742.88(8)\]
\[Z' = 1\]

5-MeO
monoclinic P2₁/c
\[a = 3.97840(10) \quad b = 16.1049(4) \quad c = 11.5198(3)\]
\[\alpha = 90.00 \quad \beta = 90.261(2) \quad \gamma = 90.00\]
\[V = 738.09(3)\]
\[Z' = 1\]
Chapter 4

Substituted Salicylic Acid Derivatives

6-MeO

monoclinic  P2_1/n

\[
\begin{align*}
a &= 6.6697(2) & b &= 9.3476(4) & c &= 12.2016(5) \\
\alpha &= 90.00 & \beta &= 104.305(2) & \gamma &= 90.00 \\
V &= 737.13(5) \\
Z' &= 1
\end{align*}
\]

3-NO_2

monoclinic  P2_1/c

\[
\begin{align*}
a &= 3.5943(2) & b &= 21.115(2) & c &= 10.7227(10) \\
\alpha &= 90.00 & \beta &= 98.950(6) & \gamma &= 90.00 \\
V &= 803.87(12) \\
Z' &= 1
\end{align*}
\]

5-NO_2

triclinic  P-1

\[
\begin{align*}
a &= 5.1246(5) & b &= 8.7762(8) & c &= 9.2674(9) \\
\alpha &= 62.252(6) & \beta &= 75.292(6) & \gamma &= 82.654(7) \\
V &= 356.76(6) \\
Z' &= 1
\end{align*}
\]

4-ACM

orthorhombic  Pna2_1

\[
\begin{align*}
a &= 13.5482(8) & b &= 5.0245(3) & c &= 12.9394(6) \\
\alpha &= 90.00 & \beta &= 90.00 & \gamma &= 90.00 \\
V &= 880.82(8) \\
Z' &= 1
\end{align*}
\]
Chapter 4

Substituted Salicylic Acid Derivatives

5-ACM
orthorhombic P2,2,2,

\[
\begin{align*}
a &= 3.7472(4) \\
b &= 11.5109(17) \\
c &= 21.979(3)
\end{align*}
\]

\[
\begin{align*}
\alpha &= 90.00 \\
\beta &= 90.00 \\
\gamma &= 90.00
\end{align*}
\]

\[V = 948.0(2)\]

\[Z' = 1\]

4-NH₂
monoclinic P2₁/n

\[
\begin{align*}
a &= 7.1371(3) \\
b &= 3.7278(2) \\
c &= 24.4465(12)
\end{align*}
\]

\[
\begin{align*}
\alpha &= 90.00 \\
\beta &= 94.386(2) \\
\gamma &= 90.00
\end{align*}
\]

\[V = 648.51(5)\]

\[Z' = 1\]

5-NH₂
monoclinic P2₁/n

\[
\begin{align*}
a &= 3.7239(2) \\
b &= 7.3696(4) \\
c &= 23.3107(11)
\end{align*}
\]

\[
\begin{align*}
\alpha &= 90.00 \\
\beta &= 91.806(3) \\
\gamma &= 90.00
\end{align*}
\]

\[V = 639.41(6)\]

\[Z' = 1\]

4-Cl
monoclinic P2₁/c

\[
\begin{align*}
a &= 3.7241(2) \\
b &= 14.4178(8) \\
c &= 12.9156(6)
\end{align*}
\]

\[
\begin{align*}
\alpha &= 90.00 \\
\beta &= 97.933(3) \\
\gamma &= 90.00
\end{align*}
\]

\[V = 686.84(6)\]

\[Z' = 1\]
**Chapter 4**

**Substituted Salicylic Acid Derivatives**

---

#### Substituted Salicylic Acid Derivatives

**5-C1 h**  
Triclinic P-1  
*a* = 3.72890(10)  
*b* = 8.2430(4)  
*c* = 13.0565(7)  
*α* = 80.768(2)  
*β* = 87.719(3)  
*γ* = 83.755(3)  
*V* = 393.67(3)  
*Z*’ = 1

**5-C1**  
Monoclinic P2,/c  
*a* = 23.3708(10)  
*b* = 3.70890(10)  
*c* = 16.5722(7)  
*α* = 90.00  
*β* = 104.853(2)  
*γ* = 90.00  
*V* = 1388.48(9)  
*Z*’ = 2

---

**5-I**  
Monoclinic C2/c  
*a* = 38.4671(15)  
*b* = 4.5765(2)  
*c* = 19.9300(7)  
*α* = 90.00  
*β* = 118.789(2)  
*γ* = 90.00  
*V* = 3074.9(2)  
*Z*’ = 2
Chapter 4

Substituted Salicylic Acid Derivatives

SA
monoclinic $P_2_1/c$

$\begin{align*}
a &= 4.8894(3) \\
b &= 11.2411(13) \\
c &= 11.3347(13)
\end{align*}$

$\begin{align*}
\alpha &= 90.00 \\
\beta &= 91.919(7) \\
\gamma &= 90.00
\end{align*}$

$V = 622.63(11)$

$Z' = 1$

5-F
monoclinic $P_2_1/n$

$\begin{align*}
a &= 3.8184(8) \\
b &= 21.219(4) \\
c &= 8.2107(17)
\end{align*}$

$\begin{align*}
\alpha &= 90.00 \\
\beta &= 101.172(4) \\
\gamma &= 90.00
\end{align*}$

$V = 652.646$

$Z' = 1$

6-F
monoclinic $P_2_1/n$

$\begin{align*}
a &= 5.3146(2) \\
b &= 5.2118(2) \\
c &= 22.5378(10)
\end{align*}$

$\begin{align*}
\alpha &= 90.00 \\
\beta &= 91.907(3) \\
\gamma &= 90.00
\end{align*}$

$V = 623.92(4)$

$Z' = 1$

5-Br
triclinic $P - 1$

$\begin{align*}
a &= 4.805(1) \\
b &= 12.047(2) \\
c &= 14.666(3)
\end{align*}$

$\begin{align*}
\alpha &= 114.06(3) \\
\beta &= 90.40(3) \\
\gamma &= 101.19(3)
\end{align*}$

$V = 756.937$

$Z' = 2$
Figure 4.2. Crystal Packing of the SA derivatives.
Conformational Analysis.

The analysis of molecular conformations of salicylic acid derivatives reveals the expected high similarity in all structures. The values of the ring-carboxylate torsion angle $\tau$ (Figure 4.3) lie in the range $0-6.5^\circ$ (Table 4.3). This particular geometry arises from the intra-molecular hydrogen bond between carboxylic and the hydroxyl group.

![Figure 4.3](image)

**Figure 4.3.** Geometrical parameters: carboxylic torsional angle ($\tau$).

<table>
<thead>
<tr>
<th>SA subst</th>
<th>$\tau / ^\circ$</th>
<th>D / Å</th>
<th>d / Å</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-MeO h</td>
<td>2.7 (2)</td>
<td>2.611 (1)</td>
<td>1.887 (1)</td>
</tr>
<tr>
<td></td>
<td>1.1 (2)</td>
<td>2.596 (1)</td>
<td>1.865 (1)</td>
</tr>
<tr>
<td>3-MeO</td>
<td>2.9 (2)</td>
<td>2.619 (2)</td>
<td>1.74 (2)</td>
</tr>
<tr>
<td>4-MeO</td>
<td>2.5 (2)</td>
<td>2.602 (1)</td>
<td>1.79 (2)</td>
</tr>
<tr>
<td>5-MeO</td>
<td>3.4 (2)</td>
<td>2.643 (2)</td>
<td>1.920 (1)</td>
</tr>
<tr>
<td>6-MeO</td>
<td>2.5 (2)</td>
<td>2.549 (2)</td>
<td>1.67 (4)</td>
</tr>
<tr>
<td>3-NO$_2$h</td>
<td>6.34 (1)</td>
<td>2.551 (1)</td>
<td>1.801 (1)</td>
</tr>
<tr>
<td>5-NO$_2$</td>
<td>5.2 (3)</td>
<td>2.642 (2)</td>
<td>1.914 (1)</td>
</tr>
<tr>
<td>4-ACM</td>
<td>1.7 (2)</td>
<td>2.636 (1)</td>
<td>1.813 (1)</td>
</tr>
<tr>
<td>5-ACM h</td>
<td>1.9 (7)</td>
<td>2.564 (5)</td>
<td>1.820 (3)</td>
</tr>
<tr>
<td>4-NH$_2$</td>
<td>0.8 (2)</td>
<td>2.611 (2)</td>
<td>1.79 (3)</td>
</tr>
<tr>
<td>5-NH$_2$</td>
<td>4.6 (2)</td>
<td>2.557 (2)</td>
<td>1.67 (2)</td>
</tr>
<tr>
<td>4-Cl</td>
<td>1.0 (3)</td>
<td>2.615 (3)</td>
<td>1.888 (2)</td>
</tr>
<tr>
<td>5-Cl h</td>
<td>1.0 (2)</td>
<td>2.585 (2)</td>
<td>1.81 (2)</td>
</tr>
<tr>
<td>5-Cl</td>
<td>5.2 (4)</td>
<td>2.607 (3)</td>
<td>1.877 (2)</td>
</tr>
<tr>
<td>-0.2 (4)</td>
<td>2.608 (3)</td>
<td>1.875 (2)</td>
<td></td>
</tr>
<tr>
<td>5-I</td>
<td>3.9 (6)</td>
<td>2.595 (5)</td>
<td>1.85 (7)</td>
</tr>
<tr>
<td></td>
<td>4.0 (6)</td>
<td>2.641 (5)</td>
<td>2.05 (7)</td>
</tr>
<tr>
<td>salic</td>
<td>0.4 (4)</td>
<td>2.620 (3)</td>
<td>1.891 (2)</td>
</tr>
<tr>
<td>5-F$^a$</td>
<td>4.0 (1)</td>
<td>2.615 (2)</td>
<td>1.83 (3)</td>
</tr>
<tr>
<td>6-F</td>
<td>3.3 (2)</td>
<td>2.573 (2)</td>
<td>1.96 (3)</td>
</tr>
<tr>
<td>5-Br$^b$</td>
<td>0.60 (1)</td>
<td>2.614 (5)</td>
<td>1.87 (5)</td>
</tr>
<tr>
<td></td>
<td>1.64 (1)</td>
<td>2.633 (5)</td>
<td>1.90 (5)</td>
</tr>
<tr>
<td>4-Me</td>
<td>1.4 (3)</td>
<td>2.626 (2)</td>
<td>1.750 (4)</td>
</tr>
<tr>
<td>5-Me</td>
<td>0.6 (2)</td>
<td>2.604 (2)</td>
<td>1.75 (3)</td>
</tr>
<tr>
<td>5-NO$^c$</td>
<td>-0.50</td>
<td>2.653</td>
<td>1.989</td>
</tr>
</tbody>
</table>

**Table 4.3.** Summary of the geometrical parameters as defined in Figure 4.3. ESD’s for 5-NO SA not available.

The distances O(2)···O(3) are within the range 2.55-2.65 Å, and these values suggest strong intramolecular interactions. The shorter values are observed for the 6-MeO
(2.549 Å), 4-ACM (2.549 Å), 3-NO₂ (2.551 Å) and 5-NH₂ (2.557 Å) derivatives and the highest value for 5-NO derivative (2.653 Å).

The carboxylic group mainly adopts the syn-planar conformation (Figure 4.4 a). However the 6-MeO derivative shows a anti-planar conformation (Figure 4.4b), due to a secondary IMHB occurring between the carboxylic OH group and the oxygen of the methoxy group (O(1)∙∙∙O(4) 2.538 Å) \(^{16}\).

![Figure 4.4. Conformation of the carboxylic group in the set of structures analyzed: a) Syn-planar; b) anti-planar.](image)

This last feature also explains the departure of 6-MeO derivative in the synthon choice with respect to the general tendency to form the typical carboxylic dimer. As shown in Figure 4.5, the 6-MeO derivative adopts a catemer motif built by C=O∙∙∙H-O hydrogen bonds (2.328 Å) between carboxylic groups of adjacent molecules. This arrangement is also assisted by weak C-H∙∙∙O interactions between a methoxy hydrogen and the hydroxyl group (2.699 Å).

![Figure 4.5. Chain of 6-MeO molecules assembled via catemeric supramolecular synthon.](image)
Further departures from the common carboxylic dimer are observed in the ACM derivatives: 4-ACM adopts a O-H⋯O=C hetero-synth on involving the carboxylic hydroxo group and the carbonyl of the acetylamino group (Figure 4.6 a); in the 5-ACM hydrate derivative the water molecule is interposed between the two functional groups, resulting in a different supramolecular synth on. A similar situation is observed in the case of the remaining hydrate forms, in which the water molecules interact by hydrogen bonds with the carboxylic groups of two molecules, preventing the carboxylic dimer formation (Figure 4.6 c-e). As mentioned above, it is worth noting that in contrast to what was observed in chapter 3 for the Asp derivatives [6], some SA derivatives show the tendency to crystallize as hydrates, adopting different supramolecular synthons. However, in terms of geometry, the resulting shape of the motifs derived from the two different synthons remains essentially unchanged. In fact, due to their small size and to fact that they can behave as both donor and acceptor in forming hydrogen bonds, the molecules of water act as an efficient spacer and the resulting motif in solvate forms has similar shape with respect to the dimers observed in anhydrous forms.

![Figure 4.6](image)

**Figure 4.6.** Alternative supramolecular synthons identified in the structure in study: a) 5-acetamidosalicylic acid monohydrate (5-ACM h), b) 4-acetamidosalicylic acid (4-ACM), c) 3-methoxysalicylic acid monohydrate (3-MeO h), d) 5-chlorosalicylic acid monohydrate (5-Cl h), e) 3-nitrosalicylic acid monohydrate (3-NO₂ h).

The most significant departure is found in the 5-NH₂ derivative which occurs in its zwitterionic form, deriving from a local proton transfer from the carboxylic group to the amino group. This assignment of 5-NH₂ SA as a zwitterion is based on the results of the
refinement, which gave a smaller R-factor (4.6% for the zwitterion form and 6.18% for the non-zwitterionic form) and is supported by the similar C-O distances of the carboxylic group which are respectively 1.257 Å and 1.277 Å.

The carboxylate group interacts via a hydrogen bond with the quaternary amine (O···N 2.734 Å) as shown in figure 4.7 a and c. Further interactions (Figure 4.7 b and c) involve the second carboxylate oxygen with the hydrogens of three adjacent quaternary amine groups (O···N: 2.778 Å, 2.930 Å, 3.022 Å).

![Figure 4.7](image)

**Figure 4.7.** Relevant interactions involving the carboxylate oxygens of the zwitterionic form of 5-aminosalicylic acid (5-NH$_2$): a) main supramolecular carboxylate-quaternary amine synthon, b) further interactions involving carboxylate oxygen and quaternary amine of three neighbour molecules, c) representation of both set of interactions reported in a and b. The neighbouring molecules are represented in different colours (green, yellow and red).
**XPac Analysis.**

The XPac analysis of the twenty-two SA derivatives was carried out using the Corresponding Ordered Set of Points (COSP) \[^{17}\] represented in Figure 4.8 and low filter parameters (see Chapter 2, Section 2.4). The program generated a total of 231 comparisons between all possible pairs of structures within the whole family.

![Figure 4.8. Corresponding Ordered Set of Points (COSP) defined for the XPac analysis.](image)

A diagram of the structural relationships is reported in Figure 4.9 (For more details see Appendix A2). The term Supramolecular Construct (SC) \[^{17}\], described in Chapter 1, is used to define the common geometrical arrangement occurring in two or more structures.

![Figure 4.9. Structural relationship diagram showing the relationships between supramolecular constructs (SCs) A11-A22.](image)
The following notation is used to describe the relationships reported in Figure 4.9:
The diagram is divided in different regions, each indicating a given dimension (3-D, 2-D, 1-D, 0-D). Higher similarities are positioned on the top of the diagram and the dimensions decrease going downwards. The COSP is labeled as X.
The different crystal structures are positioned on the top of the diagram. Each structure is indicated by a coloured circle. The colour represents the substituted groups (same colour means same substituent).
SCs, indicated by circles, are labelled by letters followed by two numbers. The first number defines the dimension of the SC and the second indicates an arbitrary numbering scheme.

\( A_{nm} \) SCs derive from the 0-D SC A0 (carboxylic dimer) \( X_{nm} \) is used to define SCs deriving directly from the COSP.
The relationships among the different structures and SCs are indicated by connecting lines.
Dashed lines indicate relationships between COSP (X) and those SCs which directly derive from it (e.g. the carboxylic dimer A0 is built by two COSP related by inversion symmetry).

Although, as described in the previous section, SA derivatives adopt various supramolecular synthons, and the only 0-D SC found is the carboxylic dimer. The 1-D SCs observed mainly involve stacking arrangements. These arrangements are generally observed in aromatic systems and in general for flat molecules. The stacking motifs develop along the shortest axis for all the structures. However the stacking arrangements observed show small differences (see below) and this is consistent with the differences observed in the unit cell parameters for the shortest axis (Table 4.2).
The most significant feature observed in the structures in study is the absence of isostructural sets. This is a surprising result if close molecular similarity is considered, and especially when compared to what observed in the family previously analyzed (Chapter 3, Section 3.3). However lower similarities (2-D) involve significantly different substituted derivatives which form two 2-D SCs (5-Cl and 5-NO for the first set and 5-NO, 4-Me, 4-NH\(_2\), 5-F and 3-MeO for the second set).
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A11 is a 1-D similarity common to the derivatives: 4-Cl, 5-MeO, 5-Cl, 5-NO, 4-Me, 4-NH₂, 5-F and 3-MeO (Figure 4.10). It consists of a stacking arrangement of carboxylic dimers developing along the shortest axis (the values determined for the shortest axis for the substituted derivatives involved (Table 4.2) lie in the range 3.67-3.97 Å). Apart from the 3-MeO and 5-MeO derivatives which connect via weak C-H···O hydrogen bonds between the methoxy groups of adjacent molecules (C···O distances are respectively 2.657 Å and 2.688 Å), there are no significant intermolecular interactions within this SC.

Figure 4.10. 1-D Supramolecular Construct (SC) A11 in salicylic acid (SA) derivatives: a) 4-Cl viewed approximately along the 001 direction and b) 5-F (ABENEBe) viewed approximately along the 001 direction. A11 is shown in yellow for each structure.

A similar stacking arrangement is also observed for 5-Cl h and 5-ACM h which showed the common 1-D SC X11 (Figure 4.11). Although X11 is treated as a distinct motif, because the different synthon involved, it is worth noting that the stacking arrangement is analogous to A11. This is confirmed by comparison of the values of the shortest axis which are in the range observed for the structures involved in forming A11 (3.747 Å for 5-ACM h and 3.729 Å for 5-Cl h). The only difference derives from the fact that A11 is built from the carboxylic dimer and X11 derives directly from the COSP structure. It is implicit that this SC is also common to all the structures involved in forming A11. Again, as already observed in the previous chapter, the occurrence of different supramolecular syhtons does not affect the tendency of SA derivatives to stack forming similar molecular stacking arrangements.
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Figure 4.11. 1-D Supramolecular Construct (SC) X11 in salicylic acid (SA) derivatives: a) 5-Cl viewed approximately along the 0-11 direction and b) 5-ACM viewed approximately along the 010 direction. X11 is shown in yellow for each structure.

Strictly related to X11 is a second 1-D SC labeled as X12, common to 3-NO₂, 5-NH₂, and the set of structures 5-NO, 4-Me, 4-NH₂, 5-F and 3-MeO. This arrangement consists of two SC X11 related by centres of inversion (Figure 4.12). As observed for the previous SCs, no particular directed interactions are involved in building this molecular arrangement.

Figure 4.12. 1-D Supramolecular Construct (SC) X12 (blue). 5-NO₂ viewed approximately along the 100 direction. As described in the text, X12 consists of two SC X11, related by center of inversion.

A further 1-D SC, A12, is common to 5-Me and 5-NO₂. This arrangement consists of a chain of carboxylic dimers each connected by a different set of intermolecular interactions (Figure 4.13). In the 5-Me structure the carboxylic dimers build along 100 via C-H···O weak hydrogen bonds (C···O 3.358 Å) between the methyl in position 5 and the hydroxyl group. In 5-NO₂ SCA12 develops along 001 and involves O-H···O hydrogen bonds (O···O 2.904 Å) between the carboxylic hydroxyl and one of the
oxygen of the nitro group. Note that this 1-D SC is analogous to the 1-D SC (AB1) discussed in the previous chapter (Chapter 3 Figure 3.21).

Figure 4.13. 1-D Supramolecular Construct (SC) A12 (green). a) 5-Me viewed along the 010 direction; b) 5-NO$_2$ viewed along the 010 direction.

5-NO, 4-Me, 4-NH$_2$, 5-F and 3-MeO also show a common 1-D SC with 3-MeO h, labeled as X13. This arrangement consists of a row of single molecules (Figure 4.14). In 4-Me and 4-NH$_2$, the motif involves hydrogen bonds between the hydroxyl oxygen and the hydrogen of the 4-substituted group (O⋯N and O⋯C distances are respectively 3.337 Å and 3.602 Å).
Figure 4.14. 1-D Supramolecular Construct (SC) X13 (orange). a) 5-MeO h along the 010 (left) and 100 (right) directions b) 4-NH₂ along the 010 (left) and approximately the 001 (right) directions. N-H⋯O hydrogen bonds are indicated by dashed lines. (+) is used to indicate the axis pointing towards the viewer and (-) for axis pointing away from the viewer.

A further 1-D SC, A13, consists of a steps row of carboxylic dimers (Figure 4.15 d). This is common for SA, 4-Cl and 5-NO₂ structures. The dimers are not connected by any significant intermolecular interactions.
Figure 4.15. 1-D Supramolecular Construct (SC) A13. a) A13 reported for 5-NO₂ viewed approximately along the 100 direction; b) 5-NO₂ viewed approximately along the 011 direction; c) SA viewed along the 100 direction; d) 4-Cl viewed along the 100 direction. O-H⋯O hydrogen bonds are indicated by red dashed lines. The molecules are colour-coded according to the orientation of the ring–carboxylate vector; grey = pointing towards the viewer, green = pointing away from the viewer. Instances of the SC, A13 and A13’, separated by dashed lines, are related by 2₁ screw axis and are separated by dashed lines. (+) is used to indicate the axis pointing towards the viewer and (-) for axis pointing away from the viewer.

A deep analysis of the crystal structures of 4-Cl and SA acid reveals that, though the unit cell parameters for these two structures are significantly different (Table 4.2), the two structures adopt a very similar crystal packing. As described below, A13 stacks in both structures along the shortest axis 100 adopting a slightly different stacking arrangement. Along the 001 axis each A13 is related to the adjacent A13’ (Figure 4.15 a and b) by a 2₁ screw axis. This similarity is confirmed by an XPac analysis using very high filters which gives an approximate 3-D similarity (Figure 4.16) between the two structures (Dissimilarity Index (χ): 21.2°) [19].
The analysis of the interactions also reveals that in both structures the hydroxyl group is involved in forming a hydrogen bond with the group para to the carboxylate function. In 4-Cl SA this consists of a O-H⋯Cl hydrogen bond (3.270 Å) and in SA is a C-H⋯O hydrogen bond (O⋯C is 3.645 Å). However the calculated dissimilarity index for this comparison is higher in respect to the calculation performed with low filters and the two structures are better described as having a 1-D similarity. It is worth noting that even if the unit cells parameters are different (a and c differ approximately by 1 Å and c by 3 Å), the two structures adopt analogous choices in the crystal packing formation (Figure 4.15) and these choices involve interactions occurring in the same positions of the aromatic ring In this situation, it is difficult to say whether the similar packing is a consequence of the similar interactions or the interactions assist similar choices in crystal packing.

A14 is a further 1-D SC which simply involves stacks of carboxylic dimers (Figure 4.17) and is common to 6-F, 5-Br, 4-MeO and SA. This arrangement is analogous to A11, however, as described later, there are some subtle differences involving shifting of the dimers along the direction of propagation (generally the shortest axis).
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Fig. 4.17. 1-D Supramolecular Construct (SC) A14. a) SA along the 101 direction; b) 5-Me along the 100 direction. O-H···O hydrogen bonds are indicated by red dashed lines.

As seen before for A11 and X11, related to A14 is a further 1-D SC labelled as X14. This arrangement consists of stacks of single molecules along the shortest axis (Fig. 4.18) and is found in 4-ACM and the set of structures involved in the formation of A14.

Fig. 4.18. 4-ACM: 1-D Supramolecular Construct (SC) X14 viewed approximately along the 110 direction. O-H···O hydrogen bonds are indicated by red dashed lines.

The final 1-D SC, A15 is present in the structures of 5-I and 6-F and consists of a stack of a pairs of carboxylic dimers, related by inversion symmetry (Fig. 4.19).
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Figure 4.19. 1-D Supramolecular Construct (SC) A15.  
* a) 5-I viewed approximately along the 010 direction. SC A15 and A15’ are related by 2-fold (green) and 2_1 screw axis (red).  
* b) 6-F viewed along the 100 direction. SCs A15 and A15’ are related by simple translation and 2_1 screw axis (red arrow). The molecules are colour-coded as in Figure 4.15: gold = pointing away from the viewer, black = pointing towards the viewer. Hydrogen bonds between the acid and acetyl moieties are shown in blue. Individual instances of SC A15 are separated with dashed lines.

It is worth noting that the 6-F derivative adopts two distinct stacking arrangements (A14 and A15 SCs) developing along two different axis. This result is consistent with the unit cell parameters of 6-F structure which show two very similar axes (a = 5.31 Å and b = 5.21 Å).

The last two SCs, A21 and A22 are 2-D arrangements both constructed from SC A11. A21 is present in the structures 5-NO, 4-Me, 4-NH₂, 5-F and 3-MeO. This SC consists of a row of SC A11 stacks (Figure 4.20 a-e). This arrangement also contains the 1-D SC X12 which, as previously described, is formed by two SCs X11 related by a center of inversion (Figure 4.12). Note that SC A21 can also be considered as to be formed by stacks of a chain of carboxylic dimers. This constitutes a proper 1-D SC, but has not been identified separately since it only exists as part of A21.

Apart from the 5-F and 5-NO derivatives, no intermolecular interactions of particular significance are involved in the formation of SC A21. In 5-F and 5-NO structures SC A11 built into SC A21 via a different set of interactions (Figure 4.20 a and b): in 5-F adjacent stacks of carboxylic dimers are linked by F⋯O interactions (F⋯O 2.844 Å); 5-
NO involves a $\text{N}=\text{O} \cdots \text{O}$ interaction with the carboxylic oxygen ($\text{O} \cdots \text{O} 3.032 \text{ Å}$) and a $\text{N}=\text{O} \cdots \text{H} \cdots \text{O}$ hydrogen bond with the hydroxyl group ($\text{O} \cdots \text{O} 2.744 \text{ Å}$).

**Figure 4.20.** 2-D Supramolecular Construct (SC) A21. Each molecule represents a 1D stack of molecules extending into the page and are colour-coded as in Figure 4.15: red = pointing towards the viewer, blue = pointing away from the viewer. Instances of SC A21 are indicated as separated by dashed lines. a) 5-F viewed along the 100 direction. b) 5-NO viewed along the 001 direction. c) 4-Me viewed along the 100 direction. d) 4-NH$_2$ viewed along the 010 direction. e) 3-MeO viewed along the 100 direction.
The five structures show differences along the longest axis corresponding to the different development of SC A21 along this direction (Figure 4.20). In 5-F and 3-MeO two adjacent SCs A21 (A21 and A21’) are related by a glide plane perpendicular to the sheet. In 3-MeO the adjacent SCs are connected by weak C-H···O hydrogen bond (C···O 3.047 Å) between the methoxy methyl and the hydroxo group; in 5-NO the two subsequent SCs are related by 21 screw axes parallel to the plane; in 4-NH2 the instances are related by 21 screw axes perpendicular to the plane; 4-Me develops along the longest axis by translation symmetry (A21 = A21’).

The final 2-D SC A22 is present in 5-Cl and 5-NO. This is formed by a tilted zig-zag chain of SC A11 developing in both structures along 100 (Figure 4.21 a and b).

Figure 4.21. 2-D Supramolecular Construct (SC) A22. Each molecule represents a 1D stack of molecules extending into the page and are colour-coded as in Figure 4.19 orange = pointing towards the viewer, blue = pointing away from the viewer. Instances of SC A22 are related by glide planes and shown separated by grey dashed lines. a) 5-Cl viewed along the 010 direction. The two symmetry independent molecules are indicated respectively as 1 and 2; the two different set of hydrogen bonds are indicated by different colours (red for the O···Cl and black for O-H···Cl) b) 5-NO viewed along the 00-1 direction; hydrogen bonds are indicated by black dashed lines, the 21 screw axis is shown by green arrows.

In the 5-Cl structure the 2-D arrangement arises from the reciprocal orientation of the two independent molecules in the asymmetric unit. A22 develops along 001 along the glide plane direction via different set of interactions (Figure 4.21 a); adjacent stacks of
carboxylic dimers interact with each other by O-H⋯Cl hydrogen bonds (Cl⋯O 3.217 Å) between the hydroxyl group and the chloro substituent. Stacks of the type 2 are instead connected in one case via O-H⋯Cl (Cl⋯O 3.422 Å) hydrogen bonds between the hydroxyl group and the chloro and in another case by O⋯Cl interactions involving the carboxylic oxygen (Cl⋯O 3.114 Å). In 5-NO structure A22 is formed by adjacent SC A11 related by 2_1 screw axes parallel to the plane 110 (Figure 4.21 b). As observed for 5-Cl, A22 propagates along 010 by glide planes via O-H⋯O (O⋯O 2.744 Å) hydrogen bonds between the hydroxyl group and the nitroso group.

As described in Figure 4.9, the 6-MeO derivative has no similarity with the other structures in the crystal packing. This is a direct consequence of the different supramolecular synthon adopted.

As previously discussed, the 6-MeO derivative adopts a carboxylic catemer due to the anti-planar conformation of the carboxylic group (Figure 4.5). The analysis of the crystal packing shows a different stacking arrangement which develops along the shortest axis (100) with an anti-parallel orientation between two adjacent molecules. This is shown in Figure 4.22, with the crystal packing along the three directions.

Figure 4.22. 6-MeOSA: a) anti-parallel stacking of 6-MeO along the 100 direction; b) crystal packing of 6-MeO viewed along the 100 direction; c) crystal packing of 6-MeO viewed along the 010 direction; d) crystal packing of 6-MeO viewed along the 001 direction. Different colours are used according to the orientation of molecules.
A similar behavior is also observed for the 3-MeO h structure (Figure 4.23) in which the pair of molecules stack taking a $90^\circ$ orientation along 001. Interestingly this arrangement is observed only for one of the two independent molecules of the $Z'=2$ structure. The other molecule forms stacks of pairs of molecules oriented anti-parallel.

Figure 4.23. Stacking arrangement observed in 3-methoxysalicylic acid monohydrate (3-MeO h). The number 1 and 2 are used to indicate the two symmetry independent molecules. The molecules of the type 1 are coloured coded according to the orientation of ring–carboxylate vector. A pair molecules of the type 2 stack adopting an anti-parallel orientation and are indicated as yellow and grey.

The XPac analysis clearly shows the predominance of the stacking motifs in the crystal packing of salicylic acid derivatives. It is interesting to note that the main differences between these arrangements consist in a different shifting of the adjacent molecules. Figure 4.24 shows the differences observed for the three main SCs identified.

Figure 4.24. Different stacking arrangements observed within the set of salicylic acid derivatives. The Supramolecular Constructs (SCs) are viewed along the shortest axis (left), after a $90^\circ$ rotation (center) and by a further 90 degrees rotation (right). The direction of the stacking arrangement is indicated by black arrows. a) 4-Cl as representative of the set of structures adopting the 1-D Supramolecular Construct (SC) A11. b) 5-F as representative for the 1-D Supramolecular Construct (SC) A14; c) 5-I as representative of the 1-D Supramolecular Construct (SC) A15. SCs X11, X12 and X14 are not included since they are part or strongly related to the SCs represented in figure.
Although some analogies can be observed between the three stacking arrangements described and therefore, these arrangements can be objectively considered similar, it is important to note that the term “similarity” used in this analysis is strictly related to the set of tolerance parameters adopted (see Chapter 2, Section 2.4).

Table 4.4 reports the results of the analysis of the geometrical parameters (see also Chapter 3, Section 3.3) used to define the stacking arrangements: interplanar distances, aromatic ring centroid-centroid vector and the angle of “slippage” (Figure 4.25)\(^{[20]}\). The angle between the molecular planes of molecule 1 and 2 is not reported since is observed to be approximately 0 for all the structures.

![Figure 4.25](image)

Table 4.4. Stacking descriptor parameter as described in Figure 4.25. Supramolecular Construct (SC) (where involved) is also reported for completeness. ESD’s for these parameters are estimated as <0.01 for distances and 0.1 for angles, based on values for molecular parameters.

<table>
<thead>
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<th>SA subst</th>
<th>Cen1-Cen2 (Å)</th>
<th>P1-P2 (Å)</th>
<th>(\phi) (°)</th>
<th>SC</th>
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<tr>
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<tr>
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<td>25.06</td>
<td>-</td>
</tr>
<tr>
<td>3-NO(_2)</td>
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<td>20.06</td>
<td>X11</td>
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<tr>
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<td>3.093</td>
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<td>-</td>
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<tr>
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<tr>
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<td>3.385</td>
<td>25.39</td>
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</tr>
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<tr>
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<td>21.32</td>
<td>X11</td>
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<td>52.55</td>
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</tr>
<tr>
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<td>51.44</td>
<td>A14</td>
</tr>
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<td>3.667</td>
<td>3.346</td>
<td>26.83</td>
<td>A11</td>
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</table>
As reported in table 4.4 all the inter-planar distances approximately lie in the range 3-3.8 Å. Differences are observed in the values of the cen1-cen2 distances and in the φ values. As expected, three different behaviors, correspondent to the three main families of SCs, can be defined. SC A11 and the related X11 show values of Cen1-Cen2 in the range 3.5-4 Å and φ values in the range 17-35°. SCs A14 and X14 both lie in the range 4.8-5.5 Å for the Cen1-Cen2 distance and in the range 46-57° for the φ angle. The last SC A15 shows Cen1-Cen2 values between 4.5-5.3 Å and φ angles in the range 45-62°.

Interestingly A14 and A15 show close values. However a detailed analysis reveals differences in the stacking direction, which lie along the carboxylic-carboxylic vector for A14 and along its perpendicular direction for A15. This latter feature is confirmed by the comparison of the two structures with the 6-F structure which, as previously discussed, is involved in forming both A14 and A15 SC and, as consequence shows two closely related unit cell axis with values of respectively 5.315 Å (along 010) and 5.212 Å (along 100).

The Cen1-Cen2 distance and the φ angles indicate that SC A11 is constructed by stacks of molecules which adopt a more parallel geometry than both SC A14 and SC A15. The reasons of the different displacement are still not clear since they cannot be ascribed to the substituent effect (the distribution of withdrawing and electron-donor substituent is quite uniform in the three SCs) or to particular steric hindrance and/or particular stable interaction promoting a higher shifting.

A similar tendency was previously observed in aspirin derivatives (Chapter 3, Section 3.3) where the formation of offset stacks of molecules was a recurring feature. However the comparison of the geometrical parameters reveals that aspirin derivatives adopt a more shifted arrangement with Cen1-Cen2 distance within the range 4.7-7.4 Å and φ values in the range 50-75°.

In contrast with what is observed in aspirin derivatives, in which the derivatives substituted in the same site showed 3-D or at least 2-D similarities (indicating an importance of the shape in generate the crystal packing), SA derivatives showed 1-D similarities mainly arising from the tendency to form stacking arrangements. This can arise from two different and concomitant factors.

The acetyl group in aspirin derivatives surely has an involvement in generate interactions with neighbouring molecules (as described in chapter 3 several derivatives
showed a common 0-D SC consisting in acetyl dimers) and it could have an influence in determining particular molecular arrangements.

The higher structural flexibility of aspirin derivatives could also allow, if needed, small variation in the conformation of the molecule in order to build some preferred molecular arrangements (an example of this latter feature is given by the comparison of 6MeAsp and 6-MeOSA structures in which the steric hindrance of the substituent groups affect differently the synthon choice: carboxylic dimer for the aspirin derivative and catemer for the salicylic acid derivative).

4.3. Conclusions.

Though the set of molecules chosen for this analysis show close shape similarity, the structures here analyzed clearly shown strong differences in the crystal packing. The most surprising feature is the absence of any isostructurality within the family of structures analyzed. The highest similarity occur in 2-D (SCs A21 and A22) and involve derivatives substituted at different sites and/or substituted by different groups. This is in contrast to what is observed in the aspirin derivatives (Chapter 3) in which molecules with similar substituents and/or similar site of substitution showed high similarities (3-D or 2-D). In this regard, geometrical features do not have a strong impact in generating crystal packing of SA derivatives. However the various stacking arrangements observed, which differ only in the slippage of the adjacent molecules, derive from the flat shape and the rigid conformations of SA molecules. Accordingly to the XPac analysis, the parameters which quantify, both the interplanar distances plus the aromatic ring centroid-centroid vector and the angle of “slippage” identify three main stacking arrangements which involve different substituted derivatives.

Another interesting feature of the family of molecules here analyzed is related to their tendency to crystallize as solvate forms. For these structures the synthon choice is affected by the water molecules. However, as previously described, the water molecules only behave as spacer maintaining unchanged the shape of the 0-D arrangement deriving from the alternative supramolecular synthon. The rigid conformation of the carboxylic group, due to the intramolecular O-H···O with the hydroxyl in position 2, also affects the synthon choice as observed for 6-MeO SA which adopts a catemeric motif. However, where possible, the carboxylic dimer remains the preferred choice.
At this point of the analysis would be interesting to verify how the molecules pack together if they are forced to adopt a different supramolecular synthon, crystallizing these SA derivatives as multiple component systems with a cocrystallizing agent, as described in the next chapter (Chapter 5).
References


Chapter 4

**Substituted Salicylic Acid Derivatives**


CHAPTER 5: MOLECULAR SALTS BASED ON 4-AMINOPYRIDINE-SALICYLIC ACID DERIVATIVES.

In this chapter the crystal structures of a family of 4-aminopyridinium salts of salicylic acid derivatives and their comparison with the XPac program are described and discussed.

5.1. Introduction.

As previously described (Section 1.5), cocrystals, salts and multiple component systems in general have recently gained importance in many fields such as supramolecular chemistry and pharmaceutical solid forms. The Journal Crystal Growth and Design has recently dedicated to this topic a virtual issue entitled “Pharmaceutical Cocrystals” in which the most relevant papers on this topic published in 2009 are collected [1]. Interestingly some papers focussed on salts or molecular salts [2] have been included in this issue and this is a consequence of the recent debate on the semantics of the terms cocrystal [3] and if molecular salts and cocrystals are really so different [4]. In fact it is generally recognized that cocrystals and molecular salts can adopt very similar supramolecular synthons and the only difference is related to the proton location. The resulting supramolecular synthons are generally defined as neutral or ionic. Ionic synthons are more robust and easily predicted than the neutral synthons [5]. However, as pointed out by Aakeroy in a survey of 85 salts and cocrystals [4b], molecular salt formation often results in unpredictable chemical or stoichiometric composition and structure prediction and targeted supramolecular synthesis is much more difficult for this class of compounds.

In a recent paper Nangia [2a] analyzed the hydrogen bond motifs of a series of multi-component systems based on hydroxobenzoic acid and aminopyridine. In this paper Nangia analyzed the synthon competition occurring among the four functional groups simultaneously present in the multiple component system and also showed that the presence of the hydroxyl and amino groups promote the formation of ionic PyNH\(^+\)···OOC synthon.

Following the systematic approach described in the previous chapters (Chapters 3 and 4) and bearing in mind the growing importance of salts or cocrystals, a new family of multicomponent systems has been studied. The analysis is carried out on structures involving substituted salicylic acid derivatives and aminopyridines in order to verify if
the competition of different hydrogen bond donors (NH$_2$ groups for amino pyridine and OH groups for salicylic units) and acceptors can affect the robustness of the typical carboxylate···pyridine synthon. Furthermore, in order to analyse if the close molecular similarity can be in some way extended to the crystal packing, generating, as described in the previous chapters, 1-D, 2-D or eventually 3-D similarities, a structural similarity analysis using the XPac approach$^6$ has been performed. The molecules selected for this study are those obtained by mixing in the ratio 1:1 4-aminopyridine (4-AP) and some 3, 5 and 6 substituted salicylic acids (SA) as shown in figure 5.1.

![Figure 5.1](image)

**Figure 5.1.** Molecules selected for the study: 3,5 and 6-salicylic derivatives (SA); 4-aminopyridine (4-AP).

As for the previous families (Chapter 3 and 4) the derivatives are labelled referring only the abbreviation for the substituent in the salicylic moiety (e.g. 5-Cl, 5-ACM etc.) and indicating the eventual presence of the solvent (H$_2$O = h, pyridine = Py)
5.2. Experimental Procedures.

Crystallizations.

The starting materials (see Chapter 2, Section 2.7) were mixed in 1:1 ratio and dissolved in various solvents to obtain co-crystal or salted forms (Table 5.1). Crystals suitable for X-ray study were obtained by slow evaporation from saturated solutions.

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<th>Crystal Habit</th>
</tr>
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<tr>
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</tr>
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<td>CH$_3$OH</td>
<td>Slab</td>
</tr>
<tr>
<td>pyridine</td>
<td>Plate</td>
</tr>
<tr>
<td>H$_2$O/CH$_3$OH</td>
<td>Plate</td>
</tr>
<tr>
<td>CH$_3$OH</td>
<td>Block</td>
</tr>
<tr>
<td>pyridine</td>
<td>Block</td>
</tr>
<tr>
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</tr>
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</table>

Table 5.1. Summary of the solvents used for crystallizations, crystal habits for the 4-aminopyridinium salicylates (4-APSA) derivatives under study.

Crystal Structure Determination.

A summary of the basic crystal data are given in Table 5.2. Full X-ray experimental data are provided as detailed cif files in the Appendix CD.

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<th>SG</th>
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<th>b/Å</th>
<th>c/Å</th>
<th>α/°</th>
<th>β/°</th>
<th>γ/°</th>
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<td>8.5407(2)</td>
<td>12.1504(5)</td>
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<td>90</td>
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<td>23.3169(11)</td>
<td>8.1015(4)</td>
<td>18.0588(8)</td>
<td>90</td>
<td>110.986(2)</td>
<td>90</td>
</tr>
<tr>
<td>5-ACM</td>
<td>P2$_1$/n</td>
<td>15.1705(7)</td>
<td>4.6669(2)</td>
<td>19.6506(8)</td>
<td>90</td>
<td>104.734(2)</td>
<td>90</td>
</tr>
<tr>
<td>5-MeO h</td>
<td>Pna$_2_1$</td>
<td>21.8619(15)</td>
<td>15.0658(9)</td>
<td>3.9918(3)</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>5-Me</td>
<td>P2$_1$/c</td>
<td>13.5414(3)</td>
<td>15.0598(2)</td>
<td>13.0106(2)</td>
<td>90</td>
<td>108.6450(10)</td>
<td>90</td>
</tr>
<tr>
<td>5-NO$_2$</td>
<td>P2$_1$/c</td>
<td>3.77770(10)</td>
<td>12.5991(5)</td>
<td>25.0825(10)</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>3- NO$_2$</td>
<td>P2$_1$</td>
<td>10.9737(5)</td>
<td>4.5752(2)</td>
<td>11.9808(5)</td>
<td>90</td>
<td>96.809(3)</td>
<td>90</td>
</tr>
<tr>
<td>6-F</td>
<td>Pba$_2$</td>
<td>11.655</td>
<td>11.6654(3)</td>
<td>16.9859(4)</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 5.2. Summary of the basic crystallographic data.
5.3. Results and Discussion.

Description of the Structures.

Diagrams of the representative packing for the thirteen structures analyzed are reported in Figure 5.2. These comprise eight simple binary products, three binary product hydrates and two binary product pyridine solvates.

5-CI
monoclinic P2_1/c
a = 11.9815(5)  b = 7.9626(2)  c = 12.4836(5)
α = 90.00  β = 100.400(2)  γ = 90.00
V = 1171.42(7)
Z' = 1

5-F
monoclinic P2_1/c
a = 10.7838(4)  b = 8.5407(2)  c = 12.1504(5)
α = 90.00  β = 95.099(2)  γ = 90.00
V = 1114.64(7)
Z' = 1

5-I
monoclinic P2_1/c
a = 13.6431(3)  b = 8.1066(2)  c = 12.4428(2)
α = 90.00  β = 112.279(1)  γ = 90.00
V = 1272.49(5)
Z' = 1

5-I Py
monoclinic P2_1/c
a = 18.6570(10)  b = 8.6657(5)  c = 10.9293(5)
α = 90.00  β = 102.573(4)  γ = 90.00
V = 1724.63(16)
Z' = 1
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5-1h
monoclinic  P2₁,

a = 4.400(5)  b = 18.068(5)  c = 8.581(5)

α = 90.00  β = 96.077(5)  γ = 90.00

V = 678.3(9)

Z' = 1

5-Br h
orthorhombic  Pca2₁,

a = 17.1666(5)  b = 3.8501(1)  c = 19.5610(4)

α = 90.00  β = 90  γ = 90.00

V = 1292.85(6)

Z' = 1

5-NH₂Py
monoclinic  C2c

a = 23.3169(11)  b = 8.1015(4)  c = 18.0588(8)

α = 90.00  β = 110.986(2)  γ = 90.00

V = 3185.1(3)

Z' = 1

5-ACM
monoclinic  P2₁/n

a = 15.1705(7)  b = 4.6669(2)  c = 19.6506(8)

α = 90.00  β = 104.734(2)  γ = 90.00

V = 1345.50(10)

Z' = 1
Figure 5.2. Crystal Packing of the 4-APy’SA’ derivatives.
As expected, considering the high value of $\Delta pK_a$ \[^7\] \(pK_a\) values of SA derivatives lie in the range 2-3, \(pK_a\) 4-AP: 9.17), all the compounds crystallized as molecular salts. This is not only confirmed by the identification of the pyridinium hydrogen, but also by the analysis of C-O distances for the carboxylic group and the values of the C-N-C angle of aminopyridine (Table 5.2). In fact, the typical C-O distances are approximately 1.30 Å and 1.22 Å for carboxylic acids ($\Delta r > 0.08$ Å) and in the range 1.23-1.29 Å in case of deprotonated carboxylate groups. Protonation also affects the values of the C-N-C angles of pyridines which are approximately $116-117^\circ$ for neutral pyridines and in the range $120-121^\circ$ for protonated pyridines \[^2a, 8\]. As reported in table 5.2 all the structures show values consistent with a proton transfer between the salicylic acid and the pyridine moiety (the difference between the C-O lengths $\Delta r < 0.08$ Å and C-N-C angles are in the range $119.8-121.0^\circ$).

It is also interesting to note the tendency of some of the systems under study to crystallize as solvate forms. In particular 5-MeO, 5-Br and 5-I crystallized as hydrate forms and 5-NH$_2$ and, again, 5-I crystallized as pyridine solvates. This tendency was also observed in the family of salicylic acid derivatives discussed in the previous chapter (Chapter 4, Section 4.3). Furthermore, the structures predominantly crystallize with $Z'=1$, the only exception from this common behaviour is represented by the 5-Me derivative which crystallizes with two independent molecules in the asymmetric unit. One of the two molecules shows positional disorder of the methyl group. The disorder, as described later, also affects the structure of the 5-Cl derivative, in which the pyridine moiety adopts two different orientations.

**Conformational Analysis.**

As in the salicylic acid derivatives discussed in the previous chapter (Chapter 4, Section 4.3), the family of salts show the intramolecular hydrogen bond formation between the hydroxyl group and one of the carboxylic oxygens (Figure 5.3) of the salicylic moiety. This is a typical feature of 2-hydroxyxcarboxylic acid (Chapter 4) and it is responsible for the rigid conformation adopted by the carboxylic group of salicylic acids. Furthermore, the intramolecular hydrogen bond is also recognized to have a key role in determining their acidity stabilizing the anion by resonance \[^9\].
Figure 5.3. Torsional angle $\tau_1$ and intramolecular O-H⋯O hydrogen bond for a generic 4-aminopyridinium salicylate.

The torsion angles $\tau_1$, which refers to the rotation of the carboxylate group (Figure 5.3), are close to 0° (Table 5.2) for all the structures.

<table>
<thead>
<tr>
<th></th>
<th>C-O$_\text{HN}$ (Å)</th>
<th>C-O$_\text{C2}$ (Å)</th>
<th>C-N-C (°)</th>
<th>D (Å)</th>
<th>d(Å)</th>
<th>$\tau_1$ (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Cl</td>
<td>1.276 (3)</td>
<td>1.244 (2)</td>
<td>121.0 (1)</td>
<td>2.512 (2)</td>
<td>1.58 (2)</td>
<td>1.2 (3)</td>
</tr>
<tr>
<td>5-F</td>
<td>1.281 (2)</td>
<td>1.243 (2)</td>
<td>120.3 (1)</td>
<td>2.531 (2)</td>
<td>1.79 (2)</td>
<td>2.3 (2)</td>
</tr>
<tr>
<td>5-I</td>
<td>1.285 (2)</td>
<td>1.241 (3)</td>
<td>120.8 (2)</td>
<td>2.520 (2)</td>
<td>1.77 (2)</td>
<td>-2.2 (3)</td>
</tr>
<tr>
<td>5-I Py</td>
<td>1.281 (5)</td>
<td>1.246 (5)</td>
<td>120.4 (4)</td>
<td>2.517 (5)</td>
<td>1.73 (5)</td>
<td>-1.7 (5)</td>
</tr>
<tr>
<td>5-I h</td>
<td>1.275 (3)</td>
<td>1.252 (3)</td>
<td>120.0 (2)</td>
<td>2.525 (2)</td>
<td>1.78 (2)</td>
<td>0.8 (3)</td>
</tr>
<tr>
<td>5-Br h</td>
<td>1.285 (4)</td>
<td>1.253 (4)</td>
<td>120.7 (3)</td>
<td>2.530 (3)</td>
<td>1.79 (3)</td>
<td>-4.0 (4)</td>
</tr>
<tr>
<td>5-NH$_2$ Py</td>
<td>1.278 (4)*</td>
<td>1.250 (4)*</td>
<td>120.8 (3)</td>
<td>2.505 (3)</td>
<td>1.61 (3)</td>
<td>7.9 (5)</td>
</tr>
<tr>
<td>5-ACM</td>
<td>1.261 (2)</td>
<td>1.273 (2)</td>
<td>120.1 (1)</td>
<td>2.475 (2)</td>
<td>1.72 (2)</td>
<td>4.8 (2)</td>
</tr>
<tr>
<td>5-MeO h</td>
<td>1.277 (3)</td>
<td>1.263 (3)</td>
<td>120.7 (3)</td>
<td>2.514 (3)</td>
<td>1.77 (3)</td>
<td>6.9 (4)</td>
</tr>
<tr>
<td>5-Me</td>
<td>1.261 (2)</td>
<td>1.271 (2)</td>
<td>120.6 (1)</td>
<td>2.470 (1)</td>
<td>1.71 (1)</td>
<td>1.9 (2)</td>
</tr>
<tr>
<td>5-NO$_2$</td>
<td>1.287 (2)</td>
<td>1.250 (2)</td>
<td>121.0 (1)</td>
<td>2.572 (1)</td>
<td>1.83 (1)</td>
<td>-1.2 (2)</td>
</tr>
<tr>
<td>3-NO$_2$</td>
<td>1.279 (4)</td>
<td>1.236 (3)</td>
<td>120.8 (3)</td>
<td>2.497 (3)</td>
<td>1.75 (3)</td>
<td>-1.9 (4)</td>
</tr>
<tr>
<td>6-F</td>
<td>1.285 (2)</td>
<td>1.242 (2)</td>
<td>120.3 (1)</td>
<td>2.498 (2)</td>
<td>1.69 (2)</td>
<td>-5.8 (2)</td>
</tr>
</tbody>
</table>

Table 5.3. C-O distances, C-N-C angles, O-H⋯O and O⋯O distances, torsional angle $\tau_1$ for the 4-aminopyridinium salicylate derivatives under study (* Refers to a different supramolecular synthon).

However the O⋯O distances observed in the salted forms are slightly shorter if compared to what was observed for pure salicylic acid derivatives (O⋯O distances lie in the range 2.4-2.5 Å for salicylates and in the range 2.5-2.6 Å for salicylic acids). This can be ascribed to the ionic character of the salicylic unit.

The most significant feature is provided by the supramolecular synthon $^{[10]}$ adopted by the structures under study. In fact, as expected, the COO⋯H*NPY supramolecular synthon is a very robust feature in the majority of the structures (Figure 5.2). Furthermore the supramolecular synthon also involves an additional C-H⋯O hydrogen
bond between one carboxylate oxygen and the aromatic hydrogen in ortho position to the charged pyridine nitrogen. The term “two point synthon” is generally used to distinguish this situation from the normal single COO⋯H⁺NPy supramolecular synthon which is described as “single point synthon” [2a].

Table 5.3 gives a summary of the main parameters used to describe the synthon occurring in the structures under study (see also Figure 5.4)

<table>
<thead>
<tr>
<th></th>
<th>N⋯O (Å)</th>
<th>N-H⋯O (Å)</th>
<th>C⋯O (Å)</th>
<th>C-H⋯O (Å)</th>
<th>τ₂ (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Cl</td>
<td>2.793 (3)</td>
<td>1.968 (1)</td>
<td>3.122 (5)</td>
<td>2.533 (1)</td>
<td>-2.0 (3)</td>
</tr>
<tr>
<td>5-F</td>
<td>2.738 (2)</td>
<td>1.87 (2)</td>
<td>3.191 (2)</td>
<td>2.584 (1)</td>
<td>8.0 (2)</td>
</tr>
<tr>
<td>5-I</td>
<td>2.711 (2)</td>
<td>1.84 (2)</td>
<td>3.316 (3)</td>
<td>2.712 (2)</td>
<td>2.47 (3)</td>
</tr>
<tr>
<td>5-I Py</td>
<td>2.820 (5)</td>
<td>2.04 (5)</td>
<td>3.214 (5)</td>
<td>2.66 (4)</td>
<td>-4.38 (5)</td>
</tr>
<tr>
<td>5-I h</td>
<td>2.694 (3)</td>
<td>1.84 (3)</td>
<td>-</td>
<td>-</td>
<td>3.79 (3)</td>
</tr>
<tr>
<td>5-Br h</td>
<td>2.692 (3)</td>
<td>1.84 (3)</td>
<td>-</td>
<td>-</td>
<td>52.29 (4)</td>
</tr>
<tr>
<td>5-NH₂ Py</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5-ACM</td>
<td>2.665 (2)</td>
<td>1.68 (2)</td>
<td>3.195 (2)</td>
<td>2.555 (1)</td>
<td>6.26 (2)</td>
</tr>
<tr>
<td>5-MeO h</td>
<td>2.802 (3)</td>
<td>1.92 (3)</td>
<td>3.187 (4)</td>
<td>2.590 (2)</td>
<td>6.82 (4)</td>
</tr>
<tr>
<td>5-Me</td>
<td>2.640 (1)</td>
<td>1.77 (1)</td>
<td>3.322 (2)</td>
<td>2.709 (1)</td>
<td>0.07 (2)</td>
</tr>
<tr>
<td>5-NO₂</td>
<td>2.861 (2)</td>
<td>2.00 (2)</td>
<td>3.179 (2)</td>
<td>2.665 (1)</td>
<td>10.65 (2)</td>
</tr>
<tr>
<td>3-NO₂</td>
<td>2.647 (4)</td>
<td>1.64 (4)</td>
<td>3.436 (4)</td>
<td>2.859 (2)</td>
<td>-1.48 (5)</td>
</tr>
<tr>
<td>6-F</td>
<td>2.747 (2)</td>
<td>1.87 (2)</td>
<td>3.187 (2)</td>
<td>2.602 (1)</td>
<td>-3.93 (2)</td>
</tr>
</tbody>
</table>

Table 5.4: Supramolecular synthon descriptors as shown in Figure 5.4.

The N-H⋯O distances (Table 5.3) are considerably shorter than the van der Waals radius (2.6 Å), indicating a strong interaction, as expected for ionic compounds. The C-H⋯O hydrogen bonds show C⋯O distances which lie the range of 3.122-3.322 Å.

Interestingly the N-H⋯O hydrogen bond generally involves the carboxylic oxygen lying in the same side of the hydroxyl group of the salicylic moiety (Figure 5.5 a). This is not the case for 3-NO₂ and 5-ACM, in which the carboxylic oxygen lies in the
opposite side with respect the hydroxyl group (Figure 5.5 b). Furthermore the 5-Me derivative, which crystallizes with $Z'=2$, shows both cases. The terms *syn* and *anti* are respectively used to describe the previous two cases (Figure 5.5).

![Syn and Anti](image)

**Figure 5.5.** *Syn* and *anti* conformation for the 4-aminopyridinium-salicylate supramolecular synthon. *a*) 4-aminopyridinium-6-fluorosalicylate (6-F); *b*) 4-aminopyridinium-3-nitrosalicylate (3-NO$_2$).

Departures from the general tendency to form the two point synthon are mainly observed in the hydrate structures in which the solvent molecules are interposed between the carboxylic oxygen and the aromatic hydrogen in ortho position to the heteroatom of the pyridinium component (Figure 5.6 *a-c*) in a similar manner to that observed in the previous chapter (Chapter 4, Section 4.3) for the hydrates of salicylic acid derivatives (in which the typical carboxylic dimer was disrupted by interposition of water molecules).

![Supramolecular Synthon](image)

**Figure 5.6.** Supramolecular synthon of hydrate forms. *a*) 4-aminopyridinium-5-bromosalicylate (5-Br h); *b*) 4-aminopyridinium-5-methoxysalicylate (5-MeO h); *c*) 4-aminopyridinium-5-iodosalicylate (5-I h).
In the 5-Br derivative, the presence of water affects the torsional angle value ($\tau_2 = 52.29^\circ$) and the association involves a single point synthon in which the pyridine moiety is slightly tilted (Figure 5.6 a). Interestingly, even though the torsion angle is close to 0 ($\tau_2 = 3.79^\circ$) the 5-I h shows C-H···O distances (C···O 4.224 Å and O···O 3.753 Å) consistent with a single point synthon (Figure 5.6 c). This is a consequence of the presence of the water molecule which induces a bending of the N-H···O interaction, as shown in figure 5.7 a.

Figure 5.7. Influence of the water molecule in the typical pyridine-carboxylic supramolecular synthon: a) 4-aminopyridinium-5-iodosalicylate (5-I h); b) 4-aminopyridinium-5-nitrosalicylate (5-NO$_2$). The direction and the entity of the bending is indicated by black arrows.

This is not the case for the 5-MeO derivative in which the water molecule interacts by a hydrogen bond with the carboxylic oxygen involved in forming the COO$^-$···H$^+$NPy interaction without affecting the ability of the two components to form the two point synthon (Figure 5.6 b).

The major departure from the expected synthon choice is observed in the 5-NH$_2$ derivative which crystallizes as pyridine solvate and in which a PyN···H$^+$NPy interaction between the 4-aminopyridinium component and a molecule of pyridine replace the COO$^-$···H$^+$NPy synthon (Figure 5.8 a).

Interestingly this is not observed for the pyridine solvate form of the 5-I derivative which crystallizes adopting the expected two point supramolecular synthon (Figure 5.8 b)
It is in some way surprising the fact that the 5-NH$_2$ derivative adopts this alternative supramolecular synthon. In fact as shown in figure 5.6 there is a proper exchange of the positions of the solvent molecule and the salicylate moiety which results in a PyN$^+$H$^+$$\cdots$NP$^-$ hydrogen bond extremely similar to the COO$^-$H$^+$$\cdots$NP$^-$ interactions generally observed for the other structures (N$^-$N$^+$ 2.793 Å is very similar to the lengths observed for the COO$^-$H$^+$$\cdots$NP$^-$ synthon). This is a good demonstration of the recent suggestion that salts often crystallize with unpredictable chemical or stoichiometric composition [4b]. However, these differences may arise from the competition between PyN$^+$H$^+$ and the amino group in para position in interacting with the carboxylate group of the salicylic moiety. One can argue that the COO$^-$H$^+$$\cdots$NP$^-$ interaction should be more favourable with respect to the COO$^-$H$_2$NP$^-$ because the positive charge in the aromatic nitrogen increases his ability as hydrogen bond donor. However the positive charge in the 4-aminopyridinium can be considered as delocalized between these two positions.

The synthon competition described above is even more pronounced if the 5-Cl derivative is considered (Figure 5.9). In this structure a disorder consisting of two different orientations of the aminopyridine ring are observed in a ratio 63-37%.
Figure 5.9. Disorder observed in 4-aminopyridinium-5-chlorosalicylate (5-Cl). 63% of the molecules are oriented as the red molecule and the remaining 37% are oriented as the yellow molecule.

This results in two different supramolecular synthons: \( \text{COO}^- \cdot \cdot \cdot \text{H}^+ \text{NPY} \) and \( \text{COO}^- \cdot \cdot \cdot \text{H}_2 \text{NPY} \) (Figure 5.10 a and b)

Figure 5.10. General interaction for the two different orientations of 4-aminopyridinium-5-chlorosalicylate (5-Cl).

As described in figure 5.9 the carboxylate group can interact adopting the typical two points \( \text{COO}^- \cdot \cdot \cdot \text{H}^+ \text{NPY} \) and the \( \text{COO}^- \cdot \cdot \cdot \text{H}_2 \text{NPY} \) assisted by a C-H\cdot\cdot\cdotO interaction between one of the carboxylic oxygen and the aromatic hydrogen in the ortho position with respect to the amino group (N\cdot\cdot\cdotO, C\cdot\cdot\cdotO distances respectively 2.840 Å and 3.564 Å).

A different situation is observed in the nitro-derivatives in which the nitro group behaves as competitor to the carboxylate in interacting with the amino group. This
results in a NOO···H$_2$NPy interaction reinforced by a weak PyC-H···O$_2$N hydrogen bond (Figure 5.11).
However this is a secondary interaction since both nitro derivatives form the typical COO'···H'NPy synthon observed in the majority of the structures.

![Figure 5.11. PyC-H···O$_2$N hydrogen bond for the two nitro derivatives: a) 4-aminopyridinium-3-nitrosalicylate (3-NO$_2$), b) 4-aminopyridinium-5-nitrosalicylate (5-NO$_2$).](image)

The N···O and C···O distances are respectively 3.152 Å, 3.388 Å for 5-NO$_2$ and 3.093 Å, 3.441 Å for 3-NO$_2$. The small difference could be ascribed to the different conformation of the nitro group observed for 3-NO$_2$ which is slightly tilted. In fact the torsion angle for 5-NO$_2$ and 3-NO$_2$ are respectively -1.68° and 19.84°. The higher value for 3-NO$_2$ could depend on the steric hindrance between the nitro group and the OH group.
Interestingly no isostructurality was observed among the thirteen structures under study. However partial similarity of the unit cell of some derivatives, mainly concerning the halo derivatives, is indicative of possible high dimensional structural relationships. For this purpose an X-Pac$^{[6]}$ analysis was carried out as described in the next section.

**XPac Analysis.**
In contrast to the previous analysis (see Chapter 3 and 4), in which the target systems are single component, the choice of the COSP for this new family should, in principle, include both components. Furthermore, the COSP, by definition, must be representative for the whole set of structures. However, as described above, the structures under study shown differences in the supramolecular synthon deriving from the inclusion of solvent molecules in the crystal structure or from differences in the associations (e.g. N-H···O interactions syn or anti with respect the hydroxyl group). These differences affect the relative positioning of the two components. In particular the 3-NO$_2$ and 5-ACM derivatives adopted a different reciprocal orientation deriving from the position of the
oxygen involved in forming the N-H···O hydrogen bond which is anti with respect to the hydroxyl group.

Furthermore, since the software only permits a COSP choice on single molecules (e.g. choice of COSP in molecules with Z' > 1 can carried out separately in each of the symmetry independent molecules but not simultaneously) a simultaneous choice of atoms located in both components is not possible. To obviate this last problem a new procedure has been developed which allows consideration of the two components as a single “molecule”. For this purpose a new set of CIF files have been created in which the two components are connected by a “dummy” covalent bond which replace the N-H···O hydrogen bond.

The analysis was carried out using high filters (XPac 1) and the Corresponding Ordered Set of Points (COSP) as defined in figure 5.12.

![Figure 5.12](image)

**Figure 5.12.** COSP defined for the XPac analysis: a) Syn derivatives, b) Anti derivatives.

The two COSPs in Figure 5.12 take into account the syn and anti conformation adopted by the two components.

In order to analyze the 5-NH₂ derivative, which adopts a different synthon, and those hydrate forms which showed major differences in the relative position of the two components a parallel analysis was carried out using the salicylic moiety only, as the COSP. However the results reported in the relationship diagram (see Figure 5.13) are related to the COSP shown in Figure 5.12 and if a new relationship is identified with the second set of COSP (salicylic), it will be commented on (For more details see Appendix A3).

The following notation is chosen to describe the relationships diagram:
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As for the previous analysis (Chapter 3 and 4) the diagram is divided in four regions, each indicating a given dimension (3-D, 2-D, 1-D, 0-D). The dimensions increase from the bottom of the diagram going through to the top.

The thirteen crystal structures are identified at the top of the diagram. Each structure is indicated by a coloured circle. The colour represents the substituent group (same colour means same substituent). Two structures in the same position mean 3-D similarity (e.g. 5-Cl and 5-F derivatives).

SCs, indicated by circles, are labelled by letters (the same letter means the same family of SCs) followed a number which is an arbitrary numbering scheme. When more than one SC deriving from the same family and having the same dimension is present, the letter is followed by two numbers (the first defines the dimension of the SC and the second indicates an arbitrary numbering scheme).

Instances of the 0-D Supramolecular Constructs are also reported, to show the differences between the two families of arrangements isolated. Different colours are used to differentiate the two components of the salts: yellow for the salicylate moiety and red for the aminopyridinium.

All the relationships among the different structures and SCs are indicated by connecting lines.

![Diagram](image)

**Figure 5.13.** Structural similarities identified among the structures in study.

The most significant feature concerns the two different behaviours observed for the structures under study. As reported in Figure 5.13, two families of SCs can be
identified, labelled respectively M (monomer) and D (dimer). The family M derives directly from the 0-D SC M0, which can be considered as the primary SC. This is not observed in the hydrate forms 5-I and 5-Br, which showed some differences in the geometry of the supramolecular synthon, due to the presence of the water molecules and in the pyridine solvate of 5-NH₂ derivatives which adopts a different supramolecular synthon.

The family D derives from the 0-D SCs labelled as D01 (Figure 5.13) which is a dimeric arrangement obtained from M0 by additional inversion symmetry.

Interestingly the 5-MeO h, 5-ACM, 5-NO₂ and 3-NO₂ derivatives show relationships within the family M and the halo-derivatives 5-Cl, 5-F, 5-I, 5-I Py, 6-F and the 5-Me derivatives show preferentially relationships within family D.

Only one 3-D similarity has been observed, which relates the 5-Cl and 5-F derivatives. However, as described below the two structures show some small differences in the packing arrangements.
**Supramolecular Constructs M.**

The family of SCs M, directly obtained from M0, contains three 1-D SCs labelled respectively as M11, M12, M13 and one 2-D SC labelled as M2.

M11 is the first 1-D SC which consists of a stacking arrangement of the salicylate-aminopyridinium pair (Figure 5.14 a and b) which develops along the shorter axis. This arrangement is common for the 5-MeO h, 5-ACM, 5-NO2 and 3-NO2 derivatives. No significant intermolecular interactions are systematically involved in generating the stack of molecules. The only exception is presented by the 5-ACM derivative in which the salicylic moieties are connected via N-H···O and C-H···O hydrogen bonds between the acetamido groups of adjacent molecules (N···O and C···O respectively 2.904 Å and 3.176 Å).

![Figure 5.14](image)

**Figure 5.14.** 1-D Supramolecular Construct (SC) M11: a) 4-aminopyridinium-3-nitrosalicylate (3-NO2) derivative viewed along the 00-1 direction; b) 4-aminopyridinium-5-acetylaminosalicylate (5-ACM) viewed along the -10-1 direction.

Table 5.4 summarizes the geometrical parameters used to characterize the stacking as previously described for aspirins and salicylic acid derivatives (Chapters 3 and 4).

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<td>010</td>
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**Table 5.5.** Molecular stacking descriptors as previously described in Chapter 3 and 4. ESD’s for these parameters are estimated as <0.01 for distances and 0.1 for angles, based on values for molecular parameters.
Interestingly the four structures show some differences in the stacking arrangements; in particular in 5-ACM and 3-NO₂ the values of Cen1-Cen2 distances are higher with respect the other two derivatives involved in the common SC M11 (Cen1-Cen2 in the range 4.5 - 4.7 Å for 5-ACM and 3-NO₂ and in the range 3.3 - 4.0 Å for 5-MeO h and 5-NO₂). However an analysis using more restricted filter parameters (medium 10-18-18 XPac 1) confirms the relationship as found.

A similar stacking arrangement is also observed in 5-Br h, and 5-I h but not included in the analysis since the differences in the supramolecular synthon are not compatible with the COSP chosen for this analysis. However, as previously described, a parallel analysis using the salicylic moiety as COSP reveals a 1-D similarity very close to M11 (Figure 5.15 a and b).

![Figure 5.15](image)

**Figure 5.15.** 1-D stack as found in the two hydrates of the halo derivatives: a) 4-aminopyridinium-5-iodosalicylate (5-I) derivative viewed approximately along the 001 direction; b) 4-aminopyridinium-5-bromosalicylate (5-Br) viewed along the 10-1 direction. The salicylic moieties are coloured as orange, 4-aminopyridine moieties as yellow.

The second 1-D SC, M12, is closely related to M11 and is common to 3-NO₂, 5-ACM and 5-MeO h (Figure 5.16 a - d).
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Molecular Salts Based on 4-Aminopyridine-Salicylic Acid Derivatives

Figure 5.16. 1-D Supramolecular Construct (SC) M12: a) 4-aminopyridinium-3-nitrosalicylate (3-NO₂) derivative viewed along the 010 direction; b) 4-aminopyridinium-5-acetylaminosalicylate (5-ACM) viewed along the 010 direction. c) 4-aminopyridinium-5-methoxysalicylate (5-MeO) viewed along the 001 direction. Instances of the 1-D SC M11 are also indicated.

M12 consists of two adjacent SCs M11 related by a 2₁ screw axis and connected via N-H···O hydrogen bonds between the amino group of the pyridinium and the hydroxyl group for 5-ACM and 5-MeO h (N···O distance respectively 2.917 Å and 2.932 Å) and the nitro group for the 3-NO₂ derivative (N···O distance 2.950 Å). The 3-NO₂ derivative also shows a C-H···O hydrogen bond involving the hydroxyl group and the aromatic hydrogen in position meta to the pyridinium nitrogen (Figure 5.16 a).

The 5-NO₂ derivative, which is not involved in forming M12, shows a similar arrangement differing in the relative shifting of the two stacks M11 (Figure 5.17 a and b).
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Figure 5.17. a) 4-aminopyridinium-5-nitrosalicylate (5-NO₂); b) 4-aminopyridinium-3-nitrosalicylate (3-NO₂).

Note that, similarly to the 3-NO₂ derivative, the arrangement for the 5-NO₂ derivative is linked by weak C-H⋯O hydrogen bond but involving in this case the aromatic hydrogen in the position ortho to the pyridinium nitrogen, and the hydroxyl group of the salicylate (C⋯O distance 3.349 Å).

The third 1-D SC, M13 (Figure 5.18 a - c), is common to 5-NO₂, 3-NO₂, 5-F and 5-Cl derivatives and consists in a zig-zag infinite chain of M0 SCs which develops diagonally along the [2·10] direction for the 5-NO₂ derivative, 1-20 for the 3-NO₂, and respectively -1-10 and 110 for the 5-F and 5-Cl derivatives.

Figure 5.18. 1-D Supramolecular Construct (SC) M13: a) 4-aminopyridinium-5-nitrosalicylate (5-NO₂) derivative viewed along the 001 direction; b) 4-aminopyridinium-3-nitrosalicylate (3-NO₂) viewed along the 001 direction; c) 4-aminopyridinium-5-fluorosalicylate (5-F) viewed along the 001 direction.

Figure 5.19 a - d shows instances of the SC M13 and the interactions involved.
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Figure 5.19. Instances of the Supramolecular Construct (SC) M13: a) 4-aminopyridinium-5-nitrosalicylate (5-NO$_2$) viewed along the 100 direction; b) 4-aminopyridinium-3-nitrosalicylate (3-NO$_2$) viewed along the 010 direction; c) 4-aminopyridinium-5-fluorosalicylate (5-F) viewed along the 0-10 direction; d) 4-aminopyridinium-5-chlorosalicylate (5-Cl) viewed approximately along the 010 direction. The pyridinium···carboxylate synthon is indicated by blue dashed lines, other interactions by red dashed lines.

Note that, as consequence of the carboxylate-pyridinium anti configuration (see Figure 5.5), the 3-NO$_2$ derivative shows a departure from the group of structures involved in forming M13 which consists of a different orientation of the salicylic moiety (Figure 5.19 b). In particular, the comparison of the nitro derivatives emphasizes this difference but also highlights the importance of the directional interactions in generating the common arrangement. In fact, as shown in figure, the nitro group of both derivatives interacts via N-H···O hydrogen bond with the amino group of the pyridine moiety (N···O distances for 3-NO$_2$ and 5-NO$_2$ respectively 3.093 Å and 3.152 Å). This interaction is also reinforced by a weak C-H···O with the aromatic hydrogen in position.
meta to the PyN\(^+\) (C···O distances for 3-NO\(_2\) and 5-NO\(_2\) respectively 3.441 Å and 3.388 Å).

A similar behaviour is also observed for the 5-F derivative in which the amino group interacts with the fluoro (F···N 3.015 Å) determining a similar geometry (Figure 5.19 c). However, no analogous significant interactions are found for the 5-Cl derivative (apart a C-H···Cl contact involving the aromatic hydrogen in position meta with respect the pyridinium nitrogen with a C-H···Cl 3.268 Å) in which the Cl···N distance is approximately 5 Å (Figure 5.19 d). This last observation suggests that this molecular arrangement is the result of both directional interactions and close packing features.

It is also worth noting how important is the correct choice of the COSP (see comparison reported in Figure 5.19) in order to obtain relationships between systems which may have significant differences. In this case, in fact, the selection of two set of COSPs (see Figure 5.12) permits comparison of the two nitro derivatives which in other case would be difficult.

Strictly related to A13 is the 2-D SC M2 common to the nitro derivatives. This is built by the combination of the two 1-D SCs M11 and M13 (Figure 5.20).

![Figure 5.20. 2-D Supramolecular Construct (SC) M2 reported for 4-aminopyridinium-3-nitrosalicylate (3-NO\(_2\))](image)

The two nitro derivatives show significant differences along the 001 direction.

Figure 5.21 shows the crystal packing of the two derivatives viewed along the shortest axis. Instances of the SC M2 are also shown. The two nitro derivatives show a different development of M2 along the 001 direction.
In the 3-NO₂ derivative the SC M2 adopts two different orientations, labeled respectively as M2 and M2’, which are related by vertical 2₁ screw axes. M2 and M2’ are connected by N-H···O hydrogen bonds between the amino group of the pyridinium and the nitro group assisted by a C-H···O hydrogen bond involving the hydroxyl group and the aromatic hydrogen in position meta to the pyridinium nitrogen (Figure 5.16 b).

In the 5-NO₂ derivative one more 2₁ screw axis operates along the 010 direction, generating two more orientations labeled as M2” and M2”’ (indicated as blue in Figure 5.21 b). M2 and M2’ are related, as in the 3-NO₂ derivative, by the vertical 2₁ screw axis. The same operation relates M2” and M2”’. These instances of the SC M2 are connected by C-H···O hydrogen bond involving the hydroxyl group and the aromatic hydrogen in position ortho to the pyridinium nitrogen (Figure 5.16 a).

M2' and M2” and M2”’ and M2 are instead related by a 2₁ screw axis lying in the 011 plane and connected by N-H···O hydrogen bonds between the amino group of the pyridinium and the oxygen of the carboxylic group (N···O distances 2.796 Å).
Supramolecular Constructs D.
The second family of SCs, labelled as D, includes the halo derivatives 5-Cl, 5-F, 5-I, 5-I Py and 6-F and the 5-Me derivative. As previously described, this is not the case for the two hydrate forms 5-Br h and 5-I h, which adopt molecular arrangements close to the family M.

The group D contains a 0-D SCs D01 and a 2-D SC D2. The SCs D01, which is the precursors of the molecular arrangement of the type D, is a dimeric arrangements obtained from M0 by inversion symmetry. This is common for 5-Cl, 5-F, 5-I, 5-I Py, 6-F and the 5-Me derivative. No significant interactions are involved in forming this SC.

Interestingly the arrangement observed for the 5-I Py derivative shows some significant differences with the other derivatives related to the relative shifting of the 0-D SCs M0 and M0’ (Figure 5.22 a and b). This can arises from the steric hindrance of the pyridine molecules which interact via a N-H···N hydrogen bond with the amino group of the 4-aminopyridinium (N···N 3.058 Å).

The SC D01 contributes in generating a 1-D arrangement, common to the halo derivatives (5-Cl, 5-F, 5-I, and 5-I Py) and not included in the analysis since it is part of the higher dimension SC D2. This can be considered as a stack of SC D01 which develops along the shortest axis (Figure 5.23 a and b).
The 5-Cl, 5-F, 5-I and 5-I Py derivatives show a common 2-D SC labelled as D2. This is formed by a combination of the 1-D arrangements described above, related by $2_1$ screw axes (Figure 5.24 a - c).

Figure 5.24 shows a comparison of the crystal packing of 5-Cl and 5-I and 5-I Py derivatives, viewed along the 010 axis.
Figure 5.24. 2-D Supramolecular Construct (SC) D2: a) 4-aminopyridinium-5-chlorosalicylate (5-Cl) viewed along the 010 direction. SCs D2-D2′ are related by $2_i$ screw axis perpendicular to the sheet (green); b) 4-aminopyridinium-5-iodosalicylate (5-I) viewed along the 010 direction. SCs D2 - D2′ are related by centre of inversion (yellow); c) 4-aminopyridinium-5-iodosalicylate (5-I Py) viewed along the 010 direction. SCs D2 - D2′ are related by $2_i$ screw axis perpendicular to the sheet (green) and centre of inversion (yellow). The molecules are colour-coded according to the orientation of the ring–carboxylate vector; dark blue = pointing towards from the viewer, blue = pointing away the viewer.

The three structures mainly differ in the development of D2 along the 100 axis. In the 5-Cl and 5-I Py derivatives (Figure 5.24 a and c) the instances of the 2-D SC (D2 and D2′) are related by $2_i$ screw axes and connected by N-H···Cl hydrogen bonds for 5-Cl (N··Cl distance 3.214 Å) and I···I contacts for the 5-I Py derivative (I···I distance 3.807 Å), this not the case for the 5-I derivative (Figure 5.24 b) in which D2 and D2′ are
related by inversion symmetry and connected by C-H···I interactions involving the aromatic hydrogen in position ortho to the carboxylate. However it is interesting to note the differences related to the 5-I Py structure in which the instances of the SC D2 are more spaced. This is also confirmed by the comparison of the unit cell parameters for the four structures involved in this arrangements which show similar values for the 010 (in the range 7.9-8.6 Å) and 001 axis (in the range 10-12.5 Å) and a very different value for the 100 axis (approximately 18 Å for the 5-I Py and in the range 10-13 Å for the other halo derivatives). This is, again (see SC D01), the effect of the steric hindrance of the solvent molecules which act as spacers. However it is interesting to note that though the presence of the solvent molecules influence significantly the dimensions of the unit cell parameters, the 5-I Py derivatives adopts a crystal packing very close to the 5-Cl and 5-F derivatives (see Figure 5.24 a and c).

As shown in the relationships diagram (see Figure 5.13), 5-Cl and 5-F derivatives are related by a 3-D similarity. However, the analysis of the unit cell parameters reveals some differences along all three axes. In particular the two structures show differences of about 1 Å, 0.5 Å and 0.3 Å respectively along the 100, 010 and 001 axes. Figure 5.25 a and b show the crystal packing of the two halo derivatives viewed along the 010 axis.

![Figure 5.25. Crystal packing of: a) 4-aminopyridinium-5-chlorosalicylate (5-Cl); b) 4-aminopyridinium-5-fluorosalicylate (5-F) both viewed along the 010 axis.](image)

In particular the two derivatives show a different shift of the two adjacent SCs D2 and D2’ along the 001 and -100 direction. This also influences the interactions involved in connecting the two adjacent SCs D2 and D2’, which are in both cases N-H···X interactions (X = halogen) between the amino group of the pyridinium and the halogen in position meta of the salicylate but involving different positions (Figure 5.26 a and b).
In the 5-Cl derivative (Figure 5.26 a) the shortest contact (indicated in black) occurs between two adjacent molecules along the 100 direction (N···Cl distance 3.214 Å), in 5-F (Figure 5.26 b) this involves adjacent molecules along the 001 direction (N···F distance 3.015 Å).

5.4. Conclusions.

The robustness of the COO···H+NPy supramolecular synthon is the main common feature of this set of structures. In general the salicylate and the 4-aminopyridinium moieties interact by a strong N-H···O hydrogen bond assisted by a secondary C-H···O weak hydrogen bond, forming a “two point synthon”. This definition is ambiguous for the two nitro derivatives which, even if they adopt a conformation suitable for the formation of the “two point synthon” (low torsional angle τ2), the C-H···O interactions are significantly longer with respect those observed for the majority of the structures (C···O distances 3.510 Å for the 5-NO2 and 3.436 Å for the 3-NO2).

However, the simultaneous presence of different substituent groups or the presence of solvent molecules in the solvate forms can affect the predictability of the supramolecular synthon of some structures. In particular the amino group of the aminopyridine moiety competes with the aromatic nitrogen in forming the typical COO···H+NPy. This is mainly observed in the 5-NH2 Py derivative, in which the COO···H-NH interaction replace the COO···H+NPy synthon and in the 5-Cl derivative, in which
the two different orientations of the aminopyridine ring, observed in a ratio 63-37%, show both possibilities.

The complex structural behaviour of the molecular salts is more emphasized considering the crystal packing differences observed within the family. The XPac analysis clearly shows two different tendencies to pack. The main difference concerns the identification of two families of SCs labelled as M and D. The family of SCs M derives from the 0-D SC D0, a monomer which is formed by the two components assembled together trough the COO’⋯H-NH supramolecular synthon. This family contains the 5-NO₂ and 3-NO₂, 5-MeO, 5-ACM derivatives.

The second family of SCs, D, derives from the 0-D SC D0 which is a dimer formed by two SCs M0 related by inversion symmetry. This family contains the halo derivatives 5-Cl, 5-F, 5-I, 5-I Py, 6-F and the 5-Me derivative.

In contrast to the family of salicylic acid derivatives discussed in the previous chapter (Chapter 4), the set of salts analyzed here shows high degree of structural similarity within derivatives with similar substituted groups. This is observed for the two nitro derivatives 3-NO₂ and 5-NO₂ which show a 2-D similarity. The most significant example is given by the halo derivatives substituted in position 5 which show 3-D and 2-D similarities. Surprisingly the hydrate forms show significant differences in the crystal packing adopted and in particular 5-Br h and 5-I h adopt a crystal packing which shows closeness to the family of structures M.

Surprisingly the 5-I Py, which includes in the crystal structure molecule of the pyridine solvent, adopts a crystal packing close to the other 5-halo derivatives. The difference is mainly ascribed to the molecule of the solvent which acts as spacer, increasing some of the unit cell parameters.
References.


CHAPTER 6: CONCLUSION AND FURTHER WORK.


This thesis work has shown quite clearly that, as described in Section 1.5, crystal structure assembly is a trade-off between close packing (and in general geometrical features) and intermolecular interactions. In particular, the observation of recurring 1-D or 2-D fragments held together by different sets of directional and non-directional interactions indicates that close packing has a significant role in determining the crystal structure of a given compound. This scenario is consistent with the related ideas proposed by Dunitz and Schweitzer [1], in relation to recent studies of the alloxan structure (which, though rich in hydrogen bond donors and acceptors, does not form any strong directional intermolecular interaction), that the structure is “held together by whatever factors contribute to the cohesive energies” of specified pairs of molecules. This view has received further comment by Desiraju [2], and by Boese, Desiraju et al [3] in their report of an extended analysis of structures of further fluoroaromatics.

The analysis of the three families of salicylic acid derivatives has also shown how the type of substituents and the position of attachment can have a significant role in determining particular molecular arrangements. In particular the family of substituted aspirin derivatives showed a wide range of common molecular arrangements which might be explained considering both the similar shape (resulting from the substituents and their positions of attachment) and the directional interactions. In this regard it is worth mentioning the high similarities (3-D and 2-D) involving the 5- and 4-substituted derivatives. On the contrary, the substituted salicylic acid derivatives (Chapter 4) mainly showed 1-D similarities consisting on different types of stacking arrangements. This is an unexpected result if the rigid molecular conformation and the close shape of the molecule are considered. In this regard, the absence of the acetyl group seems to be one possible reason for such different behaviour. In particular the acetyl centrosymmetric dimer is a robust synthon observed in the majority of the aspirin derivatives, which might have an important role in defining similarities within the family.

As expected, the family of salts (Chapter 5) obtained by proton transfer between the substituted salicylic acid derivatives and the 4-aminopyridine, shown significant crystal
packing differences if compared with the previous two families. However, as in aspirin derivatives, compounds with similar substituent groups adopt similar crystal packing. In the other hand, the analysis showed the importance of particular functional group in defining robust supramolecular synthons.

The three families studied showed, apart from a small number of exceptions, predictable synthons (carboxylic dimers for the aspirins and the salicylic acids and the well known pyridine-carboxylate synthon for the salts) observed in the majority of the structures.

A further consideration concerns the occurrence of solvate forms. In particular, and differently to the other two families studied, the aspirin derivatives showed the tendency to crystallize as anhydrous or generally non-solvate forms. It is also interesting that hydrate or solvate formation in the other two families is not dominant. The combined results from this work clearly indicate that further study, particularly using the systematic approach of this present work, would be very useful.
6.2. Further Work.

Future work can thus be addressed in many directions. First of all would be of interest to increase the number of the family members by synthesizing and crystallizing more derivatives. Additionally new families might also be defined by varying the target molecules. An example could be the preparation of trifluoroacetylsalicylic acids, to study the influence of the trifluoro substituent in generating the crystal packing and eventually in disrupting the centrosymmetric acetyl dimer which has proved to be a strong feature in the aspirin derivatives.

The family of salts could be increased using more salicylic acid derivatives. Of particular interest could also be the preparation of more hydrate forms in order to identify the differences with the anhydrous form in the crystal packing. In fact, as described in Chapter 5, the hydrate forms so far analyzed showed the tendency to pack adopting molecular arrangements deriving from the monomer. The salt screening could also be extendend to molecular salts prepared using other pyridine derivatives. An example can be represented by the 3,4-diaminopyridine which can also be deprotonated in position 3, determining a family of deprotonated salts. Other relevant molecules can be represented by quinoline substituted derivatives (amino or hydroxy).

A further direction concerns the systematic search of potential polymorphs for both the aspirin and the substituted salicylic acid derivatives. The XPac procedure and in particular the relationships diagram, can be a useful guide in developing the experiments. The aim is to develop a protocol for polymorphism screening based on the XPac results. The screening could be based on seeding experiments involving derivatives which showed similar molecular arrangements. Computational studies, aimed at providing information on the stability of all the forms studied, and specifically the relative energies in all the intermolecular interactions identified would be of particular importance in selecting derivatives for seeding experiments.

For example, following from the isolation of the polymorphic form of 5-chloroaspirin (5-Cl (II)) it would be interesting try to isolate polymorphic forms of the other member of the halo isostructural set (5-iodo and 5-bromoaspirin). This could be carried out by seeding the halo derivatives with crystals of 5-Cl (II).

Further work can also be addressed on the development of other families of related compounds based on molecules of pharmaceutical interest. An example can be represented by 2-(2,6-dichloranilino) phenylacetic acid, generally known as diclofenac.
The analysis can also be extended to flexible molecules such as aliphatic carboxylic acids, in order to investigate the influence of the flexibility of the chains in determining the crystal packing.

Finally, it is obvious to point to the great value of the kind of systematic studies so far made in helping to understand the factors operative in the assembly of organic crystal structures, and that these methods, and the tools and procedures which have been developed, can, in general, enable an expansion into an almost unlimited variety of similar projects.
References.

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Table A1.1. Supramolecular Construct descriptions. SC = Supramolecular Construct; D = dimensionality; Description, ‘>’ = is related by; # = Number of structures in which construct occurs; Base = base vector of SC (see Table 2); Dependencies show lower dimensionality SCs present in given SC.
### Table A1. 2. Translation vectors with lengths (Å) (angles in the 2-D arrangements are all 90°)

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Table A1. 2. Translation vectors with lengths (Å) (angles in the 2-D arrangements are all 90°)
### Table A2.1. Supramolecular Construct descriptions.

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<th>Description</th>
<th>Figs</th>
<th>#</th>
<th>Base</th>
<th>Dependencies</th>
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<td>A0·A11→A22</td>
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**Isostructural**

Table A2.1. Supramolecular Construct descriptions. SC = Supramolecular Construct; D = dimensionality; Description, ‘>’ = is related by; # = Number of structures in which construct occurs; Base = base vector of SC (see Table 2); Dependencies show lower dimensionality SCs present in given SC.
Table A2. 2. Translation vectors with lengths (Å) and angles $\delta$ (°).

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## Table A3. 1. Supramolecular Construct descriptions. SC = Supramolecular Construct; D = dimensionality; Description, ‘>’ = is related by; # = Number of structures in which construct occurs; Base = base vector of SC (see Table 2); Dependencies show lower dimensionality SCs present in given SC.

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<th>Figs</th>
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### Isostructural 5-Cl, 5-F
### Table A3. 2. Translation vectors with lengths (Å) and angles δ (°).

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