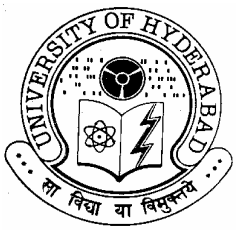
SUBSTITUENT EFFECTS ON THE FORMATION OF THE CATEMER AND DIMER IN SOME CRYSTALLINE CARBOXYLIC ACIDS

A Thesis
Submitted for the Degree of
Doctor of Philosophy

By
DINABANDHU DAS



School of Chemistry
University of Hyderabad
Hyderabad 500 046
India

February 2006

To
Ma and Baba

STATEMENT

I hereby declare that the matter embodied in this thesis entitled **"Substituent Effects on the Formation of Catemer and Dimer in Some Crystalline Carboxylic Acids"** is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad under the supervision of **Prof. Gautam R. Desiraju**.

In keeping with the general practice of reporting scientific observations due acknowledgements have been made wherever the work described is based on the findings of other investigators.

Hyderabad **Dinabandhu Das**

February 2006

CERTIFICATE

Certified that the work **"Substituent Effects on the Formation of Catemer and Dimer in Some Crystalline Carboxylic Acids"** has been carried out by **Dinabandhu Das** under my supervision and that the same has not been submitted elsewhere for a degree.

Dean
School of Chemistry

Prof. Gautam R. Desiraju
Thesis Supervisor

ACKNOWLEDGEMENT

I would like to express my deepest gratitude to my supervisor, **Prof. Gautam R. Desiraju** for his knowledge, guidance and constant encouragement during this research work. I have learnt a great deal from him and consider my association with him to be a rewarding experience.

I thank Prof. Ashwini Nangia for helpful discussions during my Ph. D. work. It is my pleasure to thank Prof. Dr. Roland Boese, Universität Duisburg-Essen, Germany for hosting me in his laboratory during September-December 2004, and introducing me to the *in situ* crystallisation method. My special heartfelt thanks for his concern regarding my livelihood there.

I thank the Dean, School of Chemistry and all the faculty members of the School for their cooperation.

I would like to acknowledge the assistance of Dr. Ram K. R. Jetti, for collecting the X-ray diffraction data on some of the compounds described in Chapter 3, under the supervision of Prof. Dr. Roland Boese. I thank Mr. Prashant Bhatt for collecting X-ray diffraction data on one of the compounds described in Chapter 2, under the supervision of Dr. D. G Billing, University of Witwatersrand, Johannesburg, South Africa.

I wish to thank my friendly and cooperative labmates Drs. R. Thaimattam, R. K. R. Jetti, P. K. Thallapally, V. S. S. Kumar, V. R. Vangala, P. Vishweshwar, S. George, S. Basavoju, and Messrs. Sairam, Srinivasulu, Bala Krishna, Malla Reddy, Sreenivas Reddy, Binoy, Rahul, Archan, Aparna, Sunil, Saikat, Prashant, Tejendar, Sreekanth, Jagadeesh, Bipul and Naren for creating a cheerful working atmosphere in the lab. I thank all my friends in the School of Chemistry for making my stay in the campus an enjoyable one. I also wish to thank all the colleagues at the Universität Duisburg-Essen for their

help during my stay in Germany, especially Mr. Sebastian Cirkel and Dr. Dieter Bläser for friendly and helpful discussions.

I appreciate the suggestions and remarks made by Binoy, Rahul, Archan, Saikat, and Prashant during my Ph. D. work.

I wish to thank to my friends Satyen, Satyanarayan, Rana, Tamal, Bobs, Abhik, Suni, Manab, Panchu, Bishu, Sandy, Binoy, Rahul, Archan, Saki, Prashant, Bipul, Prasun, Satabdi, Kedar, Jethu, Bhaswati, Sandip, Ullas, Bachha, Ghona, Arindam, Tapta, Padu, Ghata, Tonmoy, Rumpa, Anindita, Suparna, Naren, Abu, Sanjeeb, Ranjit and Nabo.

Special thanks to Naren who helped me during the preparation of my thesis.

I wish to record my thanks to CSIR, New Delhi for fellowship support. I also thank DST-DAAD for funding my visit to Germany.

I thank all the non-teaching staff of the School of Chemistry, CIL and COSIST building for their assistance on various occasions.

I don’t have enough words to express my feelings and gratitude to my family members. Affection, moral support, blessings and the best wishes of my beloved family members made me what I am and I owe everything to them.

Dinabandhu Das

PREFACE

The two terms ‘self-assembly’ and ‘molecular recognition’ are often used in supramolecular chemistry to explain the formation of supermolecules or crystals. How does this self-assembly occur? How does the molecule recognise itself? Do we have a proper understanding of these phenomena? If the answer is ‘yes’, Crystal Structure Prediction (CSP) would have been 100% successful. However, we still lack a proper understanding of intermolecular interaction and this makes CSP difficult. Sometimes, the same functional group recognises itself in different motifs. The carboxylic acid is a good example. It can form a dimer as well as a catemer. Probably the most well known, and most easily identifiable, hydrogen bonding aggregate is the carboxylic acid dimer. However, dimers of acetic and formic acids are still unattainable in the solid state. The formation of dimers and catemers in carboxylic acids is a long-standing problem in crystal engineering. This thesis is an attempt to rationalize this problem in a few carboxylic acids.

Without the carboxyl group, crystal engineering might well have lost its charm and beauty. This is the most frequently studied functional group in crystal engineering. Chapter 1 gives an overview of crystal engineering with reference to carboxylic acids. The conformational preferences of the carboxyl group are also discussed in this chapter.

The substituent exerts both steric and electronic effects on the crystal packing. However, just by looking at a single crystal structure it is not possible to deduce these effects of the substituent on the packing. To understand these effects one needs ideally to look at an entire series of crystal structures. Chapter 2 highlights the role of the substituent on the formation of catemer or dimer in 2- and 3-substituted phenylpropiolic acids.

The effect of the substituent depends upon its location on the phenyl ring. In Chapter 3, I have described the role of substituent on the formation of catemer or dimer in 4-substituted phenylpropiolic acids. In this Chapter I have compared the role of the substituent on crystal packing between the 4-substituted phenylpropiolic acids and the structurally related cubanecarboxylic acids.

After the study of monosubstituted acids it was of interest to see the behaviour of the carboxyl group in the disubstituted phenylpropiolic acids in terms of synthon formation. Chapter 4 describes all possible difluoro and dichlorophenylpropiolic acids. It is also verified the necessity of the C–H···O interactions formed by the ortho C–H group on the formation of the catemer in phenylpropiolic acids.

Since the *syn-anti* catemer is mostly restricted to the family of cubane and phenylpropiolic acids, an attempt was made to design new carboxylic acids which might show this motif. After gaining some leads from the CSD, a few phenylpyruvic acids were synthesized and their crystal structures determined and analysed. Chapter 5 highlights the role of the substituent on the formation of robust synthons in phenylpyruvic acids.

Occurrence of multiple molecules in the asymmetric unit ($Z'>1$) is a very interesting topic of research in the context of polymorphism. Appendix-I correlates the high Z' structures with polymorphism in a study of pentafluorophenol.

Crystallographic details and hydrogen bonding parameters of the crystal structures discussed in this thesis are listed in Appendix-II. A full list of atomic coordinates has been deposited with the University of Hyderabad and can be obtained from Prof. Gautam R. Desiraju (gautam_desiraju@yahoo.com).

Hyderabad *Dinabandhu Das*

February 2006

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CHAPTER ONE

CRYSTAL ENGINEERING AND CARBOXYLIC ACIDS

1.1 Introduction

Organic synthesis can be divided into two classes: covalent synthesis [1.1] and non-covalent synthesis [1.2]. Covalent synthesis is concerned with the formation and breakage of covalent bonds and non-covalent synthesis is performed utilizing non-covalent bonds. The chemistry of the second class is known as supramolecular chemistry. According to Lehn's analogy, supramolecular chemistry [1.3] is defined as "chemistry beyond the molecule". In contrast to molecular chemistry, which is predominantly based on the covalent bonding of atoms, supramolecular chemistry is based on intermolecular interactions [1.2, 1.4], i.e. on the association of two or more building blocks which are held together by intermolecular bonds. In this context, crystals might be regarded as the product of supramolecular synthesis.

Crystal engineering, which is one aspect of supramolecular chemistry, took birth more than 50 years ago while Schmidt was working with the photochemical reactions of some cinnamic acids and amides [1.5]. Over this period it was nourished and developed by different groups of scientists. Now it is a well matured and highly interdisciplinary field of science bridging chemistry with biology and physics. The significance of crystal engineering is different in different disciplines. To the chemist, crystal engineering is recognized as a way to exploit non-covalent interactions to assemble molecules in solid supermolecules. To the crystallographer, crystal engineering provides the push and additional motivation to improve methods of data collection, data storage, data mining and most importantly, to develop friendly and portable methods for direct structure determination from powder diffraction data. To the biologist, crystal engineering is the investigation of interactions between biological matrices and crystalline phases. To the

theoretician, crystal engineering is a challenge to predict crystal structures from molecular structures. In light of this broadened scope a more general and refined definition for crystal engineering was given by Desiraju as "the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties" [1.6]. Therefore the understanding of intermolecular interactions is as important to crystal engineering as the understanding of the covalent bond is to molecular chemistry.

1.2 Intermolecular interactions

Intermolecular interactions might be considered as supramolecular glue to assemble the molecules. These interactions in organic compounds can be classified as isotropic and anisotropic. Isotropic medium-range forces define molecular shape, size and close-packing. These include C···C, C···H and H···H interactions. Anisotropic, long range forces are electrostatic and involve heteroatomic interactions. From various studies employing the Cambridge Structural Database (CSD) [1.7] various important anisotropic intermolecular interactions have been characterized. These include hydrogen bonding, X···X, X···O, X···N (X= F, Cl, Br and I), S···S, S···O, S···N and π-π interactions. Among these interactions, hydrogen bonding is the most useful and reliable one for supramolecular construction. The definition and the characteristic geometrical attributes of the hydrogen bond X–H···A–Y have been studied and discussed extensively in the literature [1.8]. On the basis of strength, hydrogen bonds are classified as very strong, e.g., $[F\cdots H\cdots F]^{-}$, $[N\cdots H\cdots N]^{+}$; strong, e.g., O–H···O, N–H···O, O–H···N and weak which include C–H···O, C–H···N. Some important properties of these hydrogen bonds are given in Table 1.

Table 1 Some important properties of very strong, strong and weak hydrogen bonds (according to reference [1.8 (d)])

	Very strong	Strong	Weak
Bond energy (–kcal/mol)	15 – 40	4 – 15	<4
IR ν, relative shift	>25%	5–25%	<5%
Bond length	H–A ≈ X–H	H···A > X–H	H···A > > X–H
D (X···A) range (Å)	2.2 – 2.5	2.5 – 3.2	3.0 – 4.0
d (H···A) range (Å)	1.2 – 1.5	1.5 – 2.2	2.0 – 2.3
θ (X–H···A) range (˚)	175 – 180	130 – 180	90 – 180
Covalency	Pronounced	Weak	Vanishing
Electrostatics	Significant	Dominant	Moderate

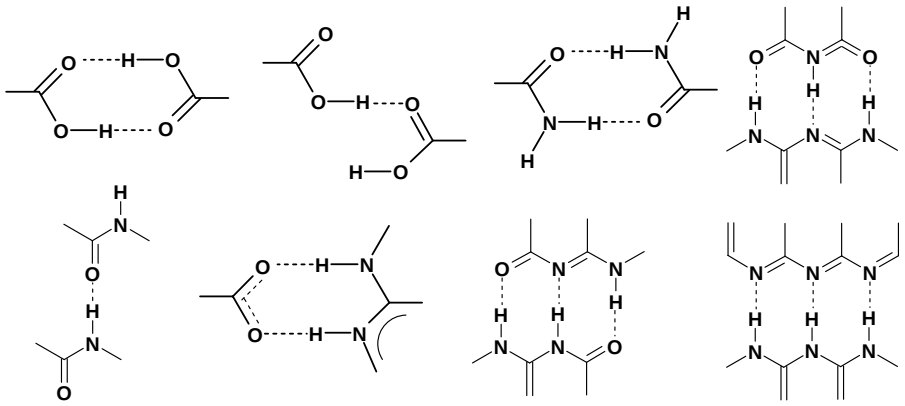
1.2.1 The C–H···O interaction in crystal engineering

The existence of C–H···O interactions was a matter of considerable controversy and dispute for a long time [1.9]. The statistical analysis of neutron diffraction crystal structures by Taylor and Kennard provided conclusive evidence for the existence of C–H···O interactions in crystals [1.10]. These authors showed that C–H···O contacts are electrostatic and that they occur within certain ranges of distance (H···O, 3.0 – 4.0 Å and angle ∠C–H···O, 90˚ – 180˚). Today there is a consensus that C–H···O bonds have significant implications in many diverse areas of structural chemistry [1.11]. These interactions are no longer considered to be an enigmatic phenomenon. Scheiner and co-workers have shown that at long distances (*D* > 3.5 Å) even relatively weak C–H···O interactions are stronger than O–H···O hydrogen bonds due to a shallower dependence of interaction energy on distance [1.12]. Gatti *et al.* have described the fundamental properties of C–H···O interactions through analysis of theoretical and experimental electron densities [1.13]. C–H···O bond strengths often correlate with the acidity of the

hydrogen attached to the carbon atom and therefore methyne and methylene groups are stronger donors than methyl groups [1.14]. This was shown spectroscopically [1.15] and through a variety of computational treatments [1.12]. Wang *et al.* and others have reported that C–H···O hydrogen bonding can play a significant structural role in determining molecular conformations [1.16]. Recently, a few studies report that C–H···O bonds persist in solution, thus driving the structural properties of molecules with biological and pharmaceutical interest [1.17].

1.3 Supramolecular synthons

Analysis and rationalization of crystal packing is a primary activity in crystal engineering. Analysis of an individual crystal structure leads to the identification of intermolecular interactions pertaining to that specific structure. The geometrical properties of intermolecular interactions and their chemical characteristics can be studied reliably by statistical analysis. There is no doubt that the statistical approach to crystal engineering is an insight into the various ways in which the interactions can be grouped together to form substructural units. These substructural units have been variously termed as motifs, building-blocks, patterns, couplings and synthons. The term *supramolecular synthon*, introduced by Desiraju, is defined as "a structural unit within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions" [1.2(a)]. Supramolecular synthons are of significance in crystal engineering because they are the smallest structural units which contain all the information inherent in the recognition events through which molecules assemble into supermolecules. The aim of crystal engineering is to control the way supramolecular synthons are assembled in the solid state, in order to achieve a designed structure possessing desired properties [1.6]. Scheme 1 shows some representative supramolecular synthons.



Scheme 1. Some representative supramolecular synthons.

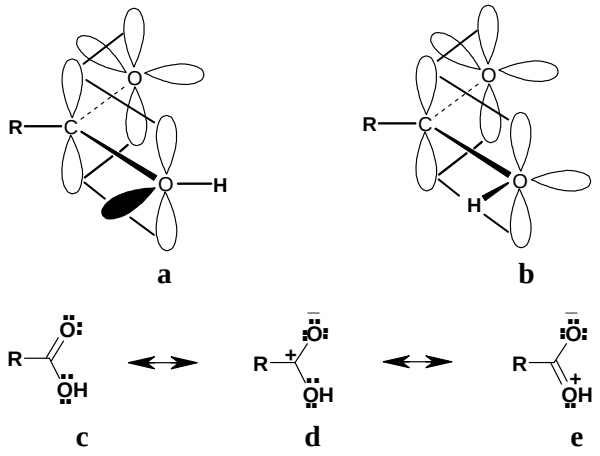
1.4 The carboxyl group and its conformations

Carboxyl groups, consisting of a hydrogen bond donor and an acceptor, are among the best investigated hydrogen bond functionalities in crystal engineering [1.18]. This group occurs in two distinct conformations, *synplanar* (**I**) and *antiplanar* (**II**). The s*ynplanar* conformation is more stable (≈ 2 kcal mol^{-1}) than the *antiplanar* conformation [1.19]. The three dimensional representations **a** and **b** correspond to the *syn* (**I**) and *anti* (**II**) forms respectively. The stability of these conformations can be explained by electronic effects. Two types of electronic effects can be proposed, namely primary and the secondary [1.20].

I **II**

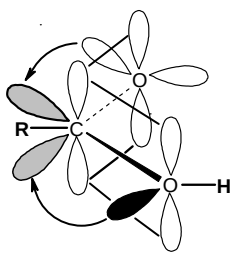
The primary electronic effect is effectively due to the delocalization of electron pairs between the hydroxyl oxygen and the carbonyl group as shown by the resonance structures **c**, **d** and **e**. The primary electronic effect can be viewed as the result of $n \rightarrow \pi^*$

interactions. This effect does not make any energy difference between the two conformations of the carboxyl group.

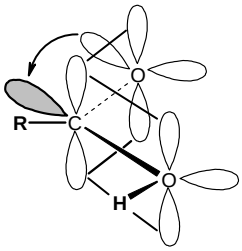


The secondary electronic effects in carboxyl group are essentially similar to the anomeric effect [1.21] involving the $n \rightarrow \sigma^*$ interaction. The carbonyl oxygen in both the *syn* (**a**) and *anti* (**b**) conformation of the carboxyl group has an electron pair oriented antiperiplanar to the C–O(H) bond, and an $n \rightarrow \sigma^*$ interaction should therefore exist because this electron pair orbital can overlap with the antibonding orbital (σ^*) of the C–O(H) bond. In the *syn* conformation (**a**), there is the possibility for another anomeric effect because the hydroxyl oxygen has an electron pair which is oriented antiperiplanar to the C–O σ bond of the carbonyl group. This electron pair orbital can therefore overlap with the antibonding orbital (σ^*) of that bond. Thus in the *syn* conformer in addition to the primary electronic effect, there are two secondary electronic effects which are shown in three dimensions by **f** and in two dimensions by **g**. On the other hand in the *anti* conformer there is only one secondary electronic effect as shown in three dimensions by **h** and in two dimensions by **i**. Thus it can be concluded that the greater stability of the *syn* conformation (**I**) in comparison with the *anti* conformation (**II**) in the carboxyl group

would be due to this secondary electronic effect (anomeric effect). Accordingly **I** is the only conformation present in most carboxylic acid crystal structures.



f



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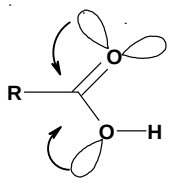

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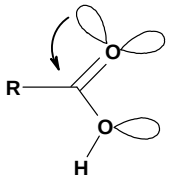
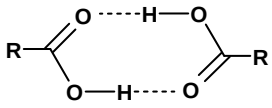


i

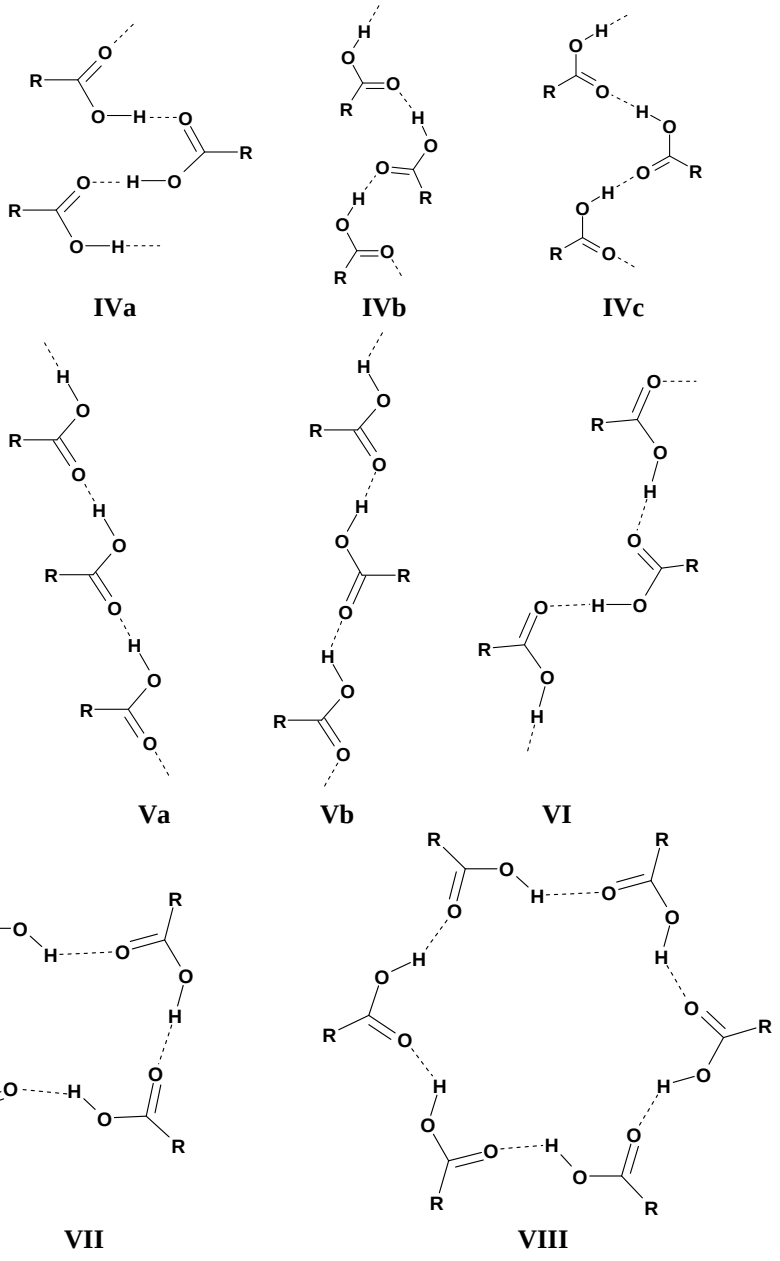
A computational study of acetic acid showed that **I** is the most stable conformer in the gas phase by 5.1 kcal mol^{-1} [1.22]. However in aqueous solution the *anti*-form (**II)** is stabilized. This is because the dipole moment of **II** is larger than **I**. The larger dipole moment of the anti-conformer (**II**) gives rise to a larger electrostatic contribution which leads to a stronger interaction with water molecules of the solvent [1.23]. Therefore the solvation energy of **II** is larger by ≈ 3.4 kcal mol^{-1} than **I**. As a result, the *anti*-form is only about 1.7 kcal mol^{-1} less stable than the *syn* form. However, in the crystal structure of some 4-substituted phenylpropiolic [1.24] and cubanecarboxylic acids [1.25], conformations **I** and **II** co-exist; in a very few acids only conformation **II** is present [1.26]. This may be because of inter or intramolecular interactions which can compensate for the ≈ 2 kcal mol^{-1} destabilization energy of **II**.

1.5 Synthons formed by the carboxyl group



III

Since the carboxyl group possesses a hydrogen bond donor as well as an acceptor site, the functionally unelaborated carboxylic acids can associate via O–H···O hydrogen bonds to the zero-dimensional dimer (**III**) or the one-dimensional catemer [1.18]. The term *catemer* was suggested first by Berney to describe an infinite chain of molecular units which are closely linked [1.27]. In this thesis the term *catemer* is used to describe a chain of carboxyl groups linked to each other by O–H···O bonds. Since the carboxyl group occurs in two distinct conformations, *syn* (**I**) and *anti* (**II**), three types of catemer can be formed i. e. *syn-syn* (**IV**), *anti-anti* (**V**) and *syn-anti* (**VI**). Leiserowitz has showed that the *syn* conformation (**I**) can be arranged in three distinct packing modes (**IVa-IVc**) [1.18]. In the case of the *anti* conformation (**II**), the carboxyl group can be associated in two types of arrangements, **Va** and **Vb**. The carboxyl group can also be linked with a combination of *syn* (**I**) and *anti* (**II**) conformers to form the *syn-anti* catemer motif (**VI**). Functionally unelaborated carboxylic acids can also form the tetramer (**VII**) and hexamer (**VIII**) synthon [1.28]. All the synthons formed by carboxyl groups are shown in Scheme 2.



Scheme 2. Synthons formed by carboxyl groups.

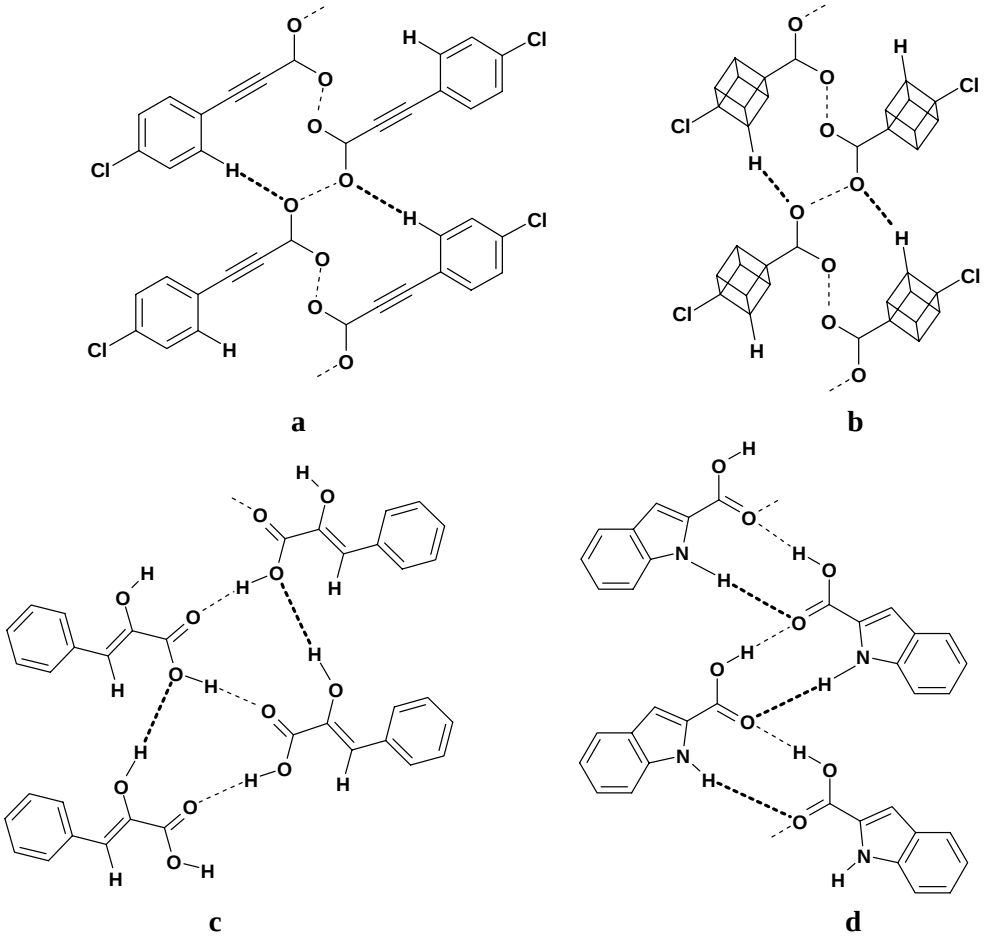
1.6 Carboxylic acids in the CSD

The CSD (Version 5.27, November 2005, total entries 3,55,064) [1.7] was searched to evaluate the number of crystal structures containing the synthon **III-VIII** formed by carboxylic acids. A total of 11020 hits was obtained for the carboxyl group. These hits contain 4043 entries of metal atom free, non-ionic, single-residue organic carboxylic acids. Of these, 1338 hits (33.09%) were the *syn-syn* dimer (**III**). A manual search of the remaining 2705 compounds revealed 98, 5 and 11 hits for the *syn-syn* (**IV**), the *anti-anti* (**V**) and the *syn-anti* (**VI**) catemers respectively. One *syn-anti* catemer was observed in an organometallic acid (Refcode GADKUS) [1.29]. In the remaining 2590 hits, the carboxyl group is hydrogen bonded to other basic groups or is exclusively intramolecularly hydrogen bonded or forms closed *n*-mers ($n \neq 2$) (**VII** and **VIII**). This statistical study of crystal structures in the CSD showed that the dimer motif (**III**) occurs in 95% of monocarboxylic and in 85% of dicarboxylic acids when there is no other hydrogen bonding groups present. In a nonrestricted dataset, where competing functional groups are present, only 33% of the carboxylic acid dimer (**III**) and 2.8% of the catemer motif (**IV-VI**) are observed. This is consistent with an earlier study [1.30] which concluded that the cyclic dimer predominates in monofunctional acids.

1.7 Mimicry of C–H···O, O–H···O and N–H···O interactions

Although the C–H···O interaction is weaker than its N–H···O or O–H···O counterparts, it can sometimes play a similar role in crystal packing [1.31]. There are a few crystal structures where the C–H···O hydrogen bonds, formed by highly activated C–H groups, are essentially identical to the N–H···O or O–H···O hydrogen bonds [1.32]. The similar role played by C–H···O, O–H···O and N–H···O hydrogen bonds are exemplified by the crystal structures of 4-chlorophenylpropiolic [1.24(a)], 4-chlorocubanecarboxylic [1.25(b)], phenylpyruvic [1.33] and indole-2-carboxylic acid [1.34]. In all these

structures, the carboxyl group forms the catemer synthon. In the first two acids, this catemer is stabilized by C–H···O interactions donated by the ortho C–H and cubyl C–H group respectively. In phenylpyruvic acid and indole-2-carboxylic acid, equivalent support is provided by the corresponding O–H···O and N–H···O hydrogen bonds (Scheme 3).



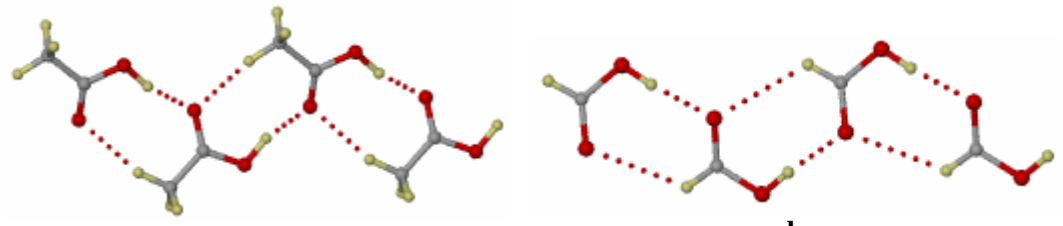
Scheme 3. O–H···O catemer in carboxylic acids. The catemers are stabilized by the supporting interactions, C–H···O in **a** and **b**, O–H···O in **c**, and N–H···O in **d** are shown in bold.

Activation of the C–H group may strengthen the C–H···O hydrogen bond. However, the C–H group in phenylpropiolic acids is already activated to an extent due to the presence of the acetylene bond adjacent to the C–H group. Therefore further activation or deactivation by the substituent is not so important for the formation of the C–H···O contact. Similarly in the cubanecarboxylic acids, the C–H activation by the cubyl skeleton (pKa~38) is itself sufficient to support the requisite C–H···O interaction.

1.8 Packing of carboxylic acids

The crystal packing of the carboxylic acids has been studied extensively by Leiserowitz [1.18] and by others [1.35]. Among all the patterns (**III-VIII**) formed by the carboxyl group, the cyclic acid dimer **III** is the most abundant hydrogen bonded motif [1.30]. This could indicate that this dimer corresponds to the lowest energy. But catemer formation is expected to occur more frequently in enantiomeric acids [1.36] where centrosymmetry is not possible. Similarly, the formation of the dimer is difficult in sterically hindered acids such as the 2,6-disubstituted benzoic acids [1.37]. Leiserowitz has mentioned that the adoption of the catemer motif depends on the nature of the residue R of R-CO_2H, where non-bulky R group prefers to form the catemer [1.18].

Motif **IVa** is unfavorable due to lone pair-lone pair repulsion of carbonyl and hydroxyl oxygen atoms. This motif is not observed in crystal structure of carboxylic acid. Motif **IVb** is observed in most of the acids which form the *syn-syn* catemer like formic, acetic acid [1.38] (Fig. 1). Motif **IVc** is found in some chiral acids [1.36] and also in α-oxalic acid [1.39].



a **b**

Fig. 1. *syn-syn* Catemer in (**a**) acetic acid and (**b**) formic acid. Note the C–H···O interactions which stabilize the catemer synthon **IVb**.

One of the most interesting phenomena in the packing of the carboxylic acids is the occurrence of rare *syn-anti* catemer synthon (**VI**). This synthon was noticed first in the crystal structure of 1,4-cubanedicarboxylic acid in 1987 by Ermer [1.25(a)]. Later this synthon was observed in 4-substituted phenylpropiolic [1.24] and other cubanecarboxylic acids [1.25(b)] in our laboratory. Recently Fronczek observed this synthon in 3-(ferrocenylcarbonyl)propionic acid [1.29]. Even among catemers, the *syn-anti* version is very uncommon indeed, being restricted to cubanecarboxylic acids and phenylpropiolic acids. Analysis of the *syn-anti* catemer structures, present in the literature, showed that synthon **VI** is stabilized by proximal C–H···O interactions (Fig. 2).

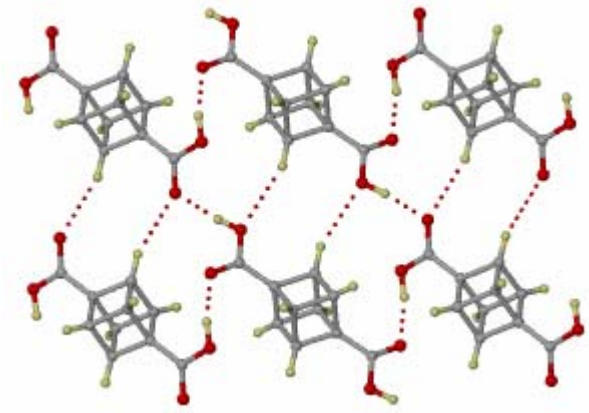
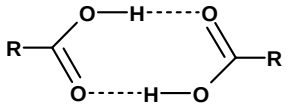


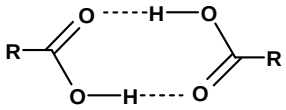
Fig. 2. Rare *syn-anti* catemer synthon **VI** in 1,4-cubanedicarboxylic acid. Note the supporting C–H···O interactions which stabilized the synthon **VI**.

Theoretical calculations for formic acid at the STO-3G level showed that the catemer motif represents the hydrogen bond arrangement with the lowest energy [1.40]. Similar calculations on acetic acid, which also forms a catemer motif in the solid phase [1.41], at different basis set levels gave similar results and showed that the catemer motif is stabilized through additional C–H···O hydrogen bonds [1.42]. Recently the lattice energies for the crystal structures of small monocarboxylic acids were calculated based on an ab initio based multipole model of the interatomic and intermolecular potential [1.43]. There are not substantial energetic differences between structures with the dimer and those with the catemer and the authors concluded that crystal packing and steric interactions of the other functional groups play a major role in determining the energy of the crystal structures. Therefore rationalization of the *syn-anti* catemer is not easy in general. While the factors that lead to catemer or dimer formation in some benzoic acids have been discussed in terms of intermolecular interactions [1.44], little has been said in terms of substituent effects for any acid. In the forthcoming chapters I have tried to explain this phenomenon in a particular family of carboxylic acids, namely the phenylpropiolic acids.

1.9 Order and disorder in the carboxyl group



IX



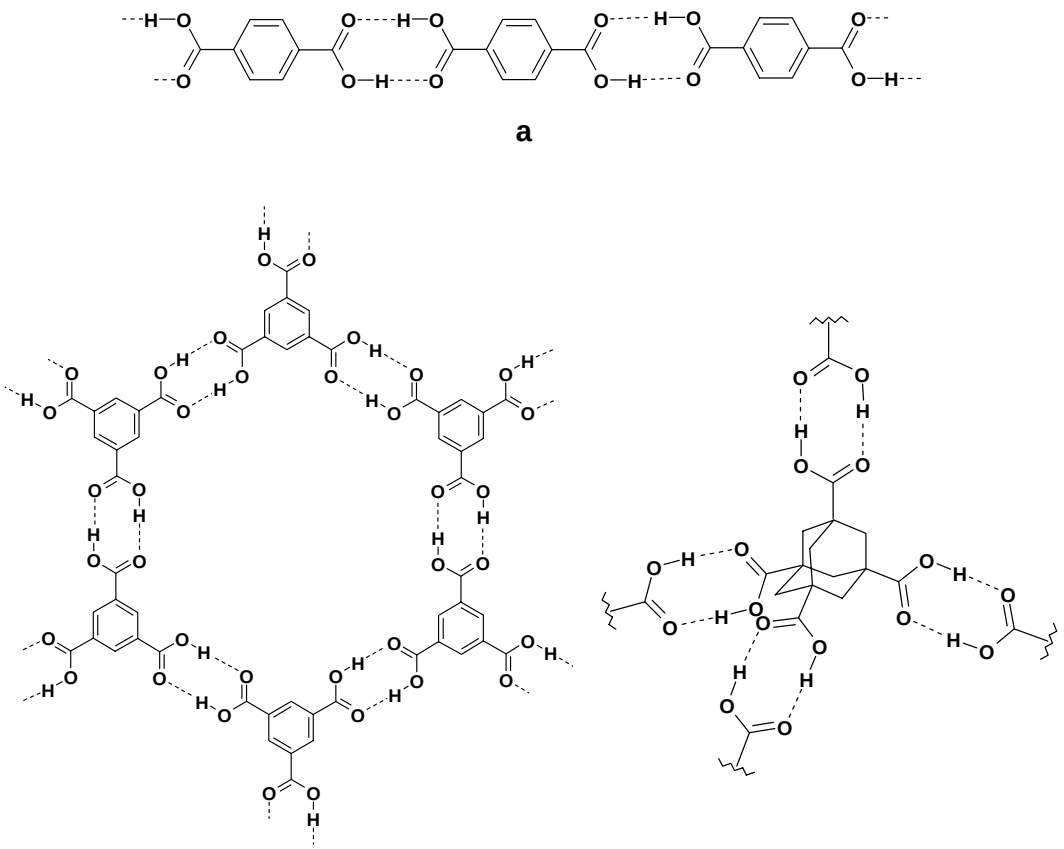
X

An interesting aspect of the structures of carboxylic acids is the presence of varying degrees of disorder of carboxyl group. In the crystal, this is manifested as the existence of both forms **IX** and **X** for the dimer. In general, disorder of a hydrogen

bonded system depends upon various factors such as: (i) the distance between donor and acceptor; (ii) the environment about the hydrogen bond; (iii) the molecular conformation and (iv) the temperature. This disorder may be either static or dynamic. Leiserowitz has mentioned that in static disorder no proton transfer occurs across the O–H···O bond [1.18]. Static disorder was also discussed by Dieterich, Paul and Curtin who were able to linearly correlate the differences in the C–O lengths with differences in the C–C–O angles in aromatic carboxylic acids [1.45]. In the case of dynamic disorder, the hydroxyl proton is delocalized; either the proton is centrally situated in a symmetric O–H–O bond and the C–O bonds of the carboxyl group are in a state of resonance, or the proton undergoes rapid oscillations across the O–H···O bond accompanied by interconversion between the carbonyl C=O and hydroxyl C–O(H) bonds. Disorder of the proton in the carboxylic acid dimer is very common and it manifests as equal lengths of the carboxyl and carbonyl C–O distances. One can imagine a tendency towards disorder of the carboxyl group based on the following two criteria: (i) the neighbouring contacts of the carbonyl and hydroxyl O atoms are of a similar nature and/or (ii) the surroundings of the carbonyl and hydroxyl O atoms may be dissimilar, yet the lattice energy difference between the two orientations (**IX**) and (**X**) of the carboxyl dimer is negligible.

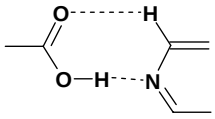
1.10 Utilization of the carboxyl group in crystal engineering

Carboxylic acids are used as important building blocks in crystal engineering to design different architectures [1.46]. The dimer synthon **III** may be used to assemble a variety of supermolecules. For example, terephthalic acid forms a one-dimensional ribbon structure [1.47], trimesic acid with its three fold molecular symmetry forms a two-dimensional hydrogen bonded honeycomb network [1.48] and adamantane-1,3,5,7-tetracarboxylic acid with its tetrahedrally disposed carboxyl functionality forms a diamondoid network [1.49] (Scheme 4).



a **b** **c**

Scheme 4. (a) Terephthalic acid forms one-dimensional tape. (b) Trimesic acid forms a two-dimensional honeycomb network structure with dimer supramolecular synthons. (c) Adamantane-1,3,5,7-tetracarboxylic acid forms diamondoid network structure with robust carboxylic acid dimer synthons.



XI

The carboxylic acid is a good co-crystallizing agent in combination with a suitable N-containing heterocycle and it is widely used in crystal engineering to obtain desirable architectures [1.50]. Synthon **XI** is a very common motif in molecular complexes of carboxylic acids.

Carboxylic acids are also used in the design of host-guest system. Jetti *et al.* have reported the utility of 4-tritylbenzoic acid as a two-component host to obtain wheel and axle adducts with different aromatic guests [1.51]. Kolotuchin *et al.* have used trimesic acid to design new host-guest materials [1.30 (a)]. Enclathration and desolvation of xylene isomers by a dicarboxylic host is described by Beketov [1.52]. In all these cases the carboxylic acids form synthon **III**.

1.11 Nucleation and polymorphism

It is obvious that without a crystal, there is no crystal engineering. Therefore the value of X-ray quality crystals is enormous to the crystal engineer. Crystal growth is a fascinating field of research. Among the various processes known for crystallization, slow evaporation of the solvent is the most popular. The factors which may influence this crystallization process are (i) solvent polarity, (ii) concentration, (iii) temperature, (iv) additives and (v) seeds [1.53]. However, little is known about the mechanism of crystallization. Recently, Banerjee *et al.* have illustrated the mechanism of crystallization in context to the crystallization of sodium saccharinate from aqueous solution [1.54]. Davey *et al.* have tried to correlate the crystallization process from the solution through crystal nucleation [1.55]. The idea of crystal nucleation is that during crystallization from solution, the nuclei or growth unit occur first and this then evolves to the final crystal.

But it is difficult to understand the correlation between the growth unit and the crystal structure. Nucleation theory brings the idea of polymorphism which is defined as the existence of two or more different crystal structures for the same compound. Ostwald made a fundamental contribution in this respect [1.56]. Ostwald's law of stages states that "from the fluid state, a crystallizing system evolves to equilibrium in stages, each stage representing the smallest possible change in free energy. Thus least stable polymorph should appear first, transform to the second least stable polymorph and so on until the most stable polymorph emerges." This means more than one minimum is present on the potential surface. One can imagine that each minimum represents one stage and each stage is one polymorph. But the main difficulty is in isolating these stages. Today the methods of studying polymorphism reminds one of McCrone's provocative statement that, "every compound has different polymorphic forms, and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound" [1.57].

Structures with multiple molecules in the asymmetric unit ($Z'>1$) are interesting in the context of polymorphism. The occurrence of polymorphism in this regard highlights the importance of kinetic and thermodynamic stability of the observed crystal structures [1.58]. Sometime high Z' may be the indication of incomplete or interrupted crystallization [1.59]. The high Z' structure may be one of the metastable states which is somehow kinetically locked. The more stable form may evolve by lowering the Z' where symmetry is more neatly expressed.

CHAPTER TWO

EFFECTS OF THE SUBSTITUENT ON THE FORMATION OF THE CATEMER IN SOME 2- AND 3-SUBSTITUTED PHENYLPROPIOLIC ACIDS

2.1 Introduction

Prediction of crystal structure from molecular structure of a small (< C_{20}) molecule is a major challenge in crystal engineering today. In 1994 Gavezzotti raised a question, "Are crystal structures predictable?" [2.1]. Today, at the beginning of 2006 a general answer to this question is still elusive. Despite significant activity in the field of Crystal Structure Prediction (CSP) [2.2], there is no software available that can reliably predict the packing in simple molecular crystals. The main difficulty in predicting the crystal structure from the molecular structure is that it is not always easy to describe the molecular aggregation via a sequential establishment of intermolecular interactions [2.3]. Molecular aggregation is a natural process which depends upon the complementary character of various functional groups [2.4]. The same functional groups are effectively recognized in different ways. The carboxyl group which is the most common functional group in the area of crystal engineering is a typical example. The carboxyl group recognizes itself in two distinct fashions, one is the cyclic dimer and the other is the infinite catemer chain [1.18]. The number of O–H···O hydrogen bond per carboxyl group is same in both motifs and this what makes CSP difficult in this case.

The usual practice in crystal engineering is the analysis of intermolecular interactions in a family of structures with the aim of understanding crystal packing [1.6]. Kitaigorodskii's close packing model [2.5] is very useful in this context. But the relevant question is "what is the driving force in crystal packing, specific intermolecular interactions or just the mutual recognition of molecular shape?" Since molecules always try to pack as closely as possible in the crystal, it is difficult to answer this question by

looking at just one crystal structure. In fact, both intermolecular interactions and molecular shapes guide crystal packing. In aromatic hydrocarbons, which do not have strong donor or acceptor groups, packing of the molecules depends upon shape factors [2.6]. To describe the packing of fused aromatic hydrocarbons Gavezzotti and Desiraju have mentioned, "…the more symmetrical the shape, the higher the packing energy and the packing coefficient. There are no exceptions to this rule" [2.7]. However in molecules that contain strong donor and acceptor groups like OH, NH_2 or COOH, the packing of molecules depends upon intermolecular interactions as well as molecular shape [1.25(b)]. When the intermolecular interactions interfere with one another, unexpected crystal structures could result [2.8] and the molecule to crystal structure relationship does not hold, as might have been expected from a functional group approach. For example, in the crystal structures of 2- and 3-aminophenols (Fig. 1), synthon interference leads to the formation of unexpected N–H···π hydrogen bonds [2.9]. This indicates that the functional group approach towards the understanding of crystal structure is not generally applicable. This lack of applicability arises because functional groups are of molecular origin whereas the crystal structure features are supramolecular in nature.

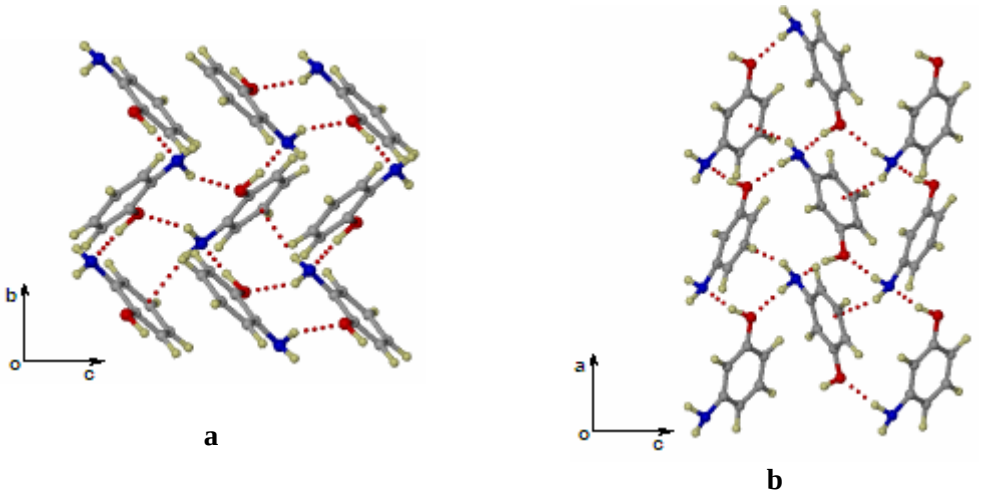
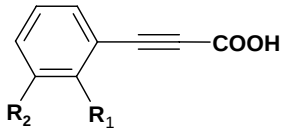


Fig. 1. Hydrogen bond in (**a**) 2-aminophenol and (**b**) 3-aminophenol

Functional groups exert both steric and electronic effects on the structure and reactivity [2.10], but separating out these two effects is difficult. In crystal engineering, steric and electronic effects are synonymous with geometrical and chemical effects on crystal packing. Geometrical factors in organic compounds can be classified as molecular shape, size and close packing [2.5]. On the other hand, chemical factors include ionic forces, strong and weak hydrogen bonds, and other weak forces whose strengths are related to the donor atoms acidity and acceptor group basicity. To summarise, observed crystal structures are the result of an interplay between various geometrical and chemical factors [2.11]. However, by just looking at a crystal structure it is not possible to deduce whether geometrical or chemical influences are responsible for any particular intermolecular interaction. To critically examine this question, one needs ideally to look at an entire series of crystal structures so that chemical and geometrical effects of the substituent may be monitored one at a time, to the exclusion of other effects. This chapter highlights the role of the substituents in the formation of catemer or dimer in some 2- and 3-substituted phenylpropiolic acids (Scheme 1).



1a. R_1 = F, R_2 = H
1b. R_1 = Cl, R_2 = H
1c. R_1 = Br, R_2 = H
1d. R_1 = I, R_2 = H
1e. R_1 = CH_3, R_2 = H
1f. R_1 = OCH_3, R_2 = H
1g. R_1 = CF_3, R_2 = H

2a. R_1 = H, R_2 = F
2b. R_1 = H, R_2 = Cl
2c. R_1 = H, R_2 = Br
2d. R_1 = H, R_2 = I
2e. R_1 = H, R_2 = CH_3

Scheme 1. Phenylpropiolic acids described in this chapter.

2.2 *syn-anti* Catemer in 2- and 3-substituted phenylpropiolic acids

The *syn-anti* catemer is the common structural motif in 2-substituted phenylpropiolic acids. Except acids **1d** and **1g** all the 2-substituted acids form the *syn-anti* catemer. In the case of 3- substituted acids only **2a** forms this synthon. In the crystal structures of acids **1a, 1c, 1f** and **2a** the carboxyl groups are disordered with almost equal C–O bond lengths (Table 1), although the environments around the two oxygen atoms are quite different. In the present study it is difficult to ascertain the origin of the disorder of the carboxyl group.

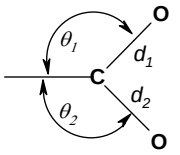


Table 1 C–O bond length and ∠C-C-O of the carboxyl group in **1a**, **1c**, **1f** and **2a**:

Acid	d_1(Å)	d_2(Å)	θ_1(˚)	θ_2(˚)
1a	1.258	1.269	119.14	118.56
1c	1.266	1.268	118.56	118.54
1f	1.265	1.272	118.96	118.13
2a	1.252	1.266	119.54	118.33

The catemers are generated by a combination of inversion centers, and translations and may be considered to be primary structural motif in acids **1a**, **1b**, **1c**, **1e**, **1f** and **2a**. These motifs are stabilized by the proximal C–H···O interactions. The catemer sub-structures in these acids are nearly identical but they are arranged in distinctive ways to generate the secondary structures. In acid **1a**, C–H···F interactions are found between 2_1-related molecules (Fig. 2). In acid **1c**, the primary motifs acquire extra stabilization from intralayer C–H···Br interactions and the secondary structures are formed by the connection of adjacent catemer chains with weak C–H···π interactions (Fig. 3). Tertiary structures are formed in **1a** and **1c** by stacking of the catemer layers along the short axis direction.

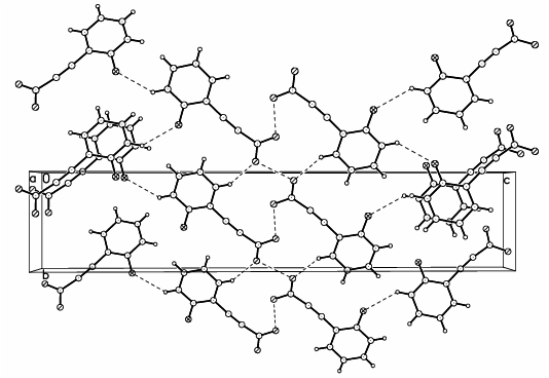


Fig. 2. Catemer motif in the crystal structure of **1a**, viewed down [100]. Notice the supporting C–H···O and C–H···F hydrogen bonds. The H-atoms of the carboxyl groups are omitted for clarity.

In **1f** these layers are arranged like a parallel staircase which is stabilized by C–H···O interactions between the layers. The staircases are arranged in a zigzag fashion leading to close packing in three dimensions (Fig. 4). In acid **2a**, secondary structures are generated by the interconnection of inversion related molecules by C–H···F interactions forming a sheet (Fig. 5). These sheets are stacked in three dimensions along the [110] direction to form the tertiary structure.

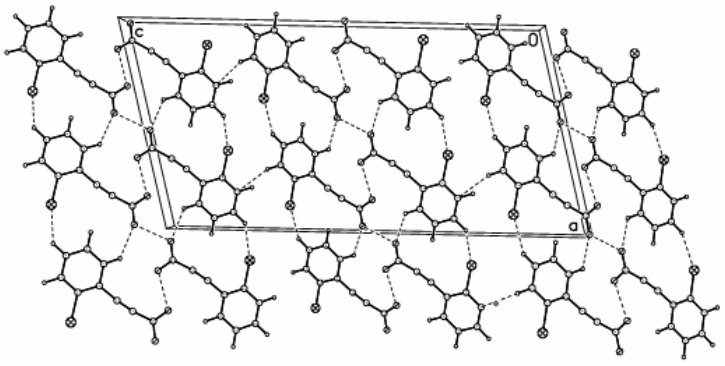


Fig. 3. Catemer motif in the crystal structure of **1c**, viewed down [010]. Notice the supporting C–H···O bond. The H-atoms of the carboxyl groups are omitted for clarity.

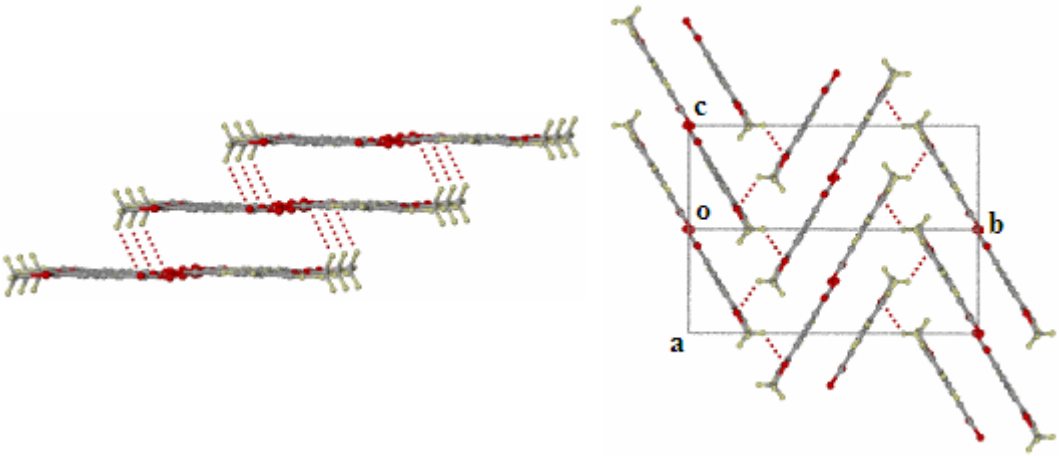


Fig. 4. (a) Staircase arrangement of catemer layers in **1f**. Note the C–H···O interactions between the layers. (b) Packing of the catemer layers in zigzag fashion in **1f**. Note the C–H···O interactions.

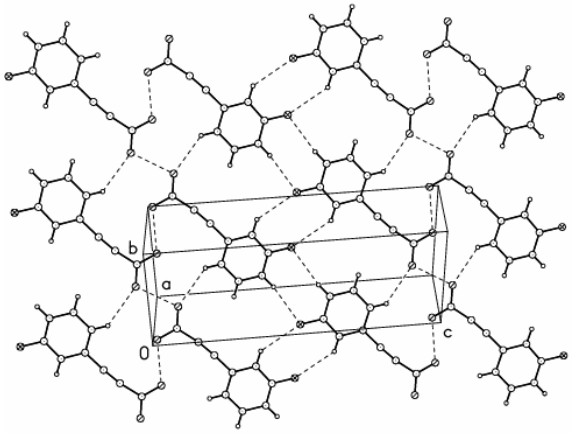


Fig. 5. Layer arrangement of the catemer motif in the crystal structure of **2a**, viewed down [100]. Notice the C–H···F hydrogen bonds which connect the catemer chains. The H-atoms of the carboxyl groups are omitted for clarity.

Acid **1b** crystallizes in space group $P2_1$ with $Z'=2$. In both the symmetry independent molecules, the carboxyl group is ordered. Aggregation of these molecules

results in an ordered *syn-anti* catemer chain as the primary structural motif (Fig. 6a). Translationally related anti-conformational molecules (Fig. 5b) are linked by C–H···Cl interactions (3.57 Å, 2.78 Å, 128˚). The catemer layers are connected by C–H···Cl interactions (3.78 Å, 2.82 Å, 168˚) in zigzag fashion along the [010] direction (Fig. 6b).

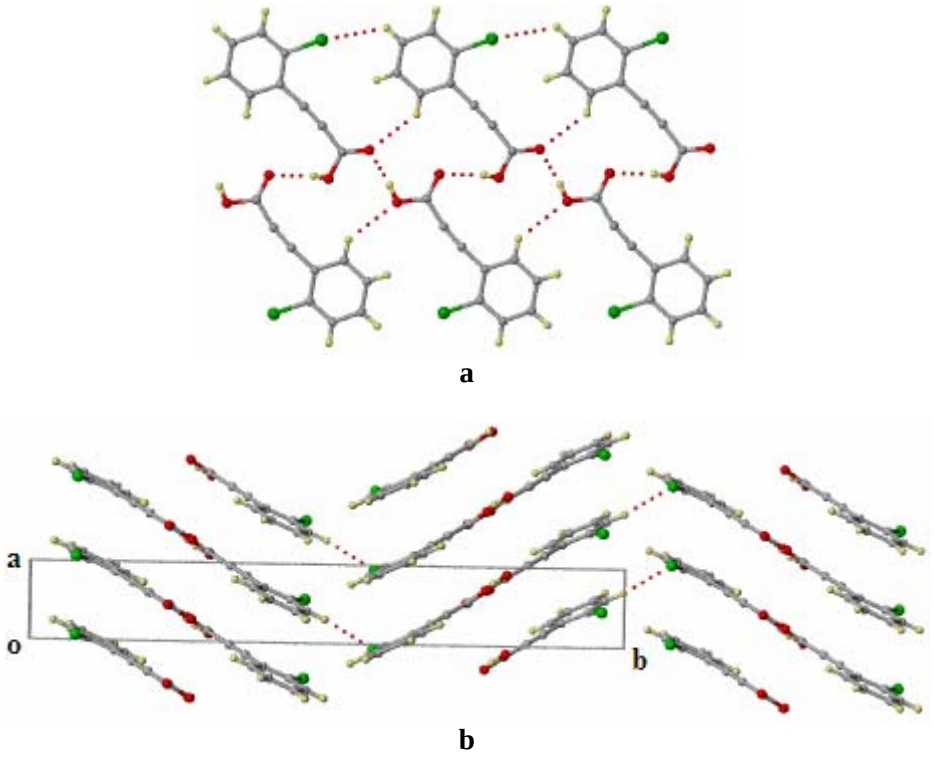


Fig. 6. (a) Ordered *syn-anti* catemer chain in **1b** and (b) Zigzag arrangement of the catemer chains along [010] direction.

2.2.1 *syn-syn* Dimer in 2-methoxyphenylpropiolic acid, 1f. A case of polymorphism in a carboxylic acid

Polymorphism is a common phenomenon in small organic molecules [2.12] but is not so common in simple carboxylic acids. In the CSD [1.7] only 51 functionally unelaborated polymorphic carboxylic acids are reported. Recently Jones *et al.* have observed a second form of maleic acid [2.13]. Oxalic [2.14] and tetrolic acids [2.15] are

known to form both the dimer and the catemer structures. In the family of phenylpropiolic acids, **1f** generates both the dimer and catemer structure. The catemer is quite similar to that found in acids **1a**, **1b** and **1c** and is easily obtained from several solvents like EtOAc, CH_3CN, *p*-xylene, mixture of hexane and EtOAc and mixture of CH_3CN and CCl_4. The dimer form of **1f** is obtained by crystallization from aqueous ethanol. In this case, the carboxyl group is ordered as is reflected from the bond distances (C=O 1.227 Å, C–O 1.311 Å). The methoxy groups provide the C–H···O contacts (2.38 Å, 3.38 Å, 153°) to link the inversion related dimers to form a two dimensional tape. These tapes are arranged in a nearly perpendicular fashion in the third dimension (Fig. 7).

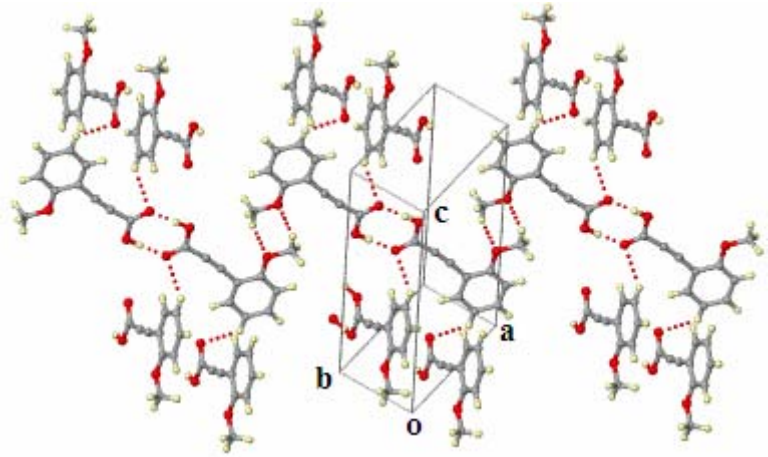


Fig. 7. Packing diagram of dimer form of **1f**. Note the O–H···O and C–H···O contacts.

2.2.2 Unusual crystal packing in 2-methylphenylpropiolic acid, 1e

Acid **1e** crystallizes in space group $P2_1/n$ with $Z'=3$. The carboxyl groups in two of molecules in the asymmetric unit are ordered and the conformations are *synplanar* and *antiplanar*. In the third molecule the proton is disordered over both the oxygen atoms with 50% occupancy in the *syn* and *anti* positions. Therefore in the crystal structure of **1e**, two types of catemer chains are observed, ordered and disordered. The packing of these catemer layers is very unusual. The disordered *syn-anti* catemer layer is sandwiched

between the two ordered *syn-anti* catemer layers. These layers are connected to each other by C–H···π interactions (2.78 Å, 140˚ and 2.88 Å, 141˚). The triple deckers are arranged in a pseudo-herringbone fashion to generate the overall packing (Fig. 8).

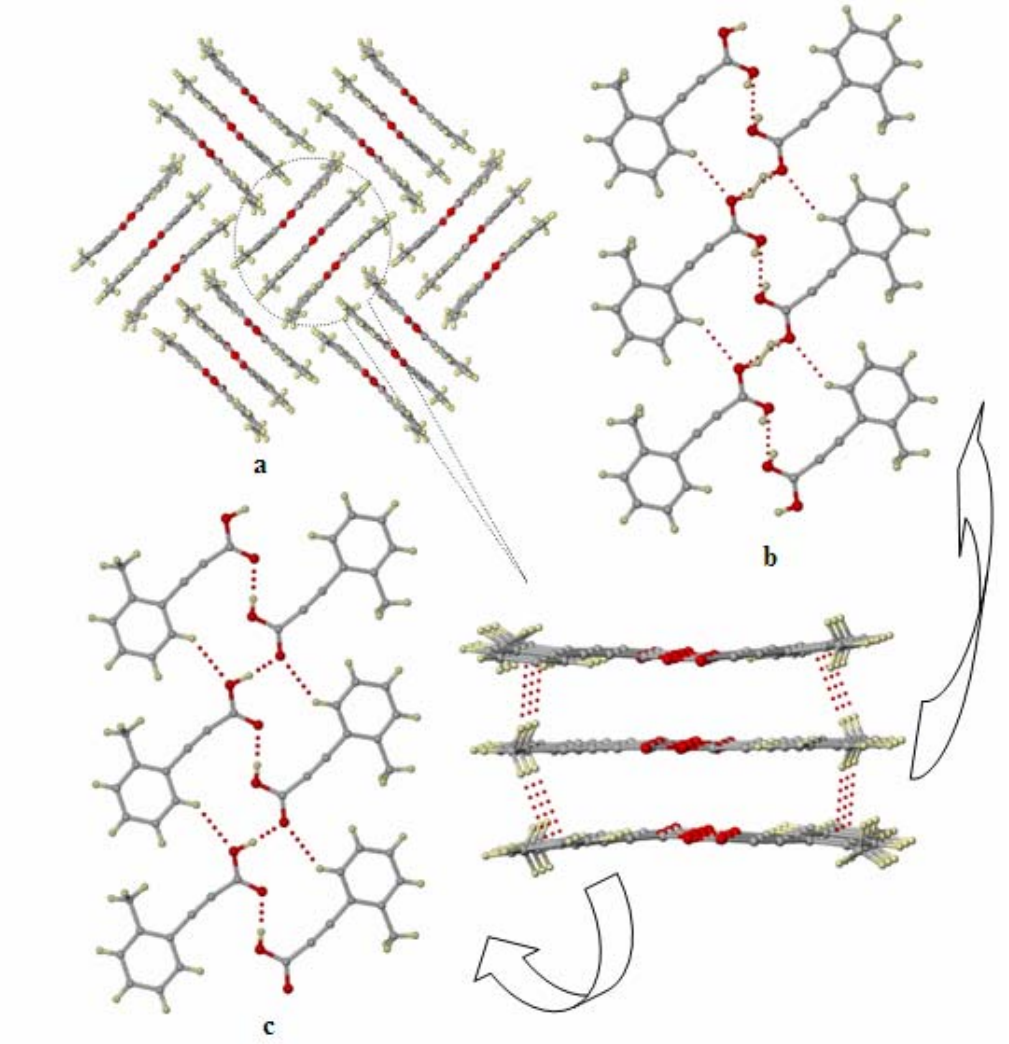
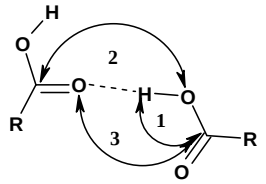


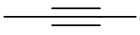
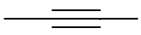
Fig. 8. Packing diagram of **1e**; (a) Triple decker blocks of mixed *syn-anti* catemers, (b) disordered *syn-anti* catemer in the middle layer of the triple decker and (c) ordered *syn-anti* catemer in the upper and lower layer of the triple decker.

2.3 *syn-syn* Catemer in 2-(trifluoromethyl)phenylpropiolic acid, 1g

Acid **1g** forms a *syn-syn* catemer as is observed in formic, acetic and β-tetrolic acids [1.38, 2.15]. The molecules are almost perpendicular to each other along the chain (Fig. 9). Acid **1g** appears in planar hydrogen-bonded arrays *via* glides of axial lengths 7.864 Å. There is an increasing distortion of the geometrical parameters of the hydrogen bond when comparing formic, acetic, β-tetrolic acid and **1g** in that order (Table 2). This distortion may be because of the increasing bulk around the carboxyl group. Adjacent catemer chains in **1g** are connected by C–H···F interactions (2.56 Å, 3.38 Å, 132°).

Table 2. Hydrogen-bond distances (Å) and angles (°) around the carboxyl groups in formic, acetic, β-tetrolic acids and **1g**.



R = H, CH_3,  CH_3 and  Ph (-2CF_3)

Acid	O–H···O	∠C-O-H (1)	∠C=O-(H)O (2)	∠C-O(H)-O(3)
Formic acid	2.58	107	122	114
Acetic acid	2.63	110	133	119
β-Tetrolic acid	2.66	111	136	121
1g	2.70	112	139	132

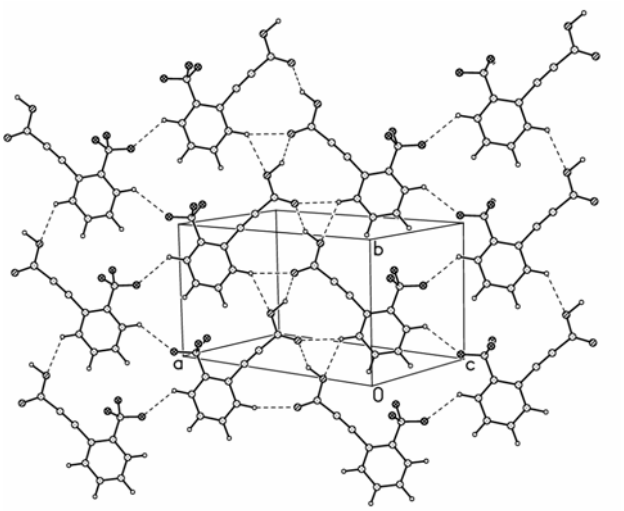


Fig. 9. Ordered *syn-syn* catemer chain in acid **1g**. Note the C–H···F interactions which link the catemer chains in a layer.

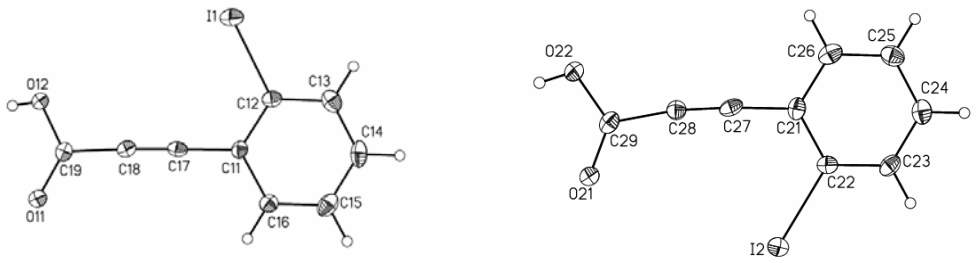
2.4 Cisoid carboxyl dimer in 2-iodophenylpropiolic acid, 1d

The most frequently observed pattern in carboxylic acids is the cyclic acid dimer involving two hydrogen bonded molecules related by a centre of inversion [1.30]. Non-centrosymmetric dimers also arise in resolved chiral acids, where no centrosymmetry is possible. For ortho and meta substitution at the benzene ring, centrosymmetric and non-centrosymmetric acid dimers are synonymous with transoid and cisoid arrangements of the substituent (Scheme 4). From the energetic and close packing point of view, the transoid configuration is the more preferable [2.5], although in principle, both configurations can exist. While the cisoid configuration of the dimer in carboxylic acids is hardly ever reported in the CSD, Patil *et al.* have stated, "In spite of the seeming rarity of the cisoid configuration, it is likely that m-substituted benzoic acids, under suitable conditions, may be induced to crystallize in polymorphic forms composed of acid dimers in the cisoid arrangement" [2.16]. m-Nitrobenzoic acid exists in two crystalline forms [2.17]. In this context, it is surprising to observe the cisoid acid dimer in **1d** which is an

ortho substituted acid. The acid crystallizes in the centrosymmetric space group $P2_1/c$ with $Z'=2$ (**a**, **b)** (Figure 10). These two molecules appear in the crystal structure with significant conformational differences at the carboxyl groups. In molecule **a**, the iodo group (I1) is transoid to the carbonyl oxygen (O11) and in molecule **b**, the iodo group (I2) is cisoid to the carbonyl oxygen (O21). In both the molecules, the carboxyl group is ordered and *synplanar*. The extent of deviation from linearity of the acetylinic bond in molecule **b** is more than that in molecule **a** (**a**: ∠C11-C17-C18 = 179.11˚ and ∠C17-C18-C19 = 176.84˚; **b**: ∠C21-C27- C28 = 176.46˚ and ∠C27-C28-C29 = 171.93˚). Effectively the cisoid dimer in **1d** is formed between two symmetry independent molecules. Screw related dimers are connected by I···O interactions (3.30Å) (Fig. 11).

Transoid Cisoid

Scheme 4



a **b**

Fig. 10. Ortep diagram of the molecules of acid **1d** present in the asymmetric unit. Notice the transoid (a) and cisoid (b) conformation of carbonyl oxygen with respect to iodine in the two molecules. The thermal-vibration ellipsoids are at the 50% probability level.

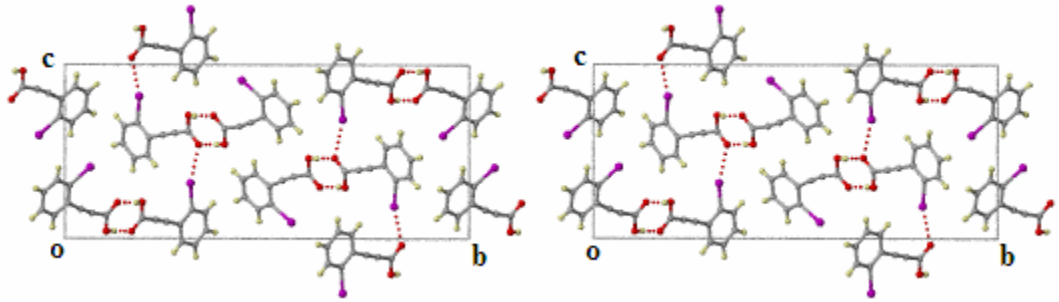


Fig. 11. Stereoview of the packing of **1d**. Notice the acid dimers are connected by I···O interactions (3.30 Å).

2.5 Centrosymmetric acid dimer in 2b, 2c, 2d and 2e

While most of the 2-substituted phenylpropiolic acids adopt the unusual *syn-anti* catemer, the scenario is very different in the 3-substituted acids. Except the 3-fluoro acid (**2a**), all the 3-substituted acids in this study (**2b-2e**) form the centrosymmetric acid dimer. The packing of all the dimeric acids is almost similar. Dimers are linked by Br···O (3.27 Å) and I···O (3.35 Å) interactions to form the tapes in **2c** and **2d** (Fig. 13). But the corresponding Cl···O seperation (3.40 Å) in **2b** are very long (Fig. 12). Possibly the halogen···O interactions are more significant in the heavier halogens and this is as might have been expected [2.18].

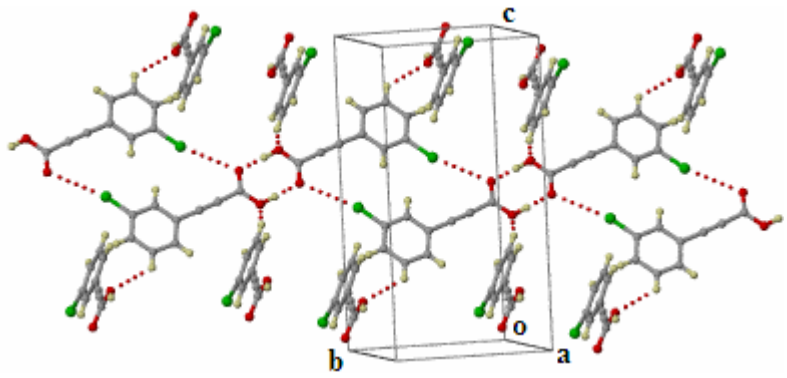


Fig. 12. Packing diagram of 3-chlorophenylpropiolic acid **2b**. Note the long Cl···O interactions (3.40 Å).

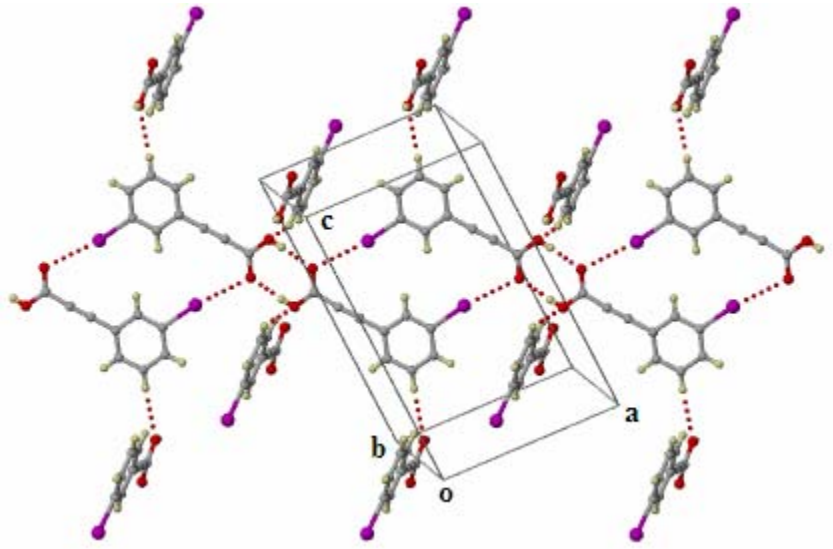


Fig. 13. Packing diagram of 3-iodophenylpropiolic acid, **2d**. Note the carboxyl dimers connected by I···O (3.35 Å) interactions. The bromo acids packs in an analogous manner.

2.6 General discussion of the phenylpropiolic acids in this chapter

Analysis of the crystal structures of ortho and meta substituted phenylpropiolic acids shows that catemer is steric sensitive. Leiserowitz has mentioned in his seminal review that "unlike the cyclic dimer, it imposes severe constraints on the size and shape of the residue R" [1.18]. This supposition explains the formation of the catemer in some of the acids reported in the literature. In the family of phenylpropiolic acids, it is observed that all the catemer chains are stabilized by C–H···O interactions provided from the ortho C–H group. Both the electron withdrawing (F, Cl, Br, I) and electron donating groups (Me, OMe) form catemers in 2-substituted phenylpropiolic acids. Therefore the significant point which emerges from this study is that the electronic effect of the substituent does not exclusively guide one to the formation of the dimer or catemer. The steric effect of the substituent could also play a critical role. Careful observation of the primary motif (catemer chain) shows that the meta hydrogen in the phenyl ring fills the

void between the substituent and the carboxyl group (Fig. 14). Thus the void space is very important to pack the molecules in the catemer motif. For all the ortho substituted acids except **1d** this space is enough to accommodate the meta hydrogen atom (Fig. 15). As a result, these acids generate the catemer motif. If the space is too narrow so that it cannot fit the meta hydrogen atom, formation of the catemer is impossible and hence the dimer is formed in 2-iodophenylpropiolic acid (**1d**) (Fig. 15). However it is difficult to explain the formation of the rare cisoid carboxyl dimer in **1d**. Although the crystallization is carried out from a variety of solvents (see the Experimental Section), a second form of this acid was not obtained.

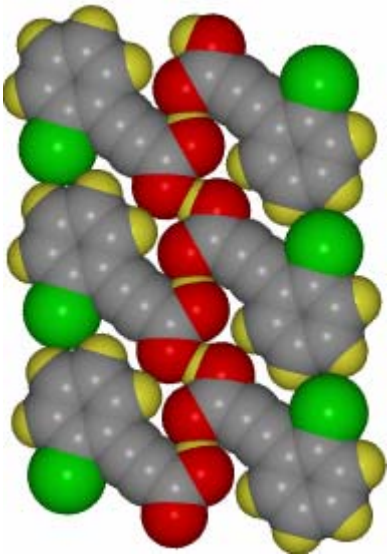


Fig. 14. Space filling model of the primary structural motif (catemer chain) in **1b**. Note, how the meta hydrogens fit the voids between the substituents and carboxyl groups.

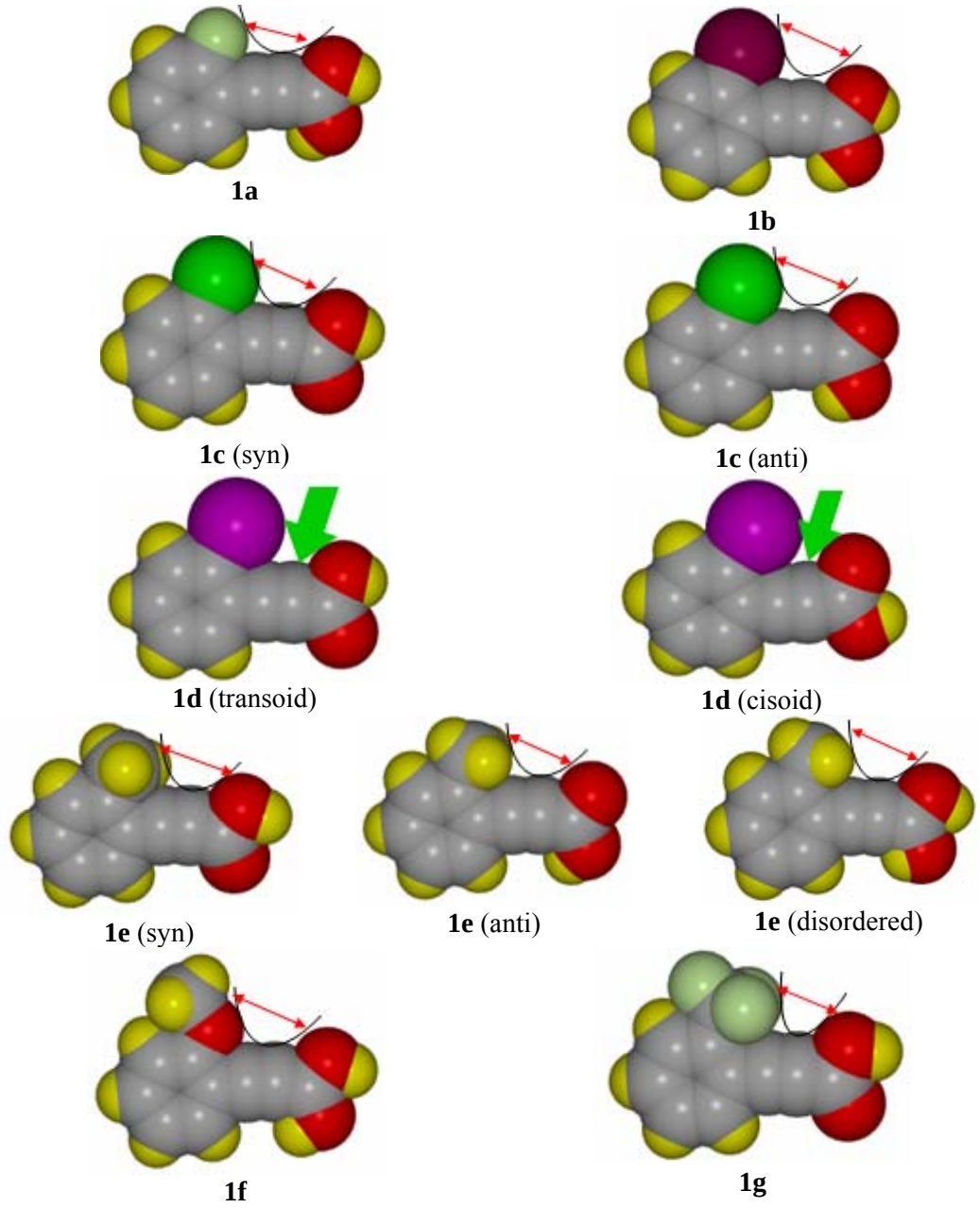


Fig. 15. Space filling model of the molecules present in the asymmetric unit of acids **1a-1g**. Note the void space between the substituent and carboxyl group indicated by arrow.

Polymorphism is observed in acid **1f** which gives both the dimer and catemer structures. Energy calculations (Cerius^2 [2.19], Compass force field) for dimer (–37.50 kcal mol^{-1}) and catemer (–26.27 kcal mol^{-1}) show the dimer structure to be more stable. However, the crystallization experiments in different solvents generally result only in the catemer indicating that the catemer structure could be a kinetically favored polymorph.

In contrast, there is enough space between the substituent and the carboxyl group in the 3-substituted phenylpropiolic acids (**2a**-**2e**) to accommodate the relevant hydrogen atom. Therefore the catemer motif is expected in all the 3-substituted acids. However, the real fact is that except 3-fluorophenylpropiolic acid, all the 3-substituted acids form dimer structures. According to Leiserowitz, the dimer affords an advantage over the catemer insofar as its packing properties are not directly dependent on the size and shape of the attached residue R [1.18]. However one should keep in mind that the effect of the substituent (both steric and electronic) depends upon the location of that substituent in the phenyl ring. An almost similar packing arrangement of the dimer in **2b**, **2c**, **2d** and **2e** signifies that the dimer is the preferred motif over the catemer for the 3-substituted acids. Analysis of the crystal structures of these acids (**2a**-**2e**) shows that the catemer motif is not compatible with close packing of molecules. Because of the small size of the fluorine atom, the bumps fit the hollows in **2a** in the catemer motifs. The bigger size of the substituent at the meta position makes the shape of the molecule such that the possible packing arrangement as dimer motif is more stable over the catemer form.

2.7 Conclusions

This chapter highlights the importance of the size and location of the substituent in the phenyl ring on the formation of the catemer or dimer motif. 2-Substituted phenylpropiolic acids prefer to form the *syn-anti* catemer motif irrespective of the electronic nature of the substituent. However, in these acids the void space between the

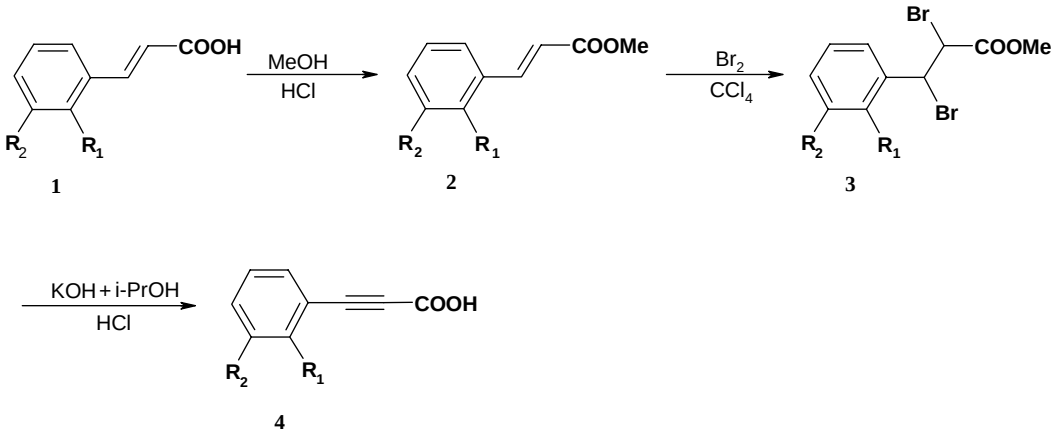
substituent and the carboxyl group is the key factor on the formation of catemer. On the other hand, in the 3-substituted acids the dimer synthon is more preferable than the catemer for a better close packed arrangement.

Polymorphism cannot be excluded in the carboxylic acids. Generally, crystallization is a kinetically controlled process. The thermodynamically stable crystal can be obtained under suitable conditions, in principle.

2.8 Experimental Section

Synthesis of 1a-1e, 1g and 2a-2e:

2- And 3-substituted phenylpropiolic acids (**1a**, **1b, 1c, 1d, 1e, 1g, 2a-2e**) were prepared by standard procedure from the corresponding cinnamic acids (**1**). Methyl cinnamates (**2**) were prepared from the acids (**1**). Bromination gave the corresponding dibromoesters (**3**). Dehydrobromination followed by hydrolysis with alcoholic KOH produced the phenylpropiolic acids (**4**). The acids **4** were purified by column chromatography.

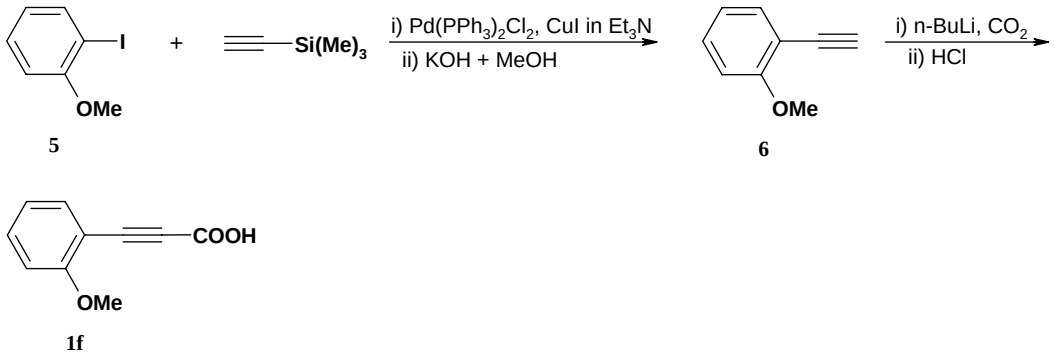


For **1a -1e** and **1g** R_1 = F, Cl, Br, I, CH_3 and CF_3; R_2 = H

For **2a -2e** R_1 = H; R_2 = F, Cl, Br, I, CH_3

Synthesis of acid 1f :

Compound **6** was prepared by a literature procedure [2.20] from 2-iodoanisole (**5**). 1.5 g of compound **6** was mixed with 15 ml dry THF in a 50 ml of two necked flask equipped with a dry nitrogen atmosphere. The temperature of the solution was maintained at –40˚ C using a dry ice bath. After 15 minutes, 7 ml of n-BuLi was added to the solution and it was stirred for 20 minutes. Then 3 g of dry ice powder were added to the solution. After stirring the mixture for 6 hours the solvent was evaporated to dryness. Compound **1f** was obtained by standard work up.



All the compounds were characterized with NMR and IR spectra. NMR were recorded at either 400 or 200 MHz on a Bruker ACF instrument. IR spectra were recorded on a Jasco 5300 spectophotometer. The details of the pure acids are given below:

2-Fluorophenylpropiolic acid (1a). IR (cm^{-1}): 2216, 1697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (m, 1H), δ 7.50 (m, 1H), δ 7.16 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.43, δ 161.33, δ 157.87, δ 134.78, δ 133.19, δ 124.34, δ 116.17, δ 84.52, δ 82.3. Melting point: 109˚C.

2-Chlorophenylpropiolic acid (1b). IR (cm^{-1}): 2214.48, 1693.65; ^{1}H NMR (400 MHz, MeOH-d_4 + $CDCl_3$): δ 7.6 (m, 1H), δ 7.45 (m, 2H), δ 7.3 (m, 1H). ^{13}C NMR (100 MHz, MeOH-d_4 + $CDCl_3$): δ 155.33, δ 137.03, δ 134.52, δ 131.48, δ 129.46, δ 126.62, δ119.88, δ 85.18, δ 82.19. Melting point: 132-134˚C.

2-Bromophenylpropiolic acid (1c). IR (cm^{-1}): 2210.62, 1697.51; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.6 (m, 2H), δ 7.3 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.23, δ 134.03, δ 132.52, δ 129.48, δ 126.46, δ 122.62, δ119.85, δ 89.18, δ 81.19. Melting point: 120-123˚C.

2-Iodophenylpropiolic acid (1d). IR (cm^{-1}): 2206.76, 1682.08; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.5 (m, 2H), δ 7.2 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.78, δ 139.23, δ 134.65, δ 132.00, δ 128.04, δ126.14, δ 101.34, δ 89.68, δ 82.69. Melting point: 146-147˚C.

2-Methylphenylpropiolic acid (1e). IR (cm^{-1}): 2195.19, 1691.72; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.14 - δ 7.58 (m, 4H), δ 2.32 (m, 3H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 155.47, δ 141.81, δ 138.61, δ 132.90, δ 130.67, δ125.69, δ 119.24, δ 84.43, δ 84.31, δ 19.20. Melting point: 90-93˚C.

2-Methoxyphenylpropiolic acid (1f). IR (cm^{-1}): 2200.76, 1695.58; ^{1}H NMR (400 MHz, DMSO-d_6): δ13.75 (s, 1H), δ 7.51 - δ 7.46 (m, 2H), δ 7.12 - 6.96(m, 2H), δ 3.51 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.15, δ 155.43, δ 134.20, δ 131.89, δ 120.08, δ110.60, δ 108.39, δ 84.18, δ 82.85, δ 55.05. Melting point: 130˚C.

2-(Trifluoromethyl)phenylpropiolic acid (1g). IR (cm^{-1}): 2226.05, 1712.94; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69 - δ 7.87 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.25, δ 154.39, δ 135.75, δ 133.31, δ 131.16, δ 129.20, δ 126.85, δ 117.34, δ 86.59, δ 79.79. Melting point: 141˚C.

3-Fluorophenylpropiolic acid (2a): IR (cm^{-1}): 2222.20, 1697.51; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.5-6.7 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ^{1} 164.82, δ 159.87, δ 157.88, δ 130.41, δ 129.15, δ120.18, δ118.48, δ 87.19, δ 80.59. Melting point: 108˚C.

3-Chlorophenylpropiolic acid (2b): IR (cm^{-1}): 2218.34, 1689.80; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67 (s, 1H), δ 7.47-7.29 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ157.48, δ134.68, δ132.89, δ131.38, δ131.23, δ129.93, δ120.90, δ 86.94, δ 80.69. Melting point: 143-145˚C.

3-Bromophenylpropiolic acid (2c): IR (cm^{-1}): 2214.48, 1685.94; ^{1}H NMR (200 MHz, MeOH-d_4): δ 7.64 (s, 1H), δ 7.41-δ 7.14(m, 3H); ^{13}C NMR (50 MHz, MeOH-d_4): δ 159.19, δ 139.21, δ 137.59, δ 135.26, δ133.97, δ126.15, δ 125.71, δ 87.77, δ 85.73. Melting point: 155-159˚C.

3-Iodophenylpropiolic acid (2d): IR (cm^{-1}): 2210.62, 1672.43; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76 (s, 1H), δ 7.61(m, 2H), δ6.97(m, 1H); ^{13}C NMR (50 MHz, MeOH-d_4): δ 146.87, δ 132.8, δ 131.56, δ 123.63, δ122.10, δ113.73, δ 85.01, δ 75.07, δ 73.49. Melting point: 182-184˚C.

3-Methylphenylpropiolic acid (2e): IR (cm^{-1}): 2210.62, 1685.94; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.30 (s, 1H), δ 7.41 (m, 3H), δ 2.37 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.43, δ 138.53, δ 138.53, δ 133.76, δ 132.06, δ 130.41, δ 128.55, δ 118.93, δ 84.85, δ 80.17, δ 21.12. Melting point: 135˚C.

Crystallization

Various solvents and solvents mixture were used for the crystallization of the acids, described in this chapter, in view of polymorphism. Unit cell parameters were determined in all the cases for which the diffraction quality single crystals were achieved.

The dimer form of acid **1f** was obtained by crystallization from aqueous EtOH. Details of the crystallizations are given in next page.

Solvent of crystallization	Status of crystallization of acid											
	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**2a**	**2b**	**2c**	**2d**	**2e**
EtOAc	N*	N	N	Y*	Y	Y	N	N	N	N	N	N
Hexane + EtOAc	N	Y	Y	Y	Y	Y	Y	N	N	N	N	Y
CH_3CN	P*	N	Y	Y	Y	Y	Y	Y	Y	Y	N	N
$CH_3CN + CCl_4$	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
$CH_3CN + CHCl_3$	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Benzene + MeOH	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Benzene + $CHCl_3$	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
HCOOH	N	N	N	N	N	N	N	N	N	N	N	N
AcOH	N	N	N	N	N	N	N	N	N	N	N	N
Aqueous EtOH	N	N	N	Y	Y	Y	Y	N	N	N	N	N
p-Xylene	-	-	-	-	Y	Y	-	N	N	N	Y	-

Y* = Single crystal obtained

N* = Precipitate

P* = Crystal obtained, but not X-ray quality

X-ray data collection and crystal structure determinations.

X-ray data of **1a-1f, 2a**, **2c** and **2e** were collected on a Bruker SMART APEX CCD [2.21] diffractometer in the University of Hyderabad, using Mo-K_α radiation (λ = 0.71073 Å). The data were reduced by Bruker AXS SAINTPLUS program [2.21] (version 6.02A); a multi-scan absorption correction was applied using the package SADABS [2.22]. X-ray data of **1g** was collected on a Enraf-Nonius-MACH-3 diffractometer at University of Hyderabad using MoK_α radiation (λ = 0.71073 Å). Unit cell parameters were determined by least-squares fit of 25 reflections. The program of WinGx [2.23] was used to reduce the data. No absorption correction was applied. In all the cases XPREP [2.24] was used to determine the space group. All the crystal structures

were solved by direct methods and refined by full matrix least-squares on F^2 using SHELXTL software [2.25] (version 6.12A). The positions of the hydrogen atoms bound to the phenyl ring in **1a-1g**, **2a**, **2b** and **2e** were generated by a riding model on idealized geometries with U_{iso}(H) = 1.2 U_{eq}(C), while the H atoms of the hydroxyl groups were located in difference Fourier maps, and these H-atoms were also refined as riding, with U_{iso}(H) = 1.5 U_{eq}(O). The hydrogen atoms of the hydroxyl groups in **1a**, **1c**, **1e**, **1f**, **2a**, **2b** and **2e** were disordered over two sites with occupancies of 0.5 each. In some cases, the U values seem to be a bit too large or too small, and this is because of poor crystal quality. All the intermolecular interactions were carried out with PLATON 2002 [2.26]. The relevant crystallographic information is given in the appendix II.

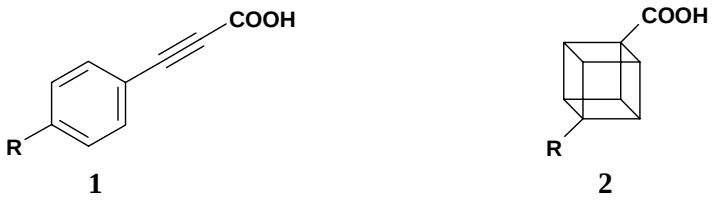
X-ray data of **2c** and **2d** were collected at the Universität Duisburg-Essen, Germany by Dr. R. K. R. Jetti under the supervision of Prof. Dr. R. Boese. X-ray data of **2c** and **2d** were collected on a SIEMENS SMART diffractometer using Mo-K_α radiation (λ = 0.71073 Å). The structure solution and refinement was done as described before.

CHAPTER THREE

IMPORTANCE OF THE ELECTRONIC EFFECT OF THE SUBSTITUENT ON THE FORMATION OF THE CATEMER IN 4-SUBSTITUTED PHENYLPROPIOLIC ACIDS

3.1 Introduction

In the previous chapter, the crystal structures of some 2- and 3-substituted phenylpropiolic acids were described. The importance of the steric role of the substituent on the formation of dimer and the rare catemer synthon was highlighted. It was also described that the effect of the substituent varies with its location in the phenyl ring. To explore the effect of the substituent on crystal packing, some 4-substituted phenylpropiolic acids were synthesized (Scheme 1). The objective of this study was two-fold: (i) to understand the role of the substituent on the formation of catemer or dimer motifs; and (ii) to compare the role of the substituent on crystal packing between these 4-substituted phenylpropiolic acids and the related 4-substituted cubanecarboxylic acids. The crystal chemistry of some 4-substituted cubanecarboxylic acids were studied previously in our laboratory [1.25(b)]. It was reported that the C–H···O hydrogen bonds play an active role in determining O–H···O catemer chains in these structures. It was mentioned that the space filling role of the substituent is significant in regulating the two structural motifs (**III** and **VI**) in cubanecarboxylic acids. In this respect I have synthesized two 4-substituted cubanecarboxylic acids (**2b** and **2f**, Scheme 1) to infer whether the substituent exerts any electronic effect. In Chapter 1 it was mentioned that *syn-anti* catemer is rare in carboxylic acid family and is restricted to phenylpropiolic and cubanecarboxylic acids. This chapter attempts to rationalize this similar phenomenon (similar at the supramolecular level) between these two structurally dissimilar carboxylic acids (dissimilar at the molecular level).



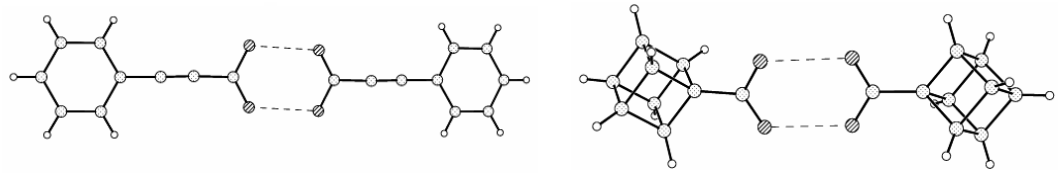
R = H	**1a**	**2a**
F	**1b**	**2b**
Cl	**1c**	**2c**
Br	**1d**	**2d**
I	**1e**	**2e**
CH_3	**1f**	**2f**
NO_2	**1g**	

Scheme 1. Molecules described in this chapter

3.2 Prior study of *syn-anti* catemer in phenylpropiolic and cubanecarboxylic acids

Prior to my study nine phenylpropiolic and ten cubanecarboxylic acids including **1a, 1c, 1d, 2a, 2c, 2d** and **2e** are noted in the CSD [3.1]. The carboxylic acid is a strong hydrogen bonding functional group with robust and reliable patterns for solid state aggregation. Yet, instead of the usually observed dimer synthon **III,** the rare catemer synthon **VI** is found in acids **1c**, **1d**, **2c**, **2d** and **2e**. However, the unsubstituted phenylpropiolic, **1a** [3.2], cubanecarboxylic acid, **2a** [1.25(b)] and several alkoxy phenylpropiolic acids [3.3] have the centrosymmetric dimer synthon **III** (Fig. 2). Kuduva *et al.* have described the crystal structures of **2a**, **2c**, **2d** and **2e** and some other cubanecarboxylic acids [1.25(b)] and concluded that the formation of the synthon **VI** was attributed to its stabilization from the C–H···O hydrogen bonds formed by acidic C–H donors and carboxyl O-acceptor atoms (Fig. 4). The catemer chains are almost identical in all the crystal structures of the corresponding family of the carboxylic acids. C–H···O interactions are observed between translation related molecules in all the crystal

structures where synthon **VI** is the primary motif. These motifs in chloro substituted acids (**1c** and **2c**) are linked by type-I Cl···Cl contacts (3.50 Å, $\theta_1 = \theta_2 = 174^\circ$ in **1c**, 3.67 Å, $\theta_1 = \theta_2 = 150^\circ$ in **2c**) (Fig. 3 and Fig. 4). Bromo and iodo substituted cubane acids (**2d** and **2e**) are isostructural and the catemer chains are connected by type-I halogen···halogen contacts (3.87 Å, $\theta_1 = \theta_2 = 151^\circ$ in **2d** and 3.84 Å, $\theta_1 = \theta_2 = 151^\circ$ in **2e**) (Fig. 5). A CSD analysis shows that type-II I···I contacts are more common than type-I contacts compared to other X···X (X=F, Cl, Br) contacts (Table 1). This could indicate that the halogens largely play a space filling role in cubanecarboxylic acids.



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

Fig. 2. (a) Crystal structure of the phenylpropiolic acid, **1a**. (b) Crystal structure of the cubane acid, **2a**. The H-atoms of the carboxyl groups are omitted for clarity.

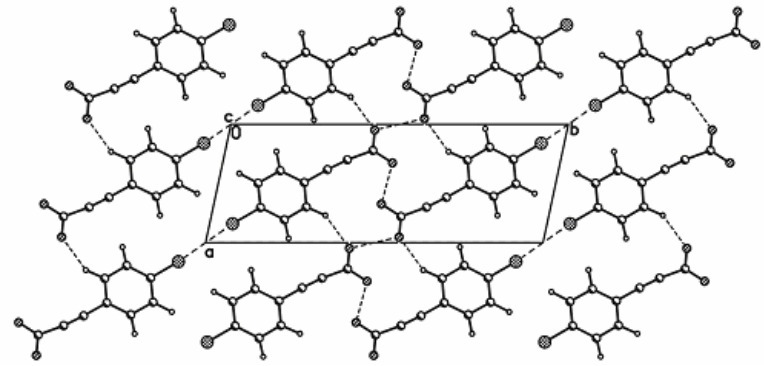


Fig. 3. Crystal structures of 4-chlorophenylpropiolic acid, **1c**. Note the type-I Cl···Cl interactions and catemer supporting C–H···O interactions. The H-atoms of the carboxyl groups are omitted for clarity.

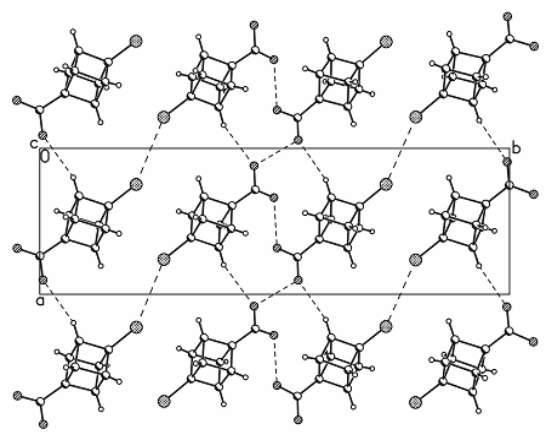


Fig. 4. Crystal structures of 4-chlorocubanecarboxylic acid, **2c**. Note the C–H···O bonds from the proximal C–H groups and also type-I Cl···Cl interactions.

Table 1. CSD study of the halogen···halogen contacts

Contacts	No of hits for Type-I	No of hits for Type-II
Cl···Cl	886	245
Br···Br	425	137
I···I	38	61

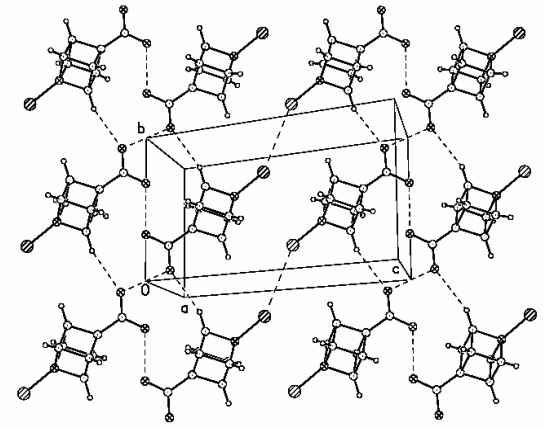


Fig. 5. Crystal structures of 4-bromocubanecarboxylic acid, **2d**. Note the type-I Br···Br interactions similar to the type-I Cl···Cl interactions as observed in **2c**. The crystal structure of the iodo derivative **2e** is identical to that of **2d**.

3.3 Crystal structures of 4-fluorophenylpropiolic acid, 1b, and 4-nitrophenylpropiolic acid, 1g

The disordered *syn-anti* catemer is observed in acids **1b** and **1g** as was mentioned in Chapter 2 for some 2- and 3-substituted phenylpropiolic acids. Both acids **1b** and **1g** crystallize with Z′=1. The carboxyl groups are almost completely disordered (**1b**: C–O, 1.260 Å, and 1.263 Å, ∠C-C-O, 119.10˚, 118.77˚; **1g**: C–O, 1.262 Å, and 1.268 Å, ∠C-C-O, 119.74˚, 118.69˚). The one-dimensional *syn-anti* catemer is the primary motif of the crystal structures. The catemer chains are supported by C–H···O hydrogen bonds with the translation related molecules. In **1b** the molecules in the catemer chains are connected by bifurcated C–H···F interactions (3.47 Å, 2.60 Å, 137˚ and 3.36 Å, 2.66 Å, 122˚) with the screw or glide related molecules (Fig. 6). On the other hand the adjacent catemer chains in **1g** are linked to each other by C–H···O hydrogen bonds to form two-dimensional sheets (Fig. 7). These sheets are stacked in the third dimension to generate full structures. The geometry of the hydrogen bond interactions are given in Appendix-II.

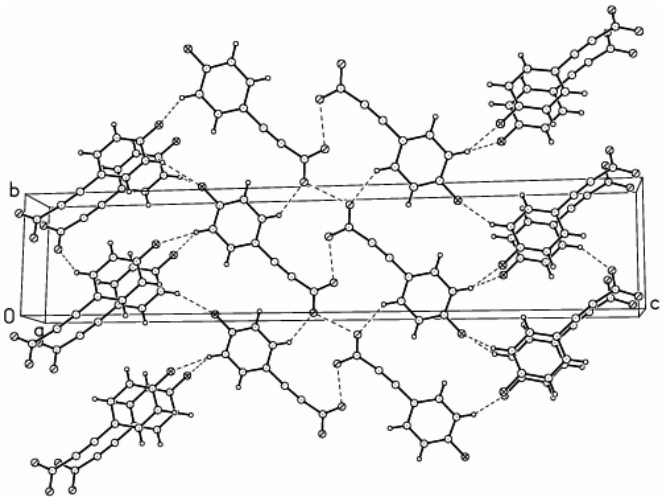


Fig. 6. Catemer motif **VI** in the crystal structure of **1b**, viewed down [100]. Notice the supported C–H···O (3.34 Å, 2.47 Å, 137˚) and the bifurcated C–H···F hydrogen bonds. The H-atoms of the carboxyl groups are omitted for clarity.

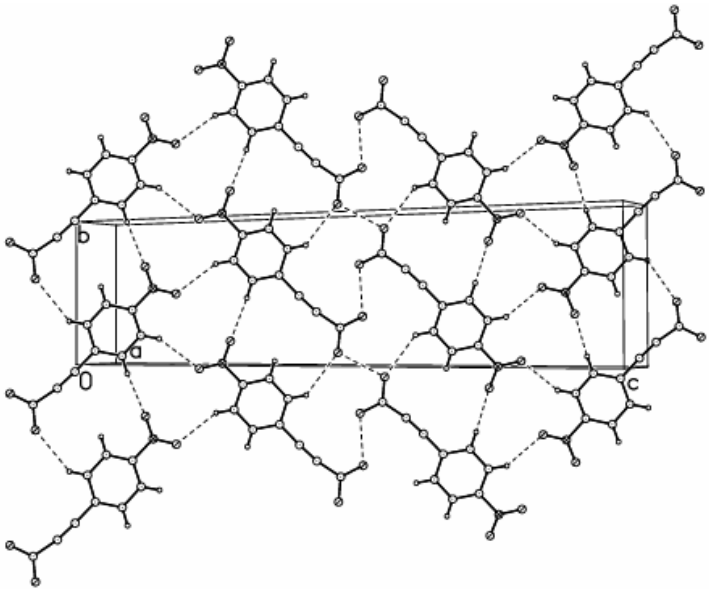


Fig. 7. Packing diagram of acid **1g** viewed down [100] to show the hydrogen-bonded catemer motif **VI**. Notice the C–H···O interactions between translation related molecules. The H-atoms of the carboxyl groups are omitted for clarity.

3.4 Ordered *syn-anti* catemer in 4-iodophenylpropiolic acid, 1e

The crystal structure of **1e** is almost identical to that of **1d**. Acid **1e** crystallizes in space group $P2_1/c$ with Z´=2. The carboxyl groups are ordered in both molecules. In one molecule, the carboxyl group adopts the *syn* conformation (**I**), whereas in the other molecule, the carboxyl group acquires the anti conformation (**II**). Molecules are arranged in a catemeric chain which constitutes the one dimensional structure. These one dimensional chains are linked by type-II I···I contacts (3.98 Å, θ_1 = 169°, θ_2 = 91°) to yield the secondary structure (Figure 8).

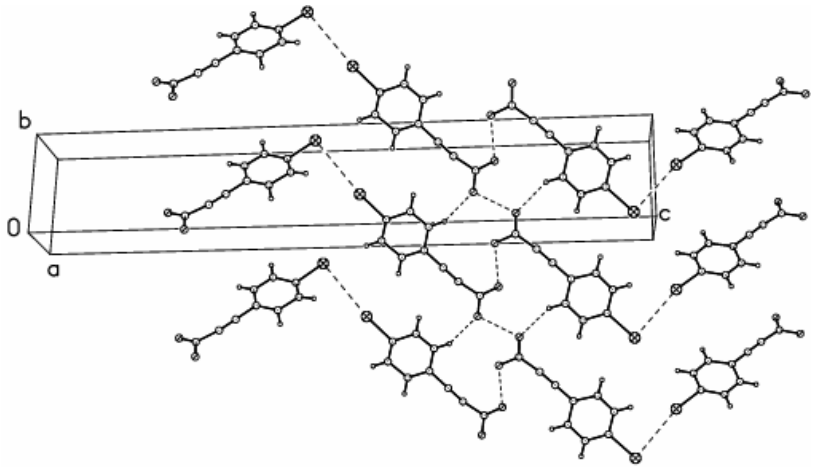
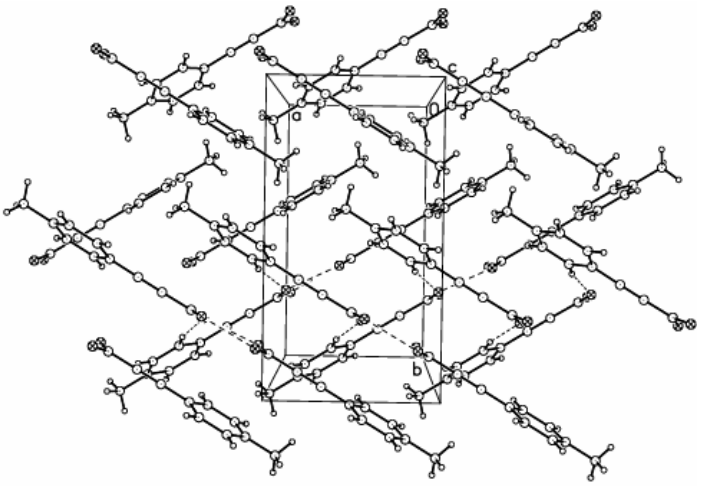


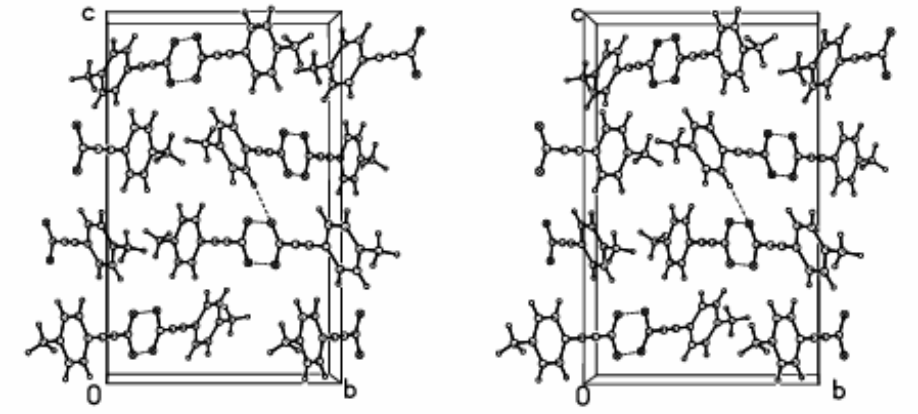
Fig. 8. Crystal structure of acid **1e** viewed down [100] to show the hydrogen-bonded catemer motif **VI** and type-II I···I interactions. Notice the C–H···O interactions (3.36 Å, 2.38 Å, 150˚ and 3.40 Å, 2.46 Å, 145˚) which stabilized the catemer chain. The H-atoms of the carboxyl groups are omitted for clarity.

3.5 Crystal structure of 4-methylphenylpropiolic acid, 1f. Violation of the chloro-methyl exchange rule

According to Kitaigorodskii's close packing principle one can anticipate that chloro and methyl groups may be exchanged in a similar fashion to form isostructural pairs due to the similarity between methyl and chloro group in terms of size and shape [2.5]. Therefore acids **1c** and **1f** are expected to have similar crystal structures. However, the crystal structure of **1f** is different than that of **1c**. Violation of the chloro-methyl exchange rule in **1c** and **1f** indicates the importance of weakly attractive Cl···Cl interactions in the arrangement of the molecules in crystals. Acid **1f** crystallizes in space group $P2_12_12_1$ with $Z'=2$. The carboxyl groups are disordered with 50% occupancy of the hydroxyl hydrogen with the *synplanar* conformation on both the oxygen atoms. The dimer is the primary motif in the crystal structure (Fig. 9).



(**a**)



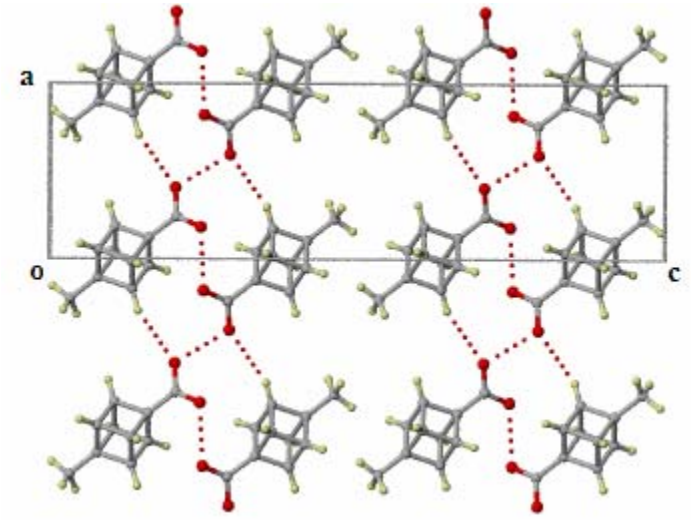
(**b**)

Fig. 9. (a) Crystal structure of **1f**, viewed down to [001] and (b) Stereoview of the packing of **1f**, viewed down [100].

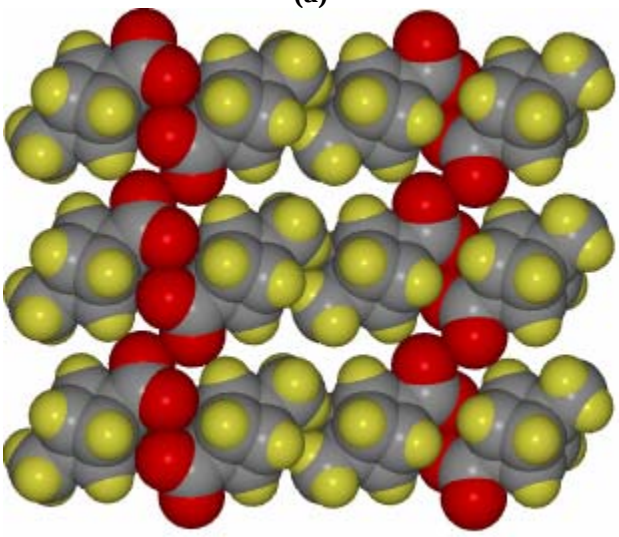
3.6 Isostructurality in 4-chlorocubanecarboxylic acid, 2c and 4-methyl cubanecarboxylic acid, 2f. Chloro-methyl exchange

The similarities between the chloro and the methyl group in terms of volume (19.9 $Å^3$ and 23.5 $Å^3$ respectively) sometimes yield similar crystal structures. This concept has been utilized in crystal engineering by Jones *et al.* and several others [3.4]. Acids, **2c** and **2f** follow the chloro-methyl exchange rule [2.5]. In both the cases, chloro and methyl groups fill the voids created by the catemer layer. The extent of isostructurality in these two acids was calculated by the unit cell similarity index, Π [3.5] which is equal to 0.027. This type of isostructural behaviour is found when crystal packing is mainly governed by the geometrical factors [3.6].

The crystal structure of 4-chlorocubanecarboxylic acid, **2c** was solved previously in the monoclinic system with space group $P2_1/n$ [1.25(b)]. The crystal structure of **2c**, was redetermined in this study in the orthorhombic system with the *Pbcn* space group (see appendix II) and is isostructural to 4-methylcubanecarboxylic acid, **2f**. Both the acids form the O–H···O catemer synthon **VI** along [100] and in both the cases the carboxylic acid groups are disordered. Additionally, the C–H···O hydrogen bonds are present between translation related molecules. Fig. 10 shows the packing diagram of **2f**.



(a)



(b)

Fig. 10. Crystal structure of 4-methylcubanecarboxylic acid, **2f.** (a) View down [010] showing the catemer synthon VI. Notice the C–H···O hydrogen bond with translation related molecules and (b) Space filling diagram that shown in (a). Notice the methyl group fill the voids created by catemer layer. The H-atoms of the carboxyl groups are omitted for clarity.

3.7 Crystal structure of 4-fluorocubanecarboxylic acid, 2b

Sometimes if changes in the molecular level are relatively small, a similar crystal structure can be expected although the critical threshold for this may vary from system to system [2.5]. In terms of size and shape, hydrogen and fluorine atoms are comparable [3.7]. Although the crystal structure of cubanecarboxylic acid, **2a** and 4-fluorocubanecarboxylic acids **2b** are not exactly similar, they are related in terms of the patterns of the carboxyl group. Both acids adopt a common dimer motif **III**. Acid, **2b** crystallizes in space group $P2_1/c$ with one molecule in the asymmetric unit. The carboxyl group is ordered and the glide related dimers are linked with C–H···O interactions along [100] (Fig. 11). Screw related dimers are connected with C–H···F hydrogen bonds forming a one dimensional tape along [101] (Fig. 12).

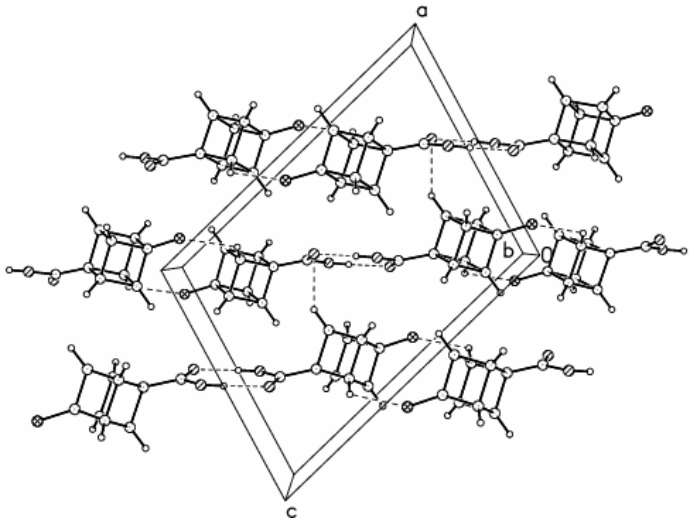


Fig. 11. Crystal structure of 4-fluorocubanecarboxylic acid. Note the C–H···O interactions which connect the glide related molecules.

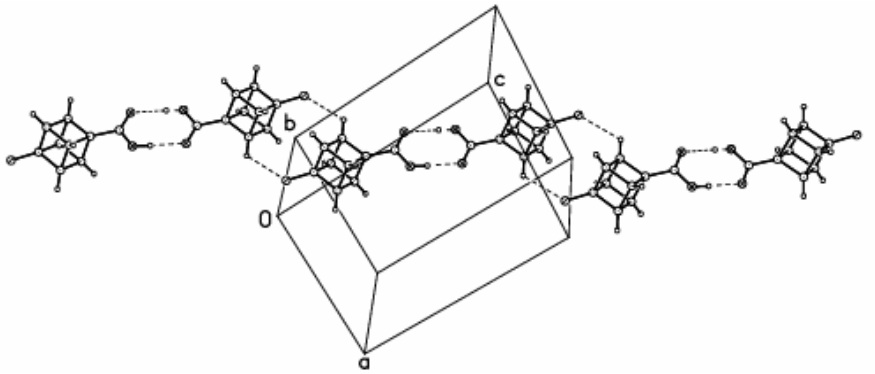


Fig. 12. One dimensional hydrogen bonded tape formed by the linking of dimers with the C–H···F interactions.

3.8 Rationalization of dimer and catemer synthons described in this chapter

4-Substituted phenylpropiolic and cubanecarboxylic acids are structurally similar in terms of synthon formation. Both families are capable of showing the rare catemer as well as the common dimer synthon. Analysis of all the crystal structure of 4-substituted acids shows that the role of the substituent is quite different in the two families.

Violation of the chloro-methyl exchange rule [1.44, 3.8] in **1c** and **1f** suggests that the substituent at para position in phenylpropiolic acids does not play a space filling role but rather that it provides additional interaction support. The chloro group has a stronger structure determining influence than the methyl group. The steering ability of the chloro group is also very important in crystal engineering, in general, and several detailed studies have been presented in the past [3.9]. Type-I Cl···Cl interactions are significant in **1c** in the context of overall stability of the crystal structure. Similarly in acids **1d** and **1e** type-II X···X interactions (X=Br and I) are important with respect to the formation of catemer. The small fluorine atom in acid **1b** and the nitro group in acid **1g** deliver sufficient attractive forces through C–H···F and C–H···O interactions respectively (see Appendix II for hydrogen bonding geometry). This suggests that the substituent exerts

some attractive interactions which lead to the formation of catemer. On the other hand the CH_3 group does not render any attractive interactions but rather deactivates the C–H group acid and therefore **1f** adopts the dimer motif. For a similar reason the methoxy substituted phenylpropiolic acids form dimers. Although the activation of the C–H group is inherent, due to the absence of the substituent which can provide some attractive interactions to stabilize the packing of the catemer chains, the unsubstituted acid **1a** forms the dimer motif.

However the substituent effect in cubanecarboxylic acids is mainly steric rather than electronic. Isostructurality of **2c** and **2f** or **2d** and **2e** indicates that the substituent at the 4-position in cubanecarboxylic acids provides only the space filling role. For the formation of the catemer in 4-substituted cubanecarboxylic acids, a bulky group is required which can stabilize the catemer synthon through close packing. This is evidenced by acids **2a** and **2b** which form a common dimer synthon. Although the inherent activation in the cubyl group was sufficient for C–H···O bond formation in **2a**, the H-atom in the 4-position of the cubyl ring is too small (unlike the Cl-group in acid **2c**) to ensure close packing of the catemer chains. The F-group, which is an isostere to H, is also not enough to stabilize the catemer sterically and therefore **2b** forms dimer. If the substituent is too large catemer formation is avoided as evidenced in 4-phenylcubanecarboxylic acids [1.25(b)].

3.9 Conclusions

Electronic and steric role of the substituent on the formation of catemer and dimer in 4-substituted phenylpropiolic and structurally related cubanecarboxylic acids are described. In case of the 4-substituted phenylpropiolic acids the substituent must have a capability to make viable the attractive interactions which are compatible with catemer formation. Acids **1a** and **1f** disqualify this query and as a result these two acids form the

dimer. On the other hand catemer formation in 4-susbtituted cubanecarboxylic acids depends entirely upon the size of the substituent. If the substituent is too small (e.g. H or F) or too big (e.g. Ph), catemer formation is not possible.

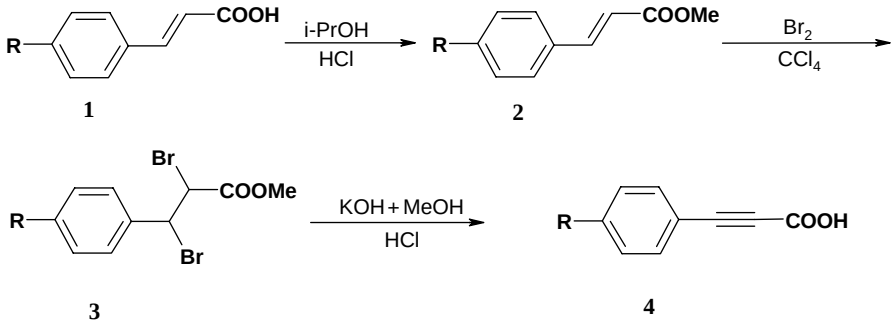
3.10 Experimental section

Synthesis

Compound **1b**, **1e**, **1f** and **1g** were prepared by standard procedures. The acid **2b** and **2f** were prepared by literature procedures. All the compounds were characterized with NMR and IR spectra. ^{1}H NMR and ^{13}C NMR were recorded at 200 and 50 MHz on a Bruker ACF instrument. IR spectra were recorded on a Jasco 5300 spectophotometer. Commercially available acid **1a** (Lancaster) was used directly for crystallization. The synthesis of acids **1b, 1e**, **1f**, **1g**, **2b** and **2f** are detailed here.

4-Substituted phenylpropiolic acids (**1b, 1e, 1f and 1g**):

4-Substituted phenylpropiolic acids (**1b, 1e, 1f and 1g**) were prepared by standard procedures from the corresponding cinnamic acids (**1**). Esters (**2**) were prepared from the acids (**1**) with isopropanol then bromination gave dibromoester (**3**). After dehydrobromination followed by hydrolysis with alcoholic KOH produced the phenylpropiolic acids (**4**). The acids **4** were purified by column chromatography.



R = F, I, CH_3, NO_2

The details of the pure acids are given below:

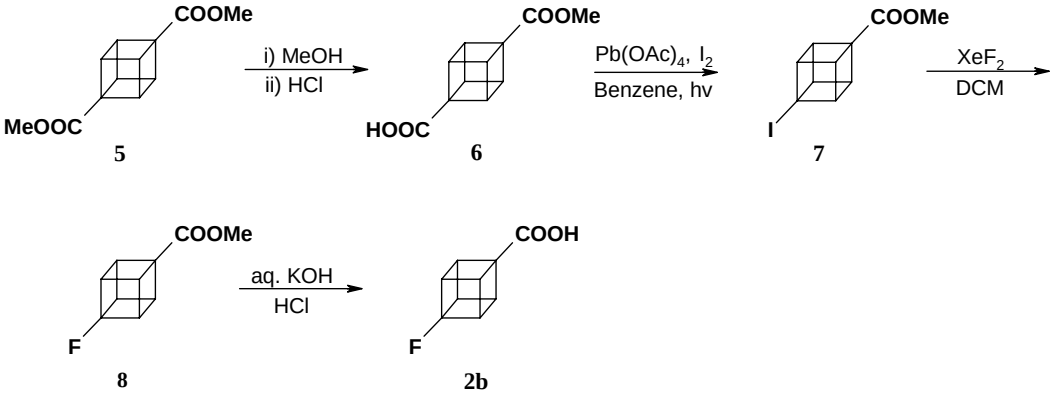
(4-Fluorophenyl)propiolic acid (**1b**). Yield 65%. IR (cm^{-1}): 2210, 1726; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.95 (s, 1H), δ 7.66 (q, 2H), δ 7.16 (t, 2H). ^{13}C NMR (50 MHz, $CDCL_3$): δ 161.72, δ 158.10, δ 135.68, δ 130.71, δ 116.46, δ 87.98, δ 80.04.

(4-Iodophenyl)propiolic acid (**1e**). Yield 50%. IR (cm^{-1}): 2222, 1684; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (d, 2H), δ 7.34 (d, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 154.35, δ 138.13, δ 134.32, δ 118.69, δ 98.59, δ 83.76, δ 83.03.

(4-Methylphenyl)propiolic acid (**1f**). Yield 60%. IR (cm^{-1}): 2197, 1676; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.35 (s, 1H), δ 7.54 (d, 2H), δ 7.23 (d, 2H), δ 2.40 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.55, δ 141.96, δ 133.35, δ 129.51, δ 116.12, δ 89.73, δ 79.88, δ 21.79.

4-Nitrophenylpropiolic acid (**1g**). Yield 60%. IR (cm^{-1}): 2214.48, 1697.51; 1521.97 ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.25 (bs, 1H), δ 8.24 (d, 2H), δ 7.88 (d, 2H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 160.5, δ 150.10, δ 127.45, δ 135.71, δ 128.4, δ 93.3, δ 82.04.

4-Fluorocubanecarboxylic acid, **2b** [3.10]



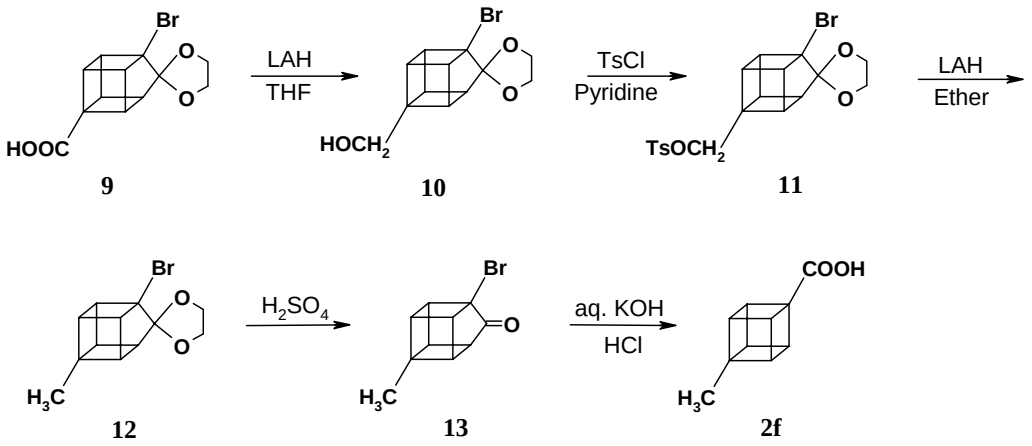
5 **6** **7** **8** **2b**

Outline of the synthesis of 4-fluorocubanecarboxylic acid, **2b**.

4-(Methoxycarbonyl)cubanecarboxylic acid (**6**) was prepared from 1,4-bis(methoxycarbonyl)cubane (**5**) as described by Eaton *et al* [3.11]. 300 mg of Compound **6** was converted into 215 mg of the methyl-4-iodocubanecarboxylate, (**7)** (51%) by irradiating in benzene solvent in presence of $Pb(OAc)_4$ and I_2 for 3 hours. 75 mg of methyl-4-fluorocubanecarboxylate**, (8)** (60%) was prepared from **7** by refluxing with XeF_2 in DCM solvent. Hydrolysis of 75 mg of compound **8** by aqueous KOH followed by acidification gave 50 mg of crude acid **2b** (72%). 35 mg of pure **2b** was obtained by sublimation.

IR (cm^{-1}): 1689, 1628. ^1H NMR (200 MHz, $CDCl_3$): δ 4.85-4.45 (m, 6H); δ 8.25 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 178.45, δ 102.68, δ 56.29, δ 54.09, δ 42.30.

4-Methylcubanecarboxylic acid, **2f** [3.12]



Outline of the synthesis of 4-methylcubanecarboxylic acid, **2f**.

THF solution of 500 mg (1.67mmole) of 1-Bromo penta cyclo[4.3.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]nonan-9-one-4-carboxylic ethylene ketal acid (**9**), prepared by the method of Chapman *et al* [3.13] was refluxed overnight with lithium aluminum hydride (70mg, 1.84 mmol) under nitrogen. After cooling and addition of ethyl acetate (1.5 ml) and 10% sulfuric acid (5

ml), the THF was distilled off and the aqueous residue extracted with $CHCl_3$ (3 × 15 ml). The $CHCl_3$ extracts were washed with 5% aqueous $NaHCO_3$ (2 X 10 ml) and water (2 × 10 ml), then dried ($MgSO_4$) and evaporated to the crude l-bromo-4-hydroxymethylpentacyclo[4.3.0.$0^{2,5}$,$0^{3,8}$,$0^{4,7}$]nonan-9-one ethylene ketal (**10**) which on recrystallization (hexane) gave 381 mg (80%) of colorless needles, mp 86.5-87.5˚C. Compound **10** was converted in the usual way to l-bromo-4-tosyloxy methylpentacyclo[4.3.0.$0^{2,5}$.$0^{3,8}$,$0^{4,7}$]nonan-9-one ethylene ketal (**11**), mp 115-117˚C. A solution of **11** (320 mg, 0.73 mmol) in dry ether (30 ml) was refluxed with lithium aluminum hydride (90 mg, 2.37 mol) for 24 h under nitrogen. The mixture was cooled and ethyl acetate (1.5 ml) was added to destroy excess hydride. A solution of 10% v/v H_2SO_4 (5 ml) was then added; the mixture was stirred for 30 min and separated, and the aqueous phase was washed with ether (3 × 15 ml). The combined organic phases were washed with 5% aqueous $NaHCO_3$ (2 × 10 ml) and water (25 ml) and dried ($MgSO_4$). Evaporation and recrystallization from methanol-water gave 137 mg (70%) of l-bromo-4-methylpentacyclo[4.3.0.$0^{2,5}$.$0^{3,8}$,$0^{4,7}$] nonan-9-one ethylene ketal (**12**) (mp 98-99.5˚C). Compound **12** (130 mg, 0.48 mmol) was stirred for 5 days in 75% w/w H_2SO_4 (10 ml). The black mixture was then poured onto ice (20 ml), filtered with Celite, and extracted with $CHCl_3$. The extracts were washed with 5% aqueous $NaHCO_3$ (20 ml) and evaporated to the crude 1-bromo-4-methylpentacyclo[4.3.0.$0^{2,5}$.$0^{3,8}$,$0^{4,7}$]nonan-9-one (**13**), 70 mg (64.4%) which was converted directly to **2f** without purification. A solution of **13** (70 mg, 0.31 mmol) in 25% w/w aqueous KOH (15 ml) was heated for two hours at 115˚C, cooled, and washed with chloroform. The aqueous phase was acidified to pH 3 by dropwise addition of concentrated HCl with stirring in an ice bath, keeping the temperature of the solution below 5˚C. The solution was extracted with $CHCl_3$ (3 × 15ml) and the extracts dried ($MgSO_4$) and evaporated to a brown solid which on extraction with hexanes gave **2f**, 25 mg (49.6%) of 4-methylcubane carboxylic acid (**2f**). mp 142.5-

143.5˚C. IR (cm^{-1}): 2976, 1674. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.15 (t, 3H), δ 3.65 (t, 3H), δ 1.28 (s, 3H).

Crystallization

Diffraction quality single crystals were achieved by recrystallising acid **1a** from benzene, **1b** from CH_3CN, **1e** from *p*-xylene and CH_3CN, **1f** from CH_3CN, **1g** from $CHCl_3$ and CH_3CN, **2b** from *p*-xylene, **2c** from $CHCl_3$ and CH_3CN and **2f** from hexane. In view of polymorphism, acids **1a**, **1b**, **1e**, **1f**, **1g** and **2b** were crystallized from few more solvents. Due to lack of compound, acids **2c** and **2f** could not be taken for crystallization from different solvents. Unit cell parameters of all the X-ray quality crystals were determined to establish identity. Details of the crystallizations are given below:

Solvent of crystallization	Status of crystallization of acid					
	1a	**1b**	**1e**	**1f**	**1g**	**2b**
EtOAc	N*	N	N	N	Y*	N
Hexane + EtOAc	N	N	Y	N	Y	N
HCOOH	N	N	N	N	N	N
AcOH	N	N	N	N	N	N
Benzene+ CH_3CN	Y	N	Y	Y	Y	N
Benzene+ $CHCl_3$	N	N	Y	N	Y	N
CH_3CN + CCl_4	Y	N	Y	Y	Y	N
MeOH	N	N	Y	N	Y	N

*Y = Single crystal obtained; *N = Precipitate obtained

X-ray data collection and crystal structure determinations.

X-ray data were collected at the Universität Duisburg-Essen, Germany by Dr. R. K. R. Jetti under the supervision of Prof. Dr. R. Boese. X-ray data of **2f** were collected on a Bruker P4 diffractometer, while those for **1a**, **1b**, **1e**, **1f**, **1g** and **2b** were collected on a SMART diffractometer using Mo-K_α radiation (λ = 0.71073 Å). The data were reduced

by Bruker AXS SAINT program [2.21] (version 6.02A); a multi-scan absorption correction was applied using the package SADABS [2.22] and XPREP [2.24] was used to determine the space group. The crystal structures were solved by direct methods and refined by full matrix least-squares on F^2 using SHELXTL software (version 6.12A) [2.25]. The position of the hydrogen atoms bound to phenyl and cubyl groups in **1a, 1b, 1e, 1f**, **1g**, **2b** and **2f** were generated by riding model on idealized geometries with U_{iso} (H) = 1.2 U_{eq} (C), while the H atoms of the hydroxyl groups were located in difference Fourier maps, and these H-atoms were also refined as riding, with U_{iso} (H) = 1.5 U_{eq} (O). The hydrogen atoms of the hydroxyl groups in **1f**, **2f**, **1b** and **1g** were disordered over two sites with occupancies of 0.5 each. In some cases, the *U* values seem to be a bit too large or too small, and this is because of poor crystal quality. All the intermolecular interactions and related calculations were carried out with PLATON 2002 [2.26] on Silicon Graphics Octane2 workstation (Table 1). The relevant crystallographic information is given in the Appendix II.

In the crystal structure of acid **1e**, the cell angle β is close to 90°, indicating an apparent orthorhombic symmetry. However, several attempts to solve the structure of this compound in the orthorhombic system failed. Further examination of the crystal structure revealed that there is no pseudosymmetry present and that the cell system is indeed monoclinic.

Redetemination of the crystal structure of 2c

X-ray data of **2c** were recollected on a Bruker AXS SMART APEX CCD diffractometer at 100K using Mo-K_α radiation at the University of Hyderabad. The structure solution and refinement was done as described before. The structure was solved in the orthorhombic system (instead of monoclinic). The position of the hydrogen atoms bound to cubyl group in **2c** were generated by riding model on idealized geometries with

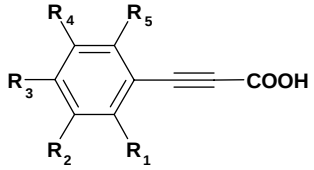
U_{iso} (H) = 1.2 U_{eq} (C), while the H atoms of the hydroxyl groups were located in difference Fourier maps, and these H-atoms were also refined as riding, with U_{iso} (H) = 1.5 U_{eq} (O). The hydrogen atom of the hydroxyl group in **2c** was disordered over two sites with occupancies of 0.5 each.

CHAPTER FOUR

CATEMER AND DIMER FORMATION IN DIFLUORO AND DICHLORO SUBSTITUTED PHENYLPROPIOLIC ACIDS

4.1 Introduction

The formation of the dimer and the catemer synthons in monosubstituted phenylpropiolic acids has been rationalized in chapter 2 and chapter 3. The study of the crystal structures of monosubstituted phenylpropiolic acids increased the interest to observe the behavior of the carboxyl group in the polysubstituted phenylpropiolic acids in terms of the synthon formation. Disubstitution of the phenyl ring results in two phenomena: (i) altering the steric crowding around the phenyl ring and (ii) changing the acidity of the aromatic C–H groups. Difluorosubstituted acids are of special interest because all the mono fluorosubstituted acids form the catemer synthon. One more concern of the present study is to verify the necessity of the C–H···O interactions formed by the ortho C–H group on the formation of the catemer in phenylpropiolic acids. Given the easy availability of the starting benzaldehydes, all possible difluoro and dichloro acids were synthesized (Scheme).



1a. $R_1 = R_2 = F$, $R_3 = R_4 = R_5 = H$ — **2a.** $R_1 = R_2 = Cl$, $R_3 = R_4 = R_5 = H$
1b. $R_1 = R_3 = F$, $R_2 = R_4 = R_5 = H$ — **2b**. $R_1 = R_3 = Cl$, $R_2 = R_4 = R_5 = H$
1c. $R_1 = R_4 = F$, $R_2 = R_3 = R_5 = H$ — **2c**. $R_1 = R_4 = Cl$, $R_2 = R_3 = R_5 = H$
1d. $R_2 = R_3 = F$, $R_1 = R_4 = R_5 = H$ — **2d.** $R_2 = R_3 = Cl$, $R_1 = R_4 = R_5 = H$
1e. $R_2 = R_4 = F$, $R_1 = R_3 = R_5 = H$ — **2e**. $R_2 = R_4 = Cl$, $R_1 = R_3 = R_5 = H$
1f. $R_1 = R_5 = F$, $R_2 = R_3 = R_4 = H$ — **2f**. $R_1 = R_5 = Cl$, $R_1 = R_3 = R_4 = H$

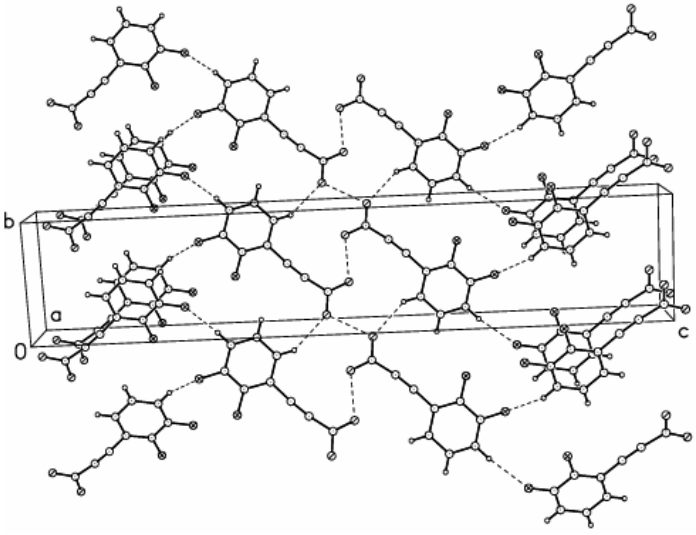
Scheme Molecules described in this chapter

4.2 Catemer synthon in difluoro and dichloro phenylpropiolic acids

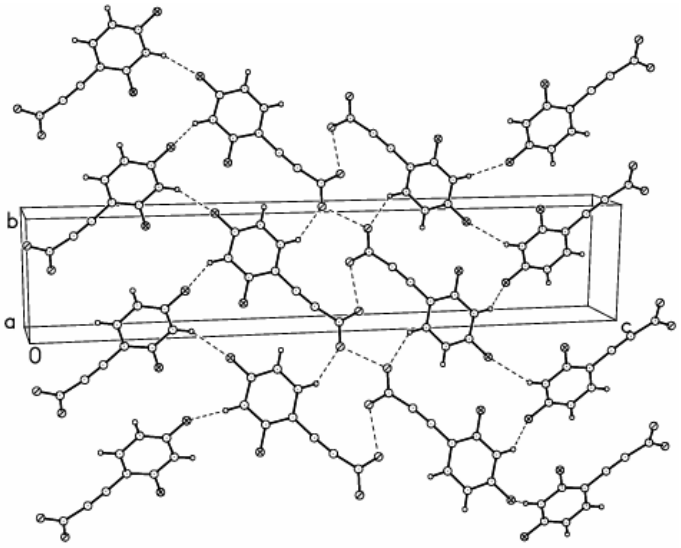
Despite crystallization from different solvents and solvents mixture, X-ray quality crystals were not achieved for acids **2a** and **2e** and powder X-ray diffraction also does not help much to correlate the structure with the congeners (see the crystallization processes as described in Experimental Section). Therefore the crystal structures of **2a** and **2e** are still unknown. Except for acids **1c**, **1f**, **2c** and **2f** all other difluoro and dichloro phenylpropiolic acids adopt catemer structures.

4.2.1 Isostructurality in 2,3-, 1a and 2,4-difluorophenylpropiolic acids, 1b and identical crystal packing in 3,4-dichlorophenylpropilic acid, 2d

Sometimes isostere groups yield similar crystal structures with almost identical unit cell axes. This phenomenon is known as the isostructurality [3.7]. Acids **1a** and **1b** are isostructural with a unit cell similarity index parameter Π [3.6] is equal to 0.021 (for crystallographic information see Appendix-II). The carboxyl group forms a disordered *syn-anti* catemer motif and the crystal packing of both **1a** and **1b** is almost identical. In the crystal structures of both acids, the 2-fluoro group remains as a bystander. The other fluoro group forms C–H···F hydrogen bonds to connect the screw related molecules (Fig. 1).



(**a**)



(**b**)

Fig. 1. (a) Crystal structure of 2,3-difluorophenylpropiolic acid, **1a** and (b) Crystal structure of 2,4-difluorophenylpropiolic acid, **1b**. Note the C–H···O interactions formed by the ortho C–H·group. The H-atoms of the carboxyl groups are omitted for clarity.

According to Kálmán's definition of isostructurality [3.6], acid **2d** is not isostructural to acids **1a** and **1b**. However the crystal packing of this acid is almost identical with the latter two (Fig. 2). In acid **2d**, the chloro groups hardly participate in the intermolecular interactions, but rather they fill the void.

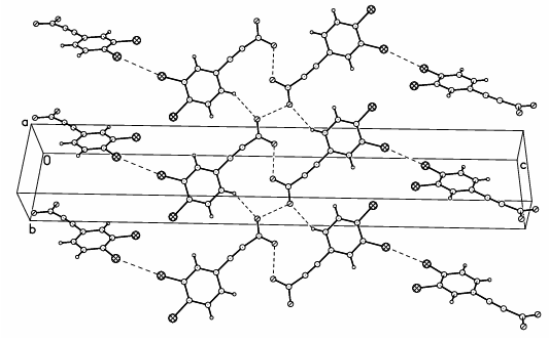


Fig. 2. Packing diagram of **2d**. Note the supporting C–H···O interactions formed by the ortho C–H·group along the catemer chain. The H-atoms of the carboxyl groups are omitted for clarity.

4.2.2 Crystal structure of 3,4-difluorophenylpropoilic acid, 1d

Among all the fluorosubstituted phenylpropiolic acids studied, only **1d** contains ordered carboxyl group. The asymmetric unit contains two molecules which are related to each other by a pseudo plane of symmetry. Due to the presence of this pseudosymmetry the fluoro group at the meta position is disordered. The carboxyl groups in **1d** form *syn-anti* catemer as was observed in 2-chlorophenylpropiolic acid (Chapter 2). The crystal packing of **1d** (Fig. 3) is almost similar with that of acids **1a** and **1b** (Fig. 1). C–H···F interactions and F···F contacts (D = 2.82 Å) are observed. These interactions seem to have no impact on the formation of the catemer but stabilize the packing.

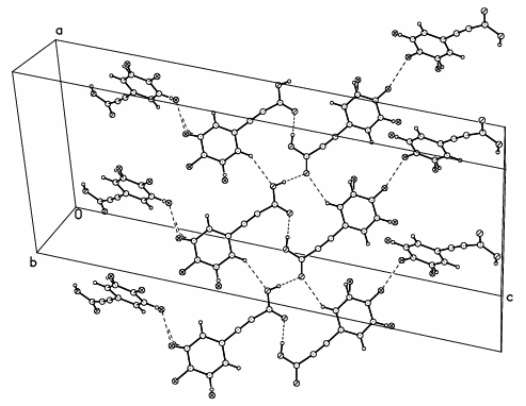


Fig. 3. Packing diagram of **1d** in a catemer chain. Note the ordered catemer chain supported by C–H···O interactions.

4.2.3 Crystal structure of 3,5-difluorophenylpropiolic acid, 1e

Acid **1e** crystallizes in space group $P2_1/c$ with $Z'=1$. Disordered carboxyl groups form the *syn-anti* catemer as observed in **1a**, **1b** and **2d**. Inversion related molecules are linked by C–H···F interactions to form a sheet. In this crystal structure too, one of the fluoro groups does not participate in intermolecular interactions (Fig. 4). The sheets are stacked in three dimensions to construct the full structure.

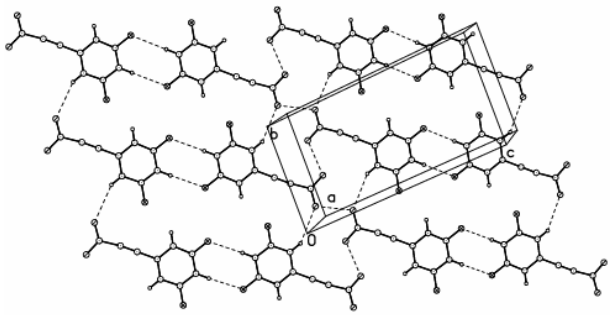


Fig. 4 Two dimensional packing arrangement of **1e**. Note the C–H···F interactions which connect the inversion related molecules. The H-atoms of the carboxyl groups are omitted for clarity.

4.2.4 *syn-syn* Catemer in 2,4-dichlorophenylpropiolic acid, 2b

Acid **2b** forms a *syn-syn* catemer as is observed in (2-trifluoromethyl)phenylpropiolic acid. The molecular structure of **2b** is different from the other phenylpropiolic acids. The plane of the carboxyl group deviates from the plane of the phenyl ring. The angle between the plane of the phenyl ring and the carboxyl group is 26˚. In this case, the crystal packing may affect the molecular structure. The gas phase calculation shows the coplanarity of phenyl ring and carboxyl group. Therefore the distortion of the molecular structure of **2b** in the crystal structure may be to avoid the steric repulsion between the chloro groups in the catemer sheet. The arrangement of the molecules along the catemer chain of **2b** is almost identical to that in acetic acid, formic acid and tetrolic acid (Fig. 5). Due to nonplanarity of the carboxyl group with the phenyl ring the catemer-supported C–H···O interactions become weak (*d* 2.76 Å, *D* 3.53 Å, θ 128˚).

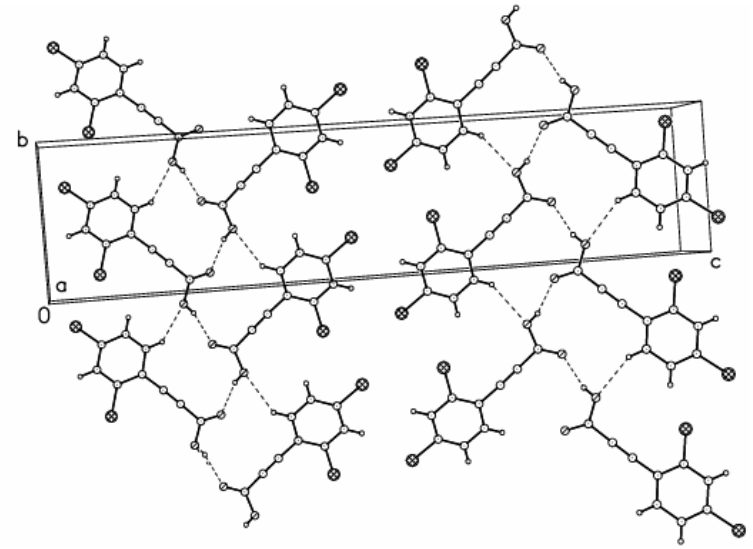


Fig. 5. Packing diagram of **2b.** Note the C–H···O interactions formed by the ortho C–H group.

4.3 Dimer synthon in 2,5-difluoro, 1c; 2,6-difluoro, 1f ; 2,5-dichloro, 2c and 2,6-dichloro, 2f, phenylpropiolic acids

The dimer synthon is observed in **1c**, **1f**, **2c** and **2f**. A poor quality crystal of **1f** yields bad refinement (R ≈ 15%) although it confirms the dimer synthon formed by the carboxyl group (see Appendix-II for the crystallographic information). Acid **1c** crystallizes in space group $P\bar{1}$ with $Z'=2$. The hydrogen bonded dimers in **1c**, associated through C–H···O and C–H···F interactions, construct a layer structure (Fig.6). Acids **2c** and **2f** crystallize with $Z'=1$ in space group $P2_1/c$ and $P2_1/n$ respectively. In these acids, screw related molecules are connected by C–H···O interactions and chloro groups fill the void to build the close packed structure (Fig. 7 and Fig. 8).

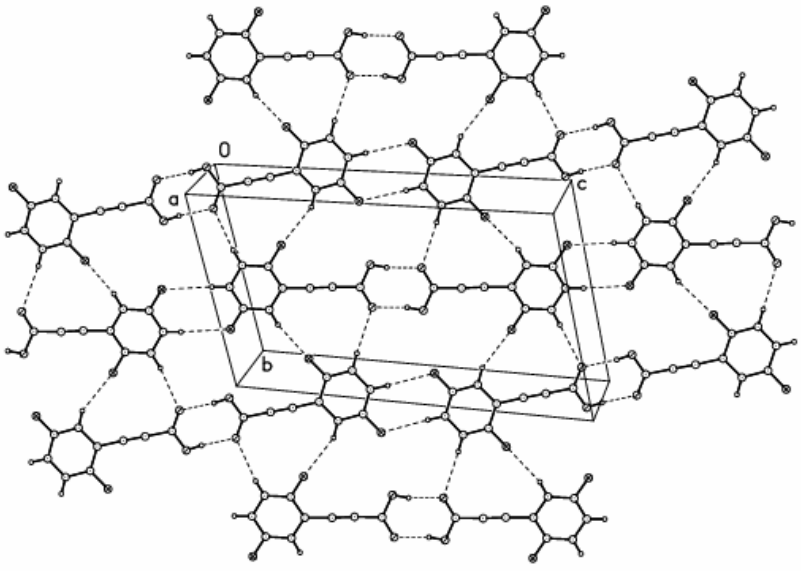


Fig. 6. Layer arrangement of the dimer motif in the crystal structure of **1c**, viewed down [100]. Notice the C–H···O and C–H···F hydrogen bonds.

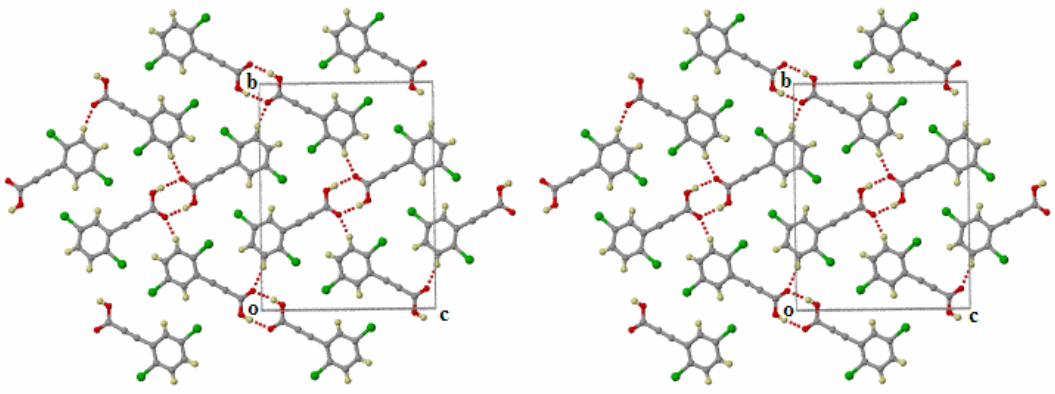


Fig. 7 Stereoview of the packing of 2,5-dichlorophenylpropiolic acid, **2c.**

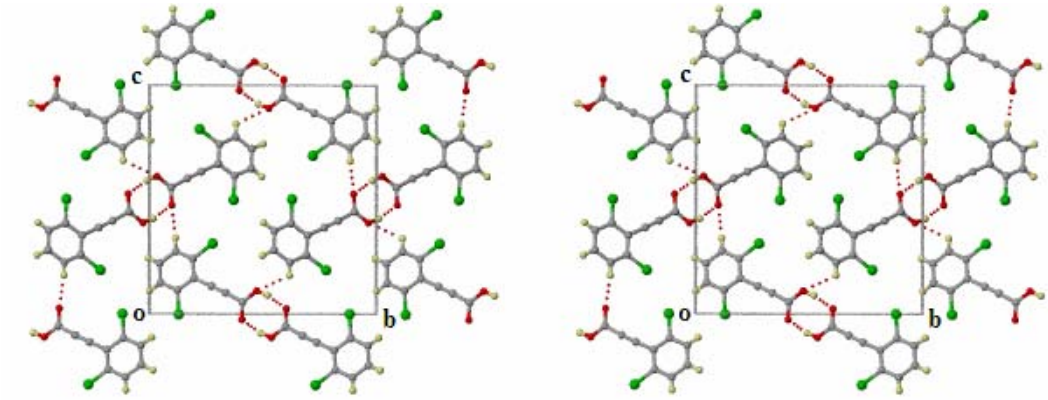


Fig. 8. Stereoview of the packing of 2,6-dichlorophenylpropiolic acid, **2f.**

4.4 Importance of C–H···O interactions on the formation of catemer in phenylpropiolic acids

Analysis of the crystal structures of difluoro and dichlorophenylpropiolic acids reveals only the steric role of the substituent on the formation of dimer or catemer motif. In the catemer structures, the substituents fill the void space. Intermolecular interactions,

rendered by the substituent, do not play a significant role on the formation of the synthon but just stabilize the crystal packing. It is observed that in the catemer structures of the phenylpropiolic acids, the catemer chain is stabilized by proximal C–H···O interactions formed by the *ortho* C–H group. It was of concern to me to see whether this interaction is really necessary for the formation of a catemer. Therefore 2,6-disubstituted acids were of more interest. The dimer synthon formed by **1f** and **2f** phenylpropiolic acids proved the necessity of the C–H···O interaction. Because of the absence of the *ortho* C–H group, the catemer chain cannot be stabilized by the C–H···O interactions. Consequently acids **1f** and **2f** form the dimer synthon. But the presence of this C–H···O interaction is not a sufficient condition for the formation of the catemer. If so, acids **1c** and **2c** also should form the catemer. The crystal structure of **1f** exhibits that all H and F-groups on the phenyl ring are engaged in hydrogen bonding to form a stable layer structure. By modeling the catemer synthon formed by the acids **1c** and **2c**, one can understand the real fact. In the case of acid **1c** the hypothetical catemer synthon would prevent the ortho fluoro group to form the hydrogen bond. F···F repulsion also may destabilize the catemer chain. In the case of acid **2c** severe chloro-chloro repulsion precludes the formation of the catemer.

A variable temperature X-ray diffraction study was carried out to show the equivalence of C–H···O and N–H···O interactions which stabilize the catemer chain in phenylpropiolic acids and indole-2-carboxylic acid (see Chapter 1). In the present study an attempt has been made to study the strength of the hydrogen bond by a variable temperature X-ray diffraction experiment. Depending upon the quality of the crystal, 3,5-difluorophenylpropiolic acid (**1e**), and indole-2-carboxylic acid were chosen. In both cases, the study was done from 100 K to 298 K. The cell parameters and the geometry of C–H···O and N–H···O hydrogen bonds are given in Tables 1 and 2.

Table 1. Variation of cell parameters and volume with temperature for acid, **1e**

Cell parameters of 3,5-difluorophenylpropiolic acid						
T (K)	**100**	**140**	**180**	**220**	**260**	**298**
a (Å)	3.7264(4)	3.7434 (5)	3.7590 (5)	3.7806 (6)	3.7944 (7)	3.8161 (6)
b (Å)	7.4178(9)	7.4233 (10)	7.4228(11)	7.4326(12)	7.4241(13)	7.4326(12)
c (Å)	14.0071(16)	14.0506(18)	14.093(2)	14.144(3)	14.157(3)	14.193(2)
α (°)	91.260(2)	91.313(2)	91.390(3)	86.395(4)	86.294(3)	86.195(2)
β (°)	97.152(2)	97.360(2)	97.591(2)	82.473(3)	82.685(3)	82.897(2)
γ (°)	98.075(2)	98.094(2)	98.095(2)	81.932(3)	81.920(3)	81.869(2)
V (Å^3)	380.05(8)	383.04(9)	385.54(10)	389.71(14)	391.19(14)	394.97(14)

Table 2. Variation of cell parameters and volume with temperature for indole-2-carboxylic acid

Cell parameters of indole-2-carboxylic acid[¶]				
T(K)	*a* (Å)	*b* (Å)	*c* (Å)	**V (Å^3)**
100	29.955(3)	6.4548(7)	3.7280 (4)	720.83(13)
160	29.986(3)	6.4555(6)	3.7485 (4)	725.63(13)
220	30.025(3)	6.4568(7)	3.7729 (4)	731.43(13)
260	30.052(4)	6.4578(8)	3.7909(5)	735.70(16)
298	30.065(4)	6.4569(9)	3.8100 (5)	739.62(18)

[¶] Orthorhombic lattice, $\alpha = \beta = \gamma = 90°$

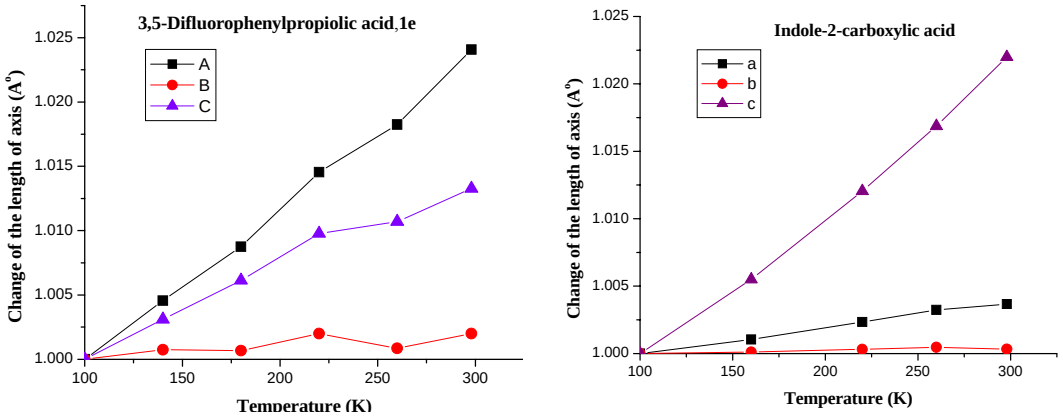


Fig.9. Variation of unit cell axis with temperature in **1e** and indole-2-carboxylic acid.

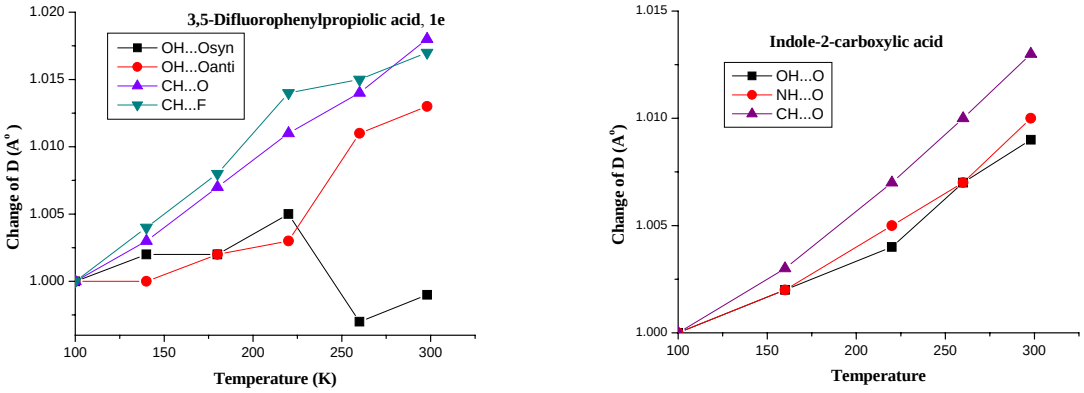


Fig. 10. Variation of hydrogen bonding geometry in **1e** and indole-2-carboxylic acid.

Fig. 9 shows the variation of the unit cell axes with temperature in acid **1e** and indole-2-carboxylic acid. In case of acid **1e** the rate of expansion of the *a* axis is the highest and of the *b* axis the lowest with increasing temperature. This is because along

the *a* axis, the catemer layers are stacked. Along the *b* axis, strong O–H···O interactions are driving the catemer synthon. Therefore this axis expands the least. Along the *c* axis, the catemer-supporting C–H···O and weak C–H···F interactions are present and this axis expands moderately. Similarly in the case of indole-2-carboxylic acid, the rate of expansion of the unit cell axes are consistent with the intermolecular interactions present in the crystal structure (Fig. 11). Fig 10 shows the variation of *D* of various intermolecular interactions in **1e** and indole-2-carboxylic acid with temperature. Since the O–H···O interaction is stronger than C–H···O and C–H···F interactions, the rate of change of *D* of C–H···O and C–H···F hydrogen bond is higher than that of O–H···O hydrogen bond. This analysis implies that the C–H···O interaction is a real one and not a consequence of the packing.

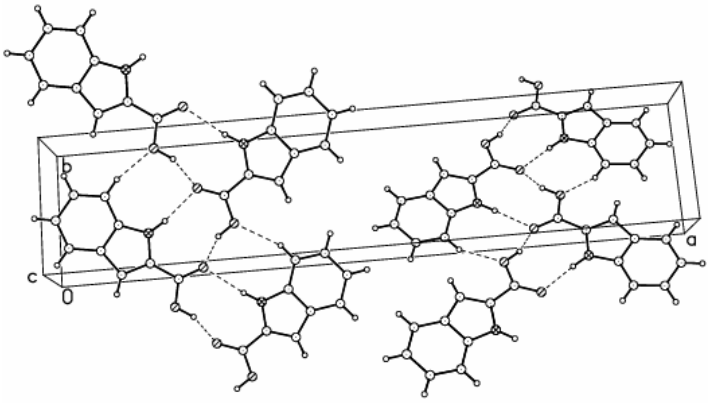


Fig. 11 Packing diagram of indole-2-carboxylic acid

4.5 Catemer, the common motif in phenylpropiolic acids

A total 26 of new crystal structures of phenylpropiolic acids have been described in this thesis. Among these, 16 acids form the catemer synthon. This implies that in this particular family of carboxylic acid, the catemer is a prefered synthon. Because of the rare occurrence of the catemer in the carboxylic acids, it is very surprising to observe this

synthon repeatedly in phenylpropiolic acids. The acetylenic bond in phenylpropiolic acids makes it different from other acids. The general consensus is that catemer is steric sensitive. Accordingly, the presence of the acetylenic bond in phenylpropiolic acids decreases the steric crowding around the carboxyl group.

With respect to the present study, the behavior of the fluoro group is very unique in terms of synthon formation, although organic fluorine is a weak acceptor. Including the three monofluoro substituted phenylpropiolic acids (described in the previous Chapter) a total of nine fluoro substituted phenylpropiolic acids have been described in this thesis. Seven of them form the rare catemer and the remaining two acids form the cyclic dimer. Therefore in the context of catemer formation the fluoro group is a very special substituent. This may be because of its small size and high electronegativity, both of which are compatible with the catemer synthon.

4.6 Conclusions

All possible difluoro and dichloro substituted phenylpropiolic acids are synthesized and the crystal structures of almost all of them have been determined. Analysis of the crystal structures has shown that the substituents mainly play a space-filling role on the formation of dimer or catemer. Acids **1a**, **1b**, **1d**, **1e**, **2b** and **2d** are compatible with the best possible close packing arrangement in the catemer synthons and acids **1c**, **1f**, **2c**, **2f** are compatible with the dimer synthon. This study also shows that the C–H···O interaction is a necessary but not a sufficient condition for catemer formation.

4.7 Experimental Section

Synthesis

All the difluoro (**1a-1f**) and dichloro (**2a-2f**) phenylpropiolic acids were synthesized by a similar procedure as was followed for the 4-substituted phenylpropiolic

acids described in chapter 3. All the compounds were characterized with NMR and IR spectra. NMR were recorded at either 400 or 200 MHz on a Bruker ACF instrument. IR spectra were recorded on a Jasco 5300 spectophotometer. Details of the acids are given below:

2,3-Difluorophenylpropiolic acid (**1a**): Yield 70%. IR (cm^{-1}): 2229.91, 1699.44; ^{1}H NMR (200 MHz, MeOH-d_4): δ 7.43- δ 6.80 (m, 3H); ^{13}C NMR (50 MHz, MeOH-d_4): δ 166.66, δ 161.52, δ 157.34, δ 133.11, δ130.80, δ127.31, δ 111.47, δ 99.19, δ 89.06 Melting point: 150 -151˚C.

2,4-Difluorophenylpropiolic acid (**1b**): Yield 50%. IR (cm^{-1}): 2222.20, 1699.44; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.74 (m, 1H), δ 7. 42 (m, 1H), δ 7. 20 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 162.35, δ 157.23, δ 134.23, δ 129.23, 123.04, δ 118.69, δ 98.59, δ 83.76, δ 83.03. Melting point: 152-155˚C.

2,5-Difluorophenylpropiolic acid (**1c**): Yield 72%. IR (cm^{-1}): 2229.91, 1699.44; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.58 (m, 1H), δ 7. 39(m, 2H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 162.70, δ 160.52, δ 135.81, 128.02, δ 120.40, δ 116.97, δ 109.29, δ 85.08, δ 80.74; Melting point: 94˚C -96˚C.

3,4-Difluorophenylpropiolic acid (**1d**): Yield 65%. IR (cm^{-1}): 2227.98, 1691.72; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.64 (m, 1H), δ 7.58 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 157.52, δ 150.25, δ 142.38, δ 130.37, δ 126.21, δ 122.37, δ 118.25, δ 86.16, δ 80.28; Melting point: 137-139˚C.

3,5-Difluorophenylpropiolic acid (**1e**): Yield 60%. IR (cm^{-1}): 2233.77, 1695.58; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.94 (m, 1H), δ 7.57 (m, 2H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 160.5, δ 150.10, δ 127.45, δ 135.71, δ 128.4, δ 93.3, δ 82.04. Melting point: 155˚C.

2,6-Difluorophenylpropiolic acid (**1f**): Yield 60%. IR (cm^{-1}): 2233.77, 1680.15; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86-δ 7.38 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.66, δ 161.52, δ 157.34, δ 133.11, δ 111.47, δ 99.19, δ 89.06. Melting point: 103˚C-108˚C.

2,3-Dichlorophenylpropiolic acid (**2a**): Yield 65%. IR (cm^{-1}): 2228.31, 1695.23; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-δ 7.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCL_3$): δ 157.63, δ 135.93, δ 133.91, δ 132.87, δ 131.28, δ 129.95, δ 120.70, δ 86.84, δ 84.03. Melting point: 170˚C-171˚C.

2,4-Dichlorophenylpropiolic acid (**2b**): Yield 65%. IR (cm^{-1}): 2218.34, 1695.58; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 1H), δ 7.49 (d, 1H), δ 7.30 (d, 1H). ^{13}C NMR (50 MHz, $CDCL_3$): δ 161.72, δ 158.10, δ 135.68, δ 130.71, δ 127.35, 121.56, δ 116.46, δ 87.98, δ 80.04. Melting point: 183-184˚C.

2,5-Dichlorophenylpropiolic acid (**2c**): Yield 60%. IR (cm^{-1}): 2220.27, 1684.01; ^{1}H NMR (400 MHz, MeOH-d_{43}): δ 7.69 (s, 1H), δ 7.33 (d, 1H), δ 7.25 (d, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 154.40, δ 135.12, δ 133.54, δ 132.55, δ 132.07, δ 131.68, δ 121.34, δ 85.87, δ 79.41; Melting point: 175-180˚C.

3,4-Dichlorophenylpropiolic acid (**2d**): Yield 65%. IR (cm^{-1}): 2231.84, 1718.73; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.57 (s, 1H), δ 7.38 (d, 1H), δ 7.28 (d, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 155.00, δ 135.08, δ 134.10, δ 132.78, δ 131.71, δ 130.59, δ 119.61, δ 83.73, δ 80.23. Melting point: 183˚C-184˚C.

3,5-Dichlorophenylpropiolic acid (**2e**): Yield 65%. IR (cm^{-1}): 2231.84, 1697.51; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), δ 7.39 (s, 2H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 154.89, δ 135.20, δ 130.47, δ 127.72, δ 126.25, δ 82.18, δ 81.23.

2,6-Dichlorophenylpropiolic acid (**2f**): Yield 65%. IR (cm^{-1}): 2235.70, 1695.58; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, 2H), δ 6.63 (d, 1H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 158.45, δ 142.00, δ 135.60, δ 131.77, δ 128.23, δ 93.78, δ 81.75. Melting point: 145-148˚C.

Crystallization

Diffraction quality single crystals were achieved by recrystallizing acids **1a-1c** and **2f** from a 1:2 mixture of MeCN and CCl_4, **1d** from a 1:1 mixture of $CHCl_3$ and MeCN, **1e** and **2d** from MeCN, **2b** from a 1:1 mixture of EtOAc and Hexane and **2c** from a 1:2 mixture of MeOH and benzene. Several solvents and solvents mixture were used for the crystallization of the acids **1f**, **2a**, and **2e**. These solvents are given below:
MeOH, aqueous EtOH, $CHCl_3$, MeCN, CCl_4, benzene, *p*-xylene, hexane, EtOAc, HCOOH, AcOH, 2:1 $CHCl_3$, and MeOH, 2:1 CCl_4 and MeCN, 1:1 hexane and EtOAc. None of these solvents yield X-ray quality crystal of **2a** and **2e**. A poor quality crystal of **1f** was obtained from a 2:1 mixture of CCl_4 and MeCN.

X-ray data collection and crystal structure determinations.

X-ray data of **1a** was collected on a Enraf-Nonius-MACH-3 diffractometer at University of Hyderabad using MoK_α radiation (λ = 0.71073 Å). Unit cell parameters were determined by least-squares fit of 25 reflections. The program of WinGx [2.23] was used to reduce the data. No absorption correction was applied. X-ray data of **1b-1f, 2b-2d** and **2f** were collected on a Bruker SMART APEX CCD diffractometer in the University of Hyderabad, using Mo-K_α radiation (λ = 0.71073 Å). The data were reduced by Bruker AXS SAINT PLUS program [2.21] (version 6.02A); a multi-scan absorption correction was applied using the package SADABS [2.22] and XPREP [2.24] was used to determine the space group of all the acids (**1a-1f**, **2b-2d** and **2f**). All the crystal structures were

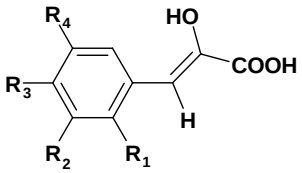
solved by direct methods and refined by full matrix least-squares on F^2 using SHELXL software [2.25] (version 6.12A). The positions of the hydrogen atoms, bound to the phenyl ring, were generated by a riding model on idealized geometries with U_{iso}(H) = 1.2 U_{eq}(C), while the H atoms of the hydroxyl groups were located in difference Fourier maps, and these H-atoms were also refined as riding, with U_{iso}(H) = 1.5 U_{eq}(O). The hydrogen atoms of the hydroxyl groups in all acids except **1c**, **1f**, **2c** and **2f** were disordered over two sites with occupancies of 0.5 each. In **1f**, the *U* values seem to be a bit too large or too small, and this is because of poor crystal quality. All the intermolecular interactions were carried out with PLATON 2002 [2.26]. The relevant crystallographic information is given in Appendix II.

CHAPTER FIVE

EFFECTS OF THE SUBSTITUENT ON THE FORMATION OF A ROBUST SYNTHON IN SOME PHENYLPYRUVIC ACIDS

5.1 Introduction

The fundamental goal of crystal engineering is to design new molecules with desired properties [1.6]. The packing of molecules in a crystal depends upon the intermolecular interactions and the shapes of the molecules [2.5]. The substituent plays an important role to steer the crystal packing [1.25b]. This has been described in the previous chapters in the context of formation of catemers and dimers in phenylpropiolic acids. It was concluded that the *syn-anti* catemer is mostly restricted to phenylpropiolic and cubanecarboxylic acids. Therefore various attempts have been taken to design new carboxylic acid molecules so that they can form catemers. The Cambridge Structural Database (CSD) [1.7] provides some information in this regard. Four phenylpyruvic acids were retrieved from the CSD [5.1]. Two of these acids (**1** and **2** in Scheme 1) form *syn-syn* catemers. Since another two phenylpyruvic acids (RASDEU, PENMUQ) form dimers, it was of interest to study the role of the substituent on the formation of catemer or dimer. Therefore, some other phenylpyruvic acids (**3-12**) were synthesized (Scheme 1) and crystal structures determined and analyzed.

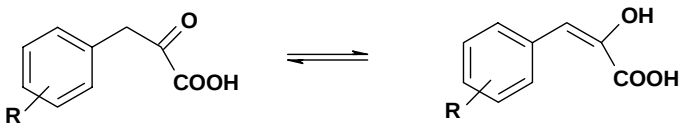


1. $R_1 = R_2 = R_4 = H$, $R_3 = H$
2. $R_1 = R_2 = R_4 = H$, $R_3 = OH$
3. $R_1 = R_2 = R_4 = H$, $R_3 = F$
4. $R_1 = R_2 = R_4 = H$, $R_3 = Cl$
5.. $R_1 = R_2 = R_4 = H$, $R_3 = NO_2$
6. $R_1 = R_2 = R_4 = H$, $R_3 = Me$
7. $R_1 = R_2 = R_4 = H$, $R_3 = OMe$
8. $R_2 = R_3 = R_4 = H$, $R_1 = F$
9. $R_1 = R_2 = F$, $R_4 = R_3 = H$
10. $R_1 = R_3 = F$, $R_2 = R_4 = H$
11. $R_2 = R_3 = F$, $R_1 = R_4 = H$
12. $R_2 = R_4 = F$, $R_1 = R_3 = H$

Scheme 1 Molecules described in this chapter.

5.2 Keto-enol tautomerism in phenylpyruvic acids

Tautomerisation is an important molecular phenomenon. Since phenylpyruvic acid is an α-ketocarboxylic acid, it can in principle exist both as a keto and an enol form as shown in Scheme 2. In 1943 Raiford *et al.* first reported tautomerism in phenylpyruvic acid [5.2]. Recently Carpy *et al.* reported that the extent of keto and/or enol form depends upon the procedure followed to prepare the acid [5.3] e. g. Cyanation–hydrolysis of $PhCH_2COCl$ yields 23% keto form of phenylpyruvic acid, whereas hydrolysis of the azalactone gave the enol form only. They also noted significant amounts of the keto form observed in the hydrolysis products of azalactones with moderate (chloro) or strong electron withdrawing groups (nitro) in the ortho position of the phenyl ring.

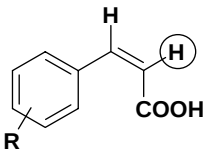


Scheme 2. Keto-enol tautomerisation in phenylpyruvic acids

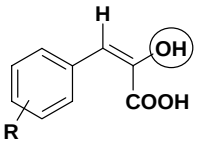
In the present study, only the enol forms of the respective phenylpyruvic acids were obtained by the hydrolysis of azalactones and this was confirmed by single crystal X-ray diffraction. In almost all the acids the plane of the phenyl ring is inclined to the plane formed by the α-hydroxy and carboxyl group.

5.3 Catemer in phenylpyruvic acids

Structurally (molecular structure), the enol form of phenylpyruvic acid is comparable with cinnamic acid (Scheme 2). The only difference is at the α-position of the carboxyl group. The α-hydrogen atoms of cinnamic acids are replaced by hydroxyl groups in phenylpyruvic acids. In fact, no cinnamic acid [5.4] forms a catemer. However, unsubstituted phenylpyruvic acid, **1** [5.5], 4-hydroxyphenylpyruvic acid, **2** [5.6] and 4-fluorophenylpyruvic acid, **3** adopt the *syn-syn* catemer (Fig.1 and Fig. 2). The one dimensional, two-dimensional as well as three-dimensional arrangements of molecules in the crystal structures of acids, **1**, **2** and **3** are almost identical. Therefore it could be suggested that the α-hydroxy group plays a role on catemer formation in phenylpyruvic acids. Obviously, the hydroxy group stabilizes the catemer by the formation of O–H···O hydrogen bond. However, the substituent in the para position of the phenyl ring also has a space filling role as is observed in cubanecarboxylic acids [1.25(b)] (Chapter 3). If the size of the substituent, in the para position is larger than fluoro (Cl, Me, OMe, NO_2) catemer formation becomes impossible. From analysis of the crystal structures of **1**, **2** and **3**, one can infer that the H, OH and F groups play a similar steric role irrespective of the nature of the substituent. This phenomenon is very common in drug molecules where F, OH and H behave as isosteres [5.7]. The hydroxy group in the para position in **2** forms an infinite O–H···O chain (Fig. 1b). But in comparison with the packing of acids **1**, **2** and **3**, these interactions can be considered as consequences of the packing.

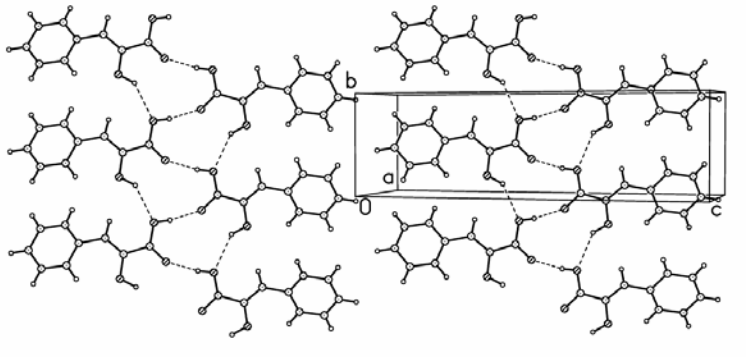


Cinnamic acids

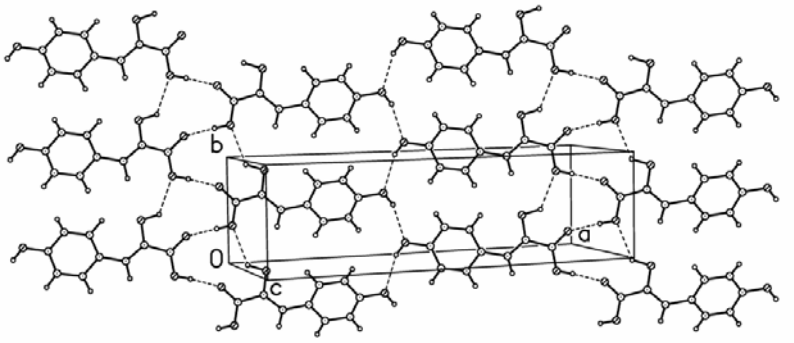


Phenylpyruvic acids

Scheme 2. Similarities and dissimilarities between the molecular structure of cinnamic acids and phenylpyruvic acids. α-Hydrogen atoms of cinnamic acids are replaced by a hydroxy group in phenylpyruvic acids indicated by circle.



(**a**)



(**b**)

Fig. 1. (a) Crystal structure of phenylpyruvic acid, **1** and (b) Crystal structure of 4-hydroxyphenylpyruvic acid, **2**. Note the catemer-supporting O–H···O hydrogen bond.

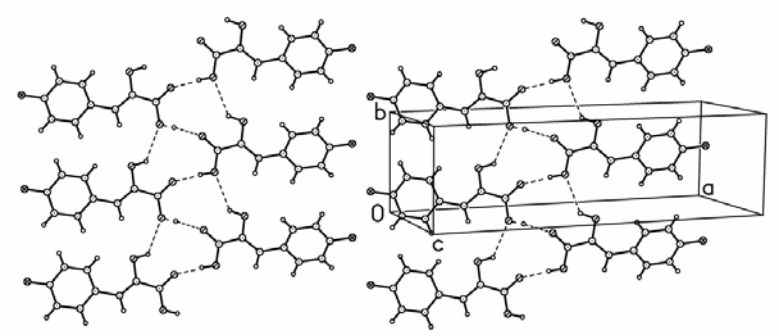


Fig. 2. Crystal structure of 4-fluorophenylpyruvic acid, **3**. Note the catemer-supporting O–H···O hydrogen bond.

5.4 Dimer in phenylpyruvic acids

In the present study, all phenylpyruvic acids except 4-fluorophenylpyruvic acid, **3**, form the common dimer synthon. Actually, dimers are not the expected motif in these acids. Due to large size of the substituents and variation of intermolecular interactions for changing the location of the substituent, acids **4-12** could not adopt the catemer motif. According to the packing of the molecules in the crystal, dimers are classified in four groups. These are explained below:

5.4.1 Dimer in 4-chlorophenylpyruvic acid, 4

The chloro group, in the para position of the phenyl ring, distinguishes acid **4** from the other phenylpyruvic acids. The larger size of the chloro compared to the fluoro group makes it impossible to form the catemer. Acid **4** crystallizes in space group $P\bar{1}$ with $Z'=1$. Translationally related centrosymmetric dimers are connected by O–H···O hydrogen bonds, formed between the α-hydroxy and carbonyl of the carboxyl groups, along [100] forming a sheet. These sheets are interconnected by type-I Cl···Cl interactions

(3.20 Å, $\theta_1 = \theta_2 = 167^\circ$) forming a layer (Fig. 3). These layers are stacked along [010] direction to construct the full structure.

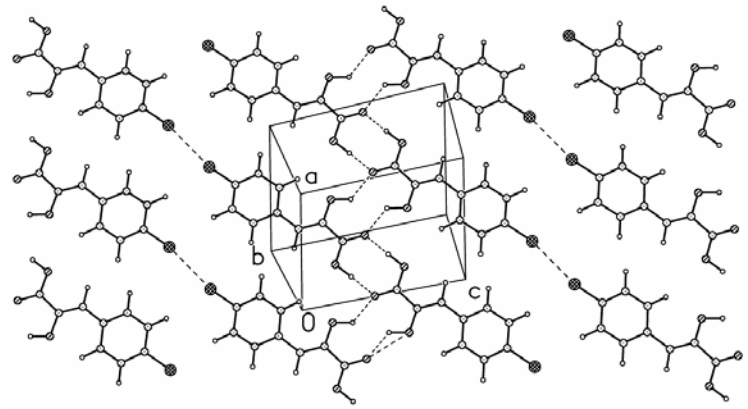


Fig. 3. Packing diagram of 4-chlorophenylpyruvic acid. Note the type-I Cl···Cl interactions between inversion related molecules

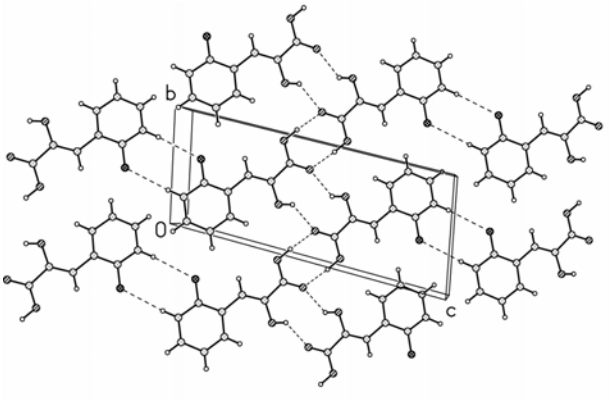
5.4.2 Isostructurality in phenylpyruvic acids

The phenomenon of isostructurality was first summarized by Kitaigorodoskii in organic compounds [2.5]. In the case of inorganic compounds this is known as isomorphism [3.5]. In the previous chapters, isostructurality is described in the phenylpropiolic and cubanecarboxylic acids. In the family of phenylpyruvic acid isostructurality is also observed. This is described below.

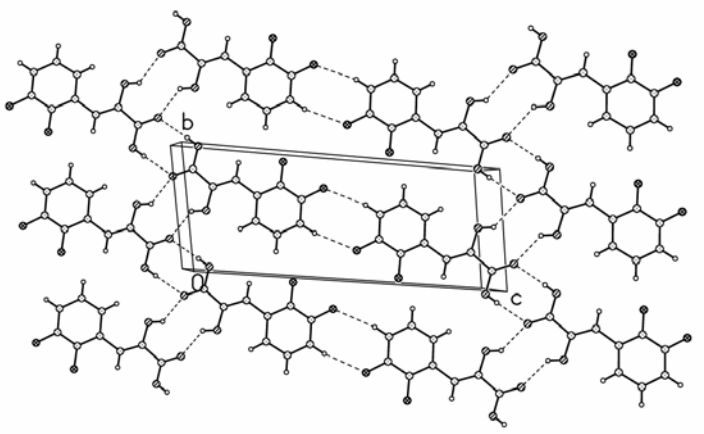
5.4.2.1 Isostructurality of 2-fluoro, 2,3-difluoro and 3,5-difluorophenylpyruvic acids, 8, 9 and 12

Acids **8**, **9** and **12** crystallize in space group $P\bar{1}$ with $Z'=1$. Unit cell parameters of these acids show that these acids are isostructural to each other (**8**: a = 3.7911(5), b = 6.6771(9), c = 16.248(2); **9**: a = 3.7362(5), b = 6.6882(9), c = 16.969(2) and **12**: a = 3.6704(4), b = 6.7796(9), c = 16.3936(18)). The packing of molecules is similar in the

three acids (Fig. 4 and Fig. 5). In each case dimers are connected by O–H···O hydrogen bonds as is observed in acid **4** to form sheets which are connected by C–H···F hydrogen bonds (**8**: 3.61 Å, 2.52 Å, 173˚;**9**: 3.56 Å, 2.53 Å, 157˚ and **12**: 3.49 Å, 2.46 Å, 158˚). In acids **9** and **12**, C–H···F hydrogen bonds are also observed between translationally related dimers (see Appendix II for hydrogen bonding geometry).



(**a**)



(**b**)

Fig. 4. (a) Packing diagram of **8** (b) Packing diagram of **9**. Note the C–H···F interactions in each case between inversion related molecules.

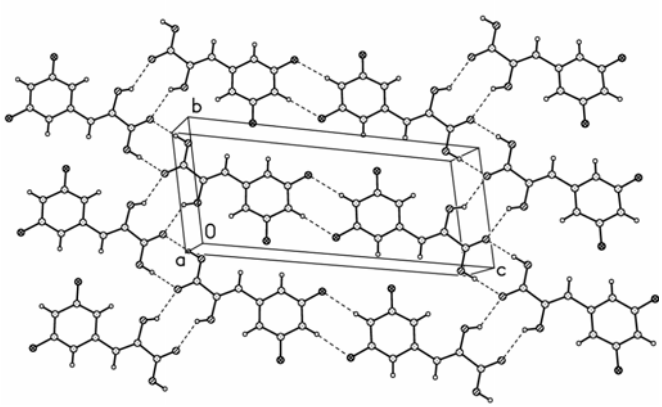


Fig. 5. Packing diagram of **12**. Note the C–H···F interactions between inversion related molecules.

5.4.2.2 Isostructurality of 2,4-difluoro and 3,4-diflurophenylpyruvic acids, 10 and 11

Acids **10** and **11** are isostructural to each other. But the isostrucutrality of these two acids are different from acids **8**, **9** and **12** (unit cell axes of **10**: a = 3.7703(6), b = 6.6112(11), c = 33.142(6) and **11**: a = 3.7199(7), b = 6.6698(12), c = 33.683(6)). This means that the c axes of acids **10** and **11** are almost double to that in acids **8**, **9** and **12**. Acids **10** and **11** crystallize in space group $P2_1/c$ with Z'=1. In both acids, the packing of molecules are almost similar (Fig. 6 and Fig. 7). Dimers are connected to each other in a similar fashion as described previously in case of other dimeric phenylpyruvic acids. Screw related molecules are connected by C–H···F hydrogen bonds (**10**: 3.33 Å, 2.46, Å 137˚ and **11**: 3.42 Å, 2.54, Å 138˚).

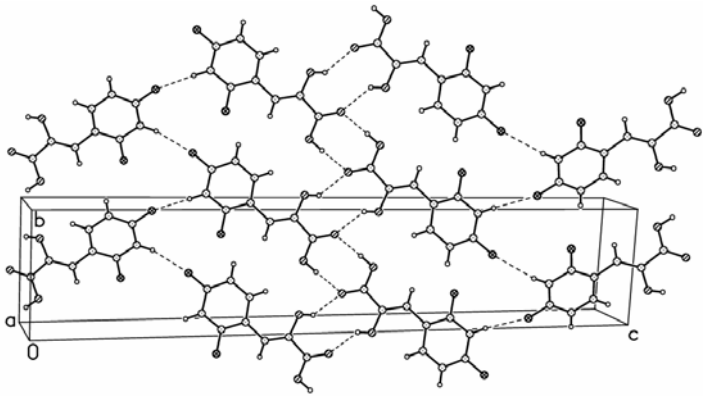


Fig. 6. Packing diagram of **10**. Note the C–H···F interaction between screw related molecules.

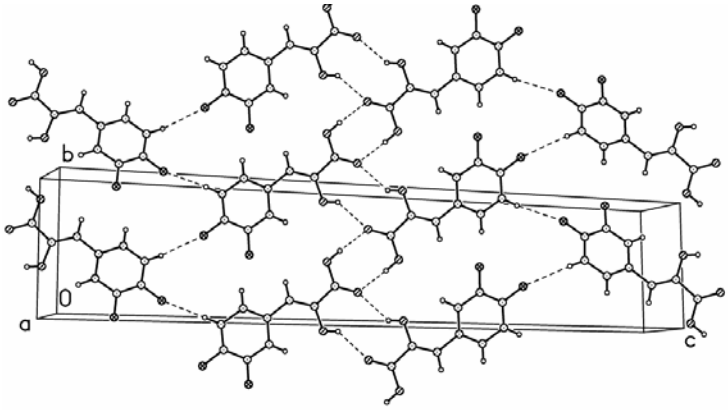
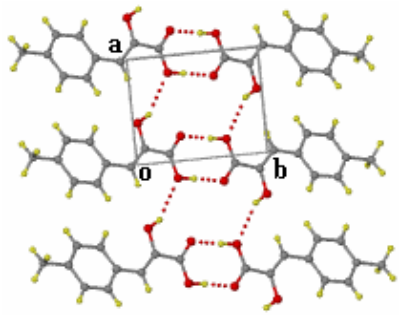


Fig. 7 Packing diagram of **11**. Note the C–H···F interactions between screw related molecules.

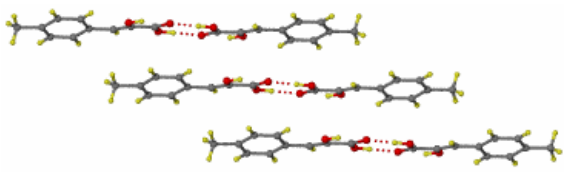
5.4.3 Dimer in 4-methyl and 4-methoxyphenylpyruvic acids, 6 and 7

Acids **6** and **7** adopt the dimer synthon. The arrangement of the dimers in these two acids is different from the other acids described previously. In these two cases the dimers are connected by O–H···O hydrogen bond formed between the α-hydroxy group and the hydroxyl oxygen of the carboxyl group. The unit cell axes of **6** and **7** are almost similar (**6**: a = 5.4529(5), b = 6.7501(7), c = 23.474(2) and **7**: a = 6.6844(7), b =

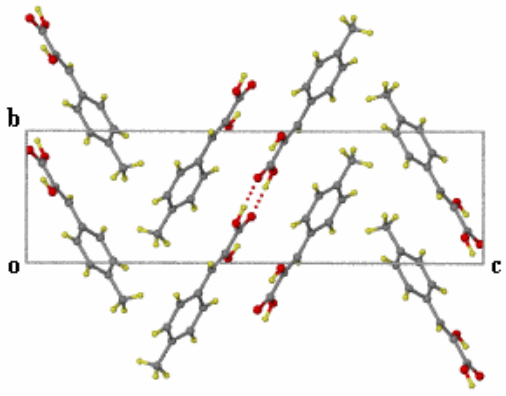
5.3844(6), c = 24.494(3)). Acid **6** crystallizes in space group $P2_1/c$ and acid **7** in $P2_1/n$. The two-dimensional and three-dimensional packing of molecules are different in **6** and **7**. In acid **6** the dimer layers are arranged in a staircase fashion in two dimensions and these staircases are arranged in a zigzag fashion to form the full structure (Fig. 8). On the other hand in acid **7** the layers (Fig. 9) formed by the dimers are stacked along the [100] direction. The layers are arranged in a zigzag fashion along the [001] direction.



(**a**)



(**b**)



(**c**)

Fig. 8. Packing diagram of 4-methylphenylpyruvic acid. (a) One-dimensional layer of the dimers. (b) Two-dimensional arrangement of the dimer layers in staircase fashion. (c) Three-dimensional arrangement of the dimer layers.

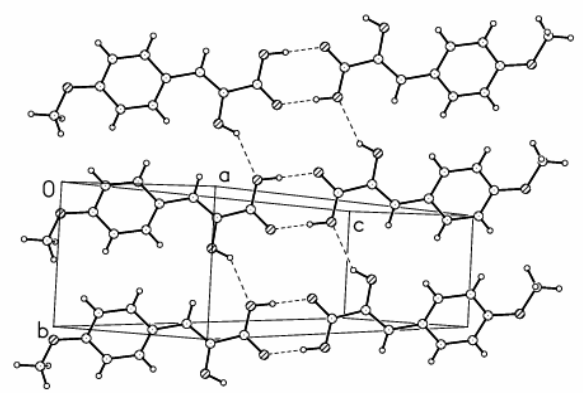


Fig. 9. Dimer layer in 4-methoxyphenylpyruvic acid

5.4.4 Dimer in 4-nitrophenylpyruvic acid, 5

The electronic nature of the nitro group is different from halo groups (F, Cl, Br and I) in terms of the hydrogen bonding ability, although both are considered as electron withdrawing groups. This may be due to presence of two acceptor atoms. Therefore the steering ability of the packing of the nitro group is different from other substituents. In the present study, the packing of the 4-nitrophenylpyruvic acid, **5** is completely different from the others, although it forms the dimer motif. Translational related dimers, linked by O–H···O interactions between the α-hydroxy and nitro groups, construct sheets. C–H···O hydrogen bonds, formed between the hydrogen atoms on the benzene ring and the carboxyl oxygen atoms, provide extra stability in the sheets. The sheets are connected by C–H···O interactions between the screw related molecules forming a layer (Fig. 10). These layers are stacked in three dimensions.

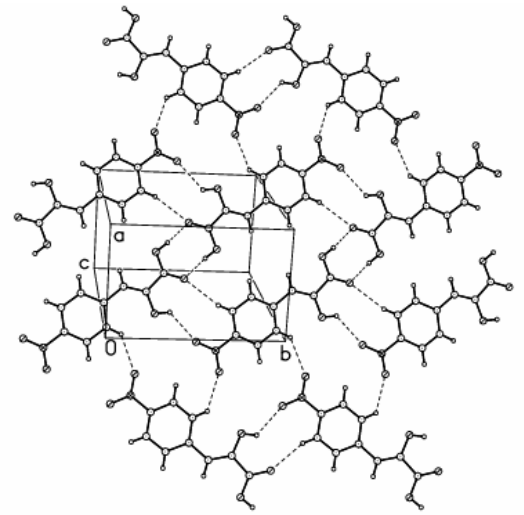
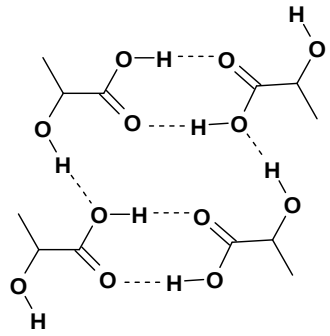
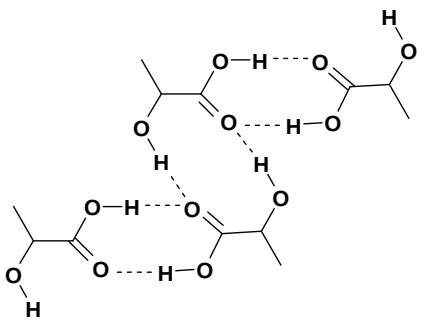


Fig. 10. Packing of 4-nitro phenylpyruvic acids. Note the C–H···O and O–H···O hydrogen bond formed by the nitro group.

5.5 Robust synthon in phenylpyruvic acids



D1



D2

Scheme 3 Synthons observed in phenylpyruvic acids

The supramolecular synthon is one of the most useful concepts in crystal engineering to design new molecules [1.2 (c)]. The significance of supramolecular synthons is described in Chapter 1. In a crystal structure various intermolecular

interactions are present but all the interactions are not equally reliable to construct robust supramolecular synthons. Robustness of a supramolecular synthon is a critical issue [5.8]. The obvious question will arise, "How do we judge robustness?" Repeated appearance of a synthon signifies its robustness. In the present study, analysis of the phenylpyruvic acids (**1-12**) reveals two robust synthons **D1** and **D2** (Scheme 3). The significant point is that the formation of **D1** and **D2** depends upon the electronic nature of the substituent. Electron donating groups (Me, OMe) construct synthon **D1**, whereas electron withdrawing groups (F, Cl) lead to **D2**. The basic difference between these two synthons is on account of the bifurcated donor. In **D1** the hydroxyl oxygen is a bifurcated donor and in **D2** the carbonyl oxygen is a bifurcated donor. However, these two synthons can be transformed to each other by the translation of the dimer unit. Fig 11 shows the transformation mechanism of **D2** to **D1** in 4-chlorophenylpyruvic acid, **4** by translation of dimer units along the [001] direction. But in the crystal structure, either **D1** or **D2** is observed. There is no experimental evidence for the transformation of **D2** to **D1.** However, it can be assumed that the intermolecular interactions play a crucial role. Due to optimization of intermolecular interactions (like Cl···Cl and C–H···F), synthon **D2** is locked in the case of electron withdrawing groups (F, Cl). Electron donating groups (like Me, OMe) do not provide any intermolecular interactions. Therefore the dimer units are more flexible and can be transformed to **D1**.

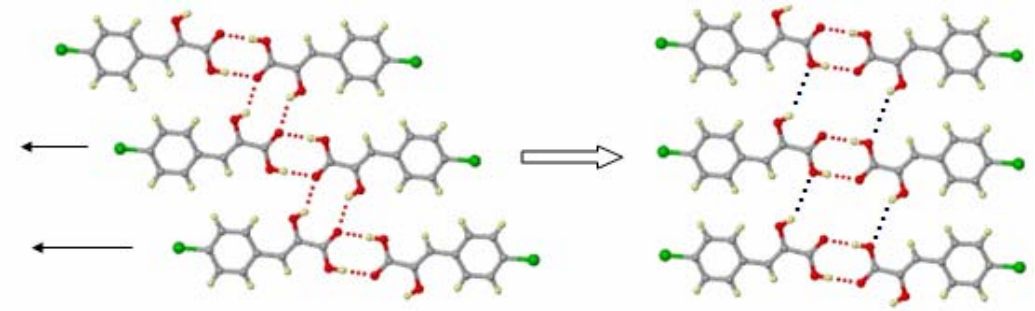


Fig. 11. Transformation of the synthon **D2** to **D1** in 4-chlorophenylpyruvic acid. **D2** is the experimentally observed synthon.

5.6 Conclusions

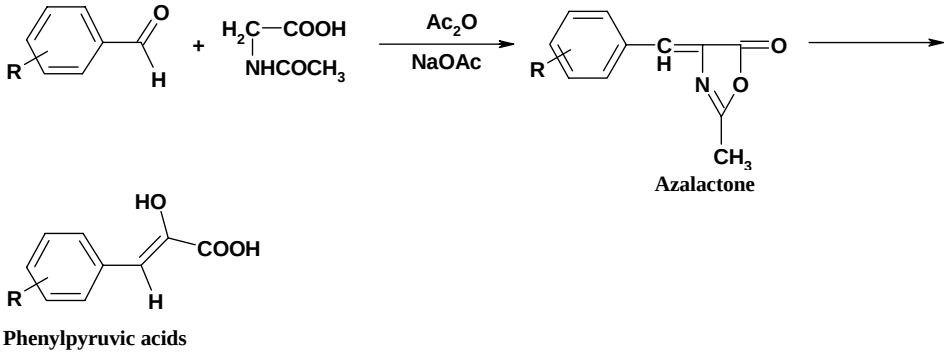
Some phenylpyruvic acids were synthesized and the crystal structures were studied to understand the role of the substituent on the formation of dimer and catemer synthon. In the case of 4-substituted phenylpyruvic acids the formation of catemer depends upon the size of the substituent. If the size of the substituent is bigger than fluoro, the acid cannot afford the catemer synthon.

Another interesting feature of this study is the formation of two different synthons **D1** and **D2** depending upon the electronic nature of the substituent. Electron donating groups (Me, OMe) lead to **D1** while electron withdrawing groups (F, Cl) form **D2**. The difference between **D1** and **D2** is on account of the bifurcated donor. In **D1** the hydroxyl oxygen is bifurcated and in **D2** the carbonyl oxygen is bifurcated donor. Dimer motifs in 4-nitrophenylpyruvic acid (**5**) arrange themselves in a different way.

5.7 Experimental Section:

Synthesis

All the pyruvic acids (**3-12**) were prepared from the corresponding azalactones, which were prepared from the corresponding aldehydes (Scheme 4).



Scheme 4 Outline of the synthesis of phenylpyruvic acids.

All the compounds were characterized with NMR and IR spectra. ^{1}H NMR and ^{13}C NMR were recorded at 400 and 100 MHz on a Bruker ACF instrument. IR spectra were recorded on a Jasco 5300 spectophotometer. The details of the acids are given below:

4-Fluorophenylpyruvic acid (3): IR (cm^{-1}): 3476.04, 1703.30; ^{1}H NMR (400 MHz, DMSO-d_6): δ9.25 (s, 1H), δ7.87 (m, 2H), δ7.25 (m, 2H), 6.4 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ165.1, δ 145.3, δ136, δ135, δ122, δ120, δ114.

4-Chlorophenylpyruvic acid (4): IR (cm^{-1}): 3470, 1701; ^{1}H NMR (400 MHz, DMSO-d_6): δ13.3 (bs, 1H), δ9.47 (s, 1H), δ7.79 (d, 2H), δ7.41 (d, 2H), 6.39 (s, 1H); ^{13}C NMR (100 MHz, MeOD-d_4): δ166.06, δ 142.44, δ133.90, δ131.31, δ130.78, δ128.28, δ108.13.

4-Nitrophenylpyruvic acid (5): IR (cm^{-1}): 3476, 1682, 1512, ^{1}H NMR (400 MHz, MeOH-d_4): δ8.5 (d, 2H), δ7.9 (d, 2H), δ 6.5 (s, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): δ165.02, δ 145.2, δ142, δ131.46, δ130, δ126.3, δ105.1

4-Methylphenylpyruvic acid (6): IR (cm^{-1}): 3477.97, 1730.30; ^{1}H NMR (400 MHz, DMSO-d_6): δ9.3 (s, 1H), δ7.65 (d, 2H), δ7.32 (d, 2H), δ 6.28 (s, 1H), δ 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ166.06, δ 142.44, δ130.90, δ131.31, δ130.78, δ128.28, δ108.13, δ 21.13.

4-Methoxyphenylpyruvic acid (7): IR (cm^{-1}): 3287, 1691.72; ^{1}H NMR (400 MHz, DMSO-d_6): δ9.2 (s, 1H), δ7.65 (d, 2H), δ7.32 (d, 2H), δ6.26 (s, 1H), 3.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ169.41, δ 166.83, δ160.22, δ131.99, δ128.12, δ 125.14, δ115.93, δ55.83.

2-Fluorophenylpyruvic acid (8): IR (cm^{-1}): 3477.97, 1701.37; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.65 (m, 1H), δ 7.50 (m, 1H), δ 7.16 (m, 2H)., δ 6.32 (s, 1H) ^{13}C NMR (100

MHz, MeOH-d_4): δ164.39, δ 157.31, δ 145.04, δ140.10, δ 133.40, δ131.29, δ129.56, δ127.24, δ104.19.

2,3-Difluorophenylpyruvic acid (9): IR (cm^{-1}): 3477.97, 1701.37; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.44- δ 6.78 (m, 3H); δ 6.32 (s, 1H) ^{13}C NMR (100 MHz, MeOH-d_4): δ 165.56, δ 161.52, δ 157.34, δ 145.36, δ 133.11, δ 128.21, δ 121.47, δ 118.19, δ 105.01.

2,4-Difluorophenylpyruvic acid (10): IR (cm^{-1}): 3470.25, 1701.37; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.74 (m, 1H), δ 7. 42 (m, 1H), δ 7. 20 (m, 1H); δ 6.30 (s, 1H) ^{13}C NMR (100 MHz, MeOH-d_4): δ 164.35, δ 160.23, δ 157.32, δ 143.84, 134.91, δ 132.69, δ 125.13, δ 120.17, δ 104.69.

3,4-Difluorophenylpyruvic acid (11): IR (cm^{-1}): 3477.97, 1705.23; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.74 (m, 1H), δ 7.65 (m, 2H). δ 6.32 (s, 1H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 164.52, δ 161.25, δ 152.38, δ 145.31, δ 135.46, δ 130.37, δ 124.37, δ 118.25, δ 105.31.

3,5-Difluorophenylpyruvic acid (12): IR (cm^{-1}): 3485.68, 1697.51; ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.94 (m, 1H), δ 7.57 (m, 2H), δ 6.33. ^{13}C NMR (100 MHz, MeOH-d_4): δ164.89, δ 160.56, δ151.39, δ131.46, δ129.45, δ127.21, δ105.12.

Crystallization

Diffraction quality single crystals were obtained by recrystallizing the acids **3-12** from the 2:1 mixture of EtOAc and hexane. Since the packing of the acid **5** is completely different from others, it was crystallized from varieties of solvents in view of polymorphism. But in all the case similar crystal structures were obtained.

X-ray data collection and crystal structure determinations

X-ray data for all the acids (**3-12**) were collected on a Bruker SMART APEX CCD diffractometer in the University of Hyderabad, using Mo-K_α radiation (λ = 0.71073 Å). The data were reduced by Bruker AXS SAINT [2.21] program (version 6.02A). A multi-scan absorption correction was applied using the package SADABS [2.22] and XPREP [2.24] was used to determine the space group. The crystal structures were solved by direct methods using SHELXS (Versions 6.12) and refined by full matrix least-squares on F^2 using SHELXTL programs (version 6.12A) [2.25]. The positions of the hydrogen atoms bound to the carboxylic H-atom position were taken from a Fourier-map and also refined as a riding group with the 1.5 fold isotropic displacement parameters of the equivalent U_{ij} of the corresponding oxygen atom. Other H-atoms were affixed and refined with the 1.2 fold isotropic displacement parameters of the equivalent U_{ij} of the corresponding carbon atom. The relevant crystallographic information is given in Appendix II.

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CHAPTER ONE

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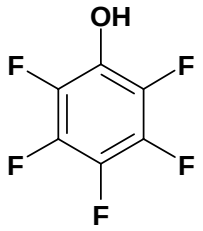
APPENDIX-I

CORRELATION BETWEEN POLYMORPHISM AND CRYSTAL STRUCTURES WITH MULTIPLE MOLECULES IN THE ASYMMETRIC UNIT (Z′ > 1). PENTAFLUOROPHENOL AS A CASE STUDY

Introduction

Polymorphism, defined as the existence of a particular compound in more than one crystal structure, is a widespread phenomenon [1]. This was first discovered in 1798, by Martin Heinrich Klaproth in $CaCO_3$ (calcite and aragonite). Almost 25 years later, Eilhardt Mitscherlich proposed that a chemical compound could exist in more than one crystalline form. Since then, polymorphism has been an important area of research. Since different crystal structures of the same chemical material possess different physicochemical properties, polymorphism has attracted huge commercial and academic interest. The important point of the occurrence of polymorphism is the variation of kinetic and thermodynamic stability of the observed crystal structures. However, the answer of the question, "Why do polymorphs form? is still not generalized. In this context, the occurrence of multiple molecules in the asymmetric unit (Z′>1) is interesting. The appearance of high Z′ crystal structures have been noted and discussed by various research groups [2]. Brock and Gavezzotti [3] independently showed that crystal structures with Z′>1 are widely distributed in hydroxyl compounds. In case of the crystal structure of steroids, Craven suggested that the occurrence of high Z′ is due to the conflict between the packing of molecules and the strong O–H···O hydrogen bonding interactions [4]. However, this suggestion has been criticized [5]. Wrong assignment of space group and pseudosymmetry also results apparently in high Z′ values [6]. In a recent account Steed has highlighted some important factors leading to the occurrence of crystal structures with Z′>1 [7]. The aim of the present study is not to find out the reason of the

formation of such structures. Rather I have tried to correlate the phenomenon of high Z′ structures with polymorphism in a study of pentafluorophenol.



Pentafluorophenol

Polymorphism in pentafluorophenol

Two different crystal structures were observed by *in situ* cryocrystallization of liquid pentafluorophenol in different experiments. In one case, pentafluorophenol crystallizes from the neat liquid in space group $P2_1/c$ with Z′=1 (**P1**) The crystal structure of **P1** consists of an infinite O–H···O–H···O–H hydrogen bonded chain (Fig. 1) as observed in several other mono and dihydric phenols [8]. In another case pentafluorophenol crystallizes in space group *Cc* with Z′=3 (**P2**) during cryocrystallization of a 1:1 mixture of pentafluorophenol and pentafluoroaniline. In the crystal structure of **P2**, the three symmetry independent molecules form discrete open O–H···O trimers. Closed O–H···O trimer synthons and helical O–H···O patterns around real and pseudo-3 and 3_1 axes are common in phenols [9] and few other discrete O–H···O oligomers also known in some phenolic compounds [10]. However, discrete O–H···O trimers are observed in a phenolic compound for the first time. These trimers in **P2** are linked by O–H···F–C bridges to form a chain (Fig. 2). Energy calculations (Cerius^2, Compass force field) for **P1** (–85.4 kJ mol^{-1}) and **P2** (–76.6 kJ mol^{-1}) show the high Z′ structure to be the less stable.

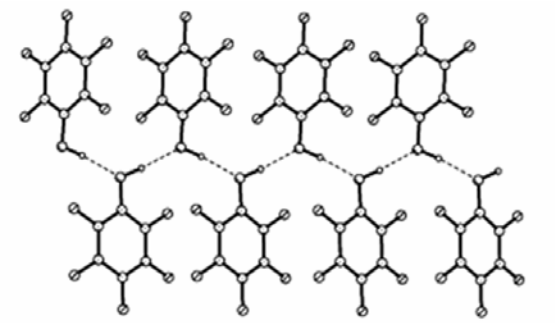


Fig. 1. Form **P1** (Z´=1) of pentafluorophenol. Note the infinite ···O–H···O–H···O–H··· pattern.

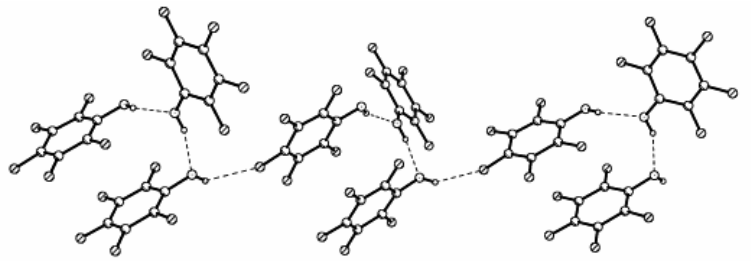


Fig. 2. Form **P2** (Z´=3) of pentafluorophenol with discrete O–H···O–H···O–H trimers. Note the weak O–H···F–C bridges.

The close structural relationship between forms **P2** and **P1** is seen in fig. 3, which gives a possible mechanism of conversion of **P2** to **P1**. The figure shows discrete trimers along [100]. Translation along [100] of entire rows of trimers would connect the trimers with O–H···O bonds to give an infinite O–H···O chain of the type seen in **P1**. While there is no experimental evidence for such a transformation of **P2** to **P1**, the packing similarities between the polymorphs, and their relative energies suggest that the infinite O–H···O synthon in **P1** evolves through the discrete open O–H···O trimers as seen in **P2**. The crystal structure of the less stable **P2** is therefore a reasonable precursor of the more stable **P1**.

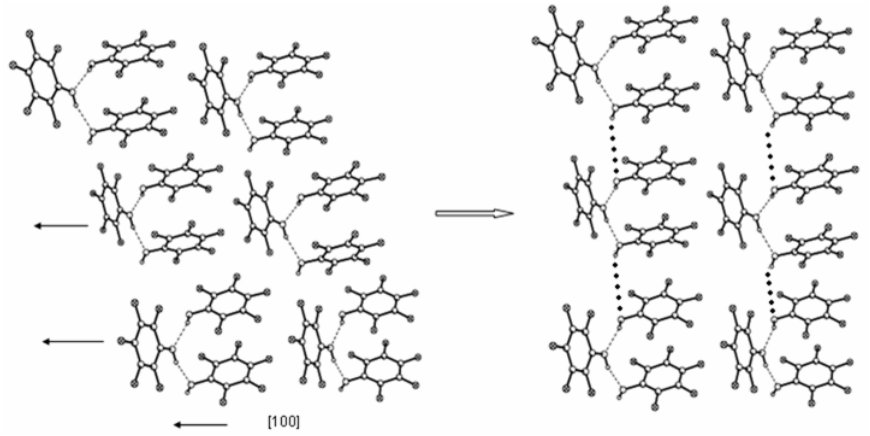


Fig. 3. A mechanism for synthon evolution, **P2** → **P1**. Shearing of trimers along [100] would form the putative O–H···O bonds shown in bold, completing the infinite (O–H···O–H···)$_n$ chain which is characteristic of **P1**.

Conclusions

Sometimes occurrence of multiple molecules (Z′>1) in asymmetric unit is an indication of polymorphism. The high Z′ structure is one of the metastable states which is kinetically locked. The more stable structure can be formed by lowering Z where symmetry expressed in more compact way. According to Steed's terminology [7] high Z′ structure is a fossil relic of the crystal nucleus of low Z′ structure. This phenomenon is nicely expressed in two crystal structures (**P1** and **P2**) of pentafluorophenol.

Experimental section

Crystallization

Low Z′ form **P1**: Semi-solid pentafluorophenol was liquefied by warming, and then filled in a 0.3 mm. diameter quartz capillary and sealed by flame sealing. The filled capillary was mounted on the goniometer and cooled to 261K. The solid was melted at

303K by slowly increasing the temperature. The mass was then cooled down to 283K and this resulted in solidification. The capillary surface was gently pressed by hand; this treatment increases both the temperature and the pressure within the capillary. This is sufficient to melt the solid. Cooling then to 277K resulted in a crystal, which was used for data collection. Data was, however, collected at 269K.

High *Z´* form **P2**: Pentafluorophenol and pentafluoroaniline were mixed in 1:1 ratio, and the procedure above was repeated except that the various temperatures in the heat-cool cycles were slightly different. The liquid inside the capillary was initially solidified at 301K. It was then melted at 298K and crystals (which were shown in the X-ray analysis to be **P2**) were finally grown at 294K. Data were collected at 292K.

X-ray data collection and crystal structure determinations

X-ray data for **P1** and **P2** were collected by me on a Siemens SMART CCD area detector system at the Universität Duisburg-Essen, Germany under the supervision of Prof. Dr. R. Boese using Mo-K_α radiation (λ = 0.71073 Å). The data were collected with a ω scan width of 0.3 deg. A total of 740 frames in one set were collected using SMART [11] keeping phi = 0 deg and chi = 0 deg. The data were reduced by Bruker AXS SAINT [11] program (version 6.02A). A multi-scan absorption correction was applied using the package SADABS [12] and XPREP [13] was used to determine the space group. The crystal structures were solved by direct methods using SHELXS (Versions 6.12) and refined by full matrix least-squares on F^2 using SHELXL programs (version 6.12A) [14]. Theta full and data parameter ratio is low because the data were collected with omega scan only. So the number of total refelctions is low. Moreover the the crystal was not growing properly after various attempts also. The position of the hydrogen atoms bound to phenyl ring were generated by riding model on idealized geometries with U_{iso} (H) = 1.2 U_{eq} (C), while in case of **P1** the H atom of the hydroxyl group was located in difference

Fourier maps and in case of **P2** the hydrogen atoms of the hydroxyl groups were generated and these H-atoms were also refined as riding, with U_{iso} (H) = 1.5 U_{eq} (O).

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APPENDIX II

Table 1. Crystallographic details of the acids discussed in this thesis

Chapter 2					
	1a	**1b**	**1c**	**1d**	**1e**
Empirical formula	$C_9H_5FO_2$	$C_9H_5ClO_2$	$C_9H_5BrO_2$	$C_9H_5IO_2$	$C_{10}H_8O_2$
Formula. wt.	164.13	180.58	225.04	272.03	160.16
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
T (K)[a]	100(2)	100(2)	100(2)	100(2)	100(2)
Space group	$P2_1/n$	$P2_1$	$C2/c$	$P2_1/c$	$P2_1/n$
a (Å)	3.8056(6)	3.7640(5)	14.7837(11)	4.8561(6)	7.5699(14)
b (Å)	6.3411(9)	27.884(4)	3.8430(3)	28.943(4)	21.518(4)
c (Å)	30.843(5)	7.5259(9)	28.983(2)	12.5658(14)	14.985(3)
α (°)	90	90	90	90	90
β (°)	92.520(2)	100.602(2)	103.9390(10)	99.6320(10)	92.258(3)
γ (°)	90	90	90	90	90
Z	4	4	8	8	12
V (Å^3)	743.57(19)	776.39(17)	1598.2(2)	1741.2(4)	2439.0(8)
D_{calc} (g/cm^3)	1.466	1.545	1.871	2.075	1.309
F (000)	336	368	880	1024	1008
μ (mm^{-1})	0.120	0.438	5.092	3.630	0.091
2θ range	5.28–52.76	2.92–52.12	2.90–52.80	2.82–52.10	3.32–52.12
Index ranges	$-4\leq h\leq 4$	$-4\leq h\leq 4$	$-18\leq h\leq 18$	$-5\leq h\leq 5$	$-9\leq h\leq 9$
	$-7\leq k\leq 6$	$-21\leq k\leq 34$	$-4\leq k\leq 4$	$-31\leq k\leq 35$	$-26\leq k\leq 26$
	$-38\leq l\leq 38$	$-9\leq l\leq 6$	$-36\leq l\leq 32$	$-15\leq l\leq 15$	$-15\leq l\leq 18$
R_1	0.0483	0.0438	0.0272	0.0362	0.0800
wR_2	0.1062	0.0925	0.0569	0.0735	0.1623
GOF	1.205	1.098	1.216	0.972	1.058
N-total[b]	6584	4042	8206	14683	20815
N-indep.[c]	1519	2119	1645	3403	4808
N-obsd.[d]	1485	2004	1514	2605	3293
Variable	117	218	117	223	337

a = Temperature of data collection; *b* = no of total reflections; *c* = no of independent reflections and *d* = no of observed reflections.

Table 1. *Continued…*

Chapter 2				
	1f (catemer)	**1f (dimer)**	**1g**	**2a**
Empirical formula	$C_{10}H_8O_3$	$C_{10}H_8O_3$	$C_{10}H_5F_3O_2$	$C_9H_5FO_2$
Formula. wt.	176.16	176.16	214.14	164.13
Crystal system	monoclinic	monoclinic	monoclinic	triclinic
T (K)[a]	100(2)	100(2)	298(2)	100(2)
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P\bar{1}$
a (Å)	7.5666(9)	8.7511(4)	13.750(3)	3.8378(6)
b (Å)	17.373(2)	5.0628(3)	7.8640(16)	6.1078(9)
c (Å)	7.1160(8)	19.1804(9)	8.3060(17)	15.695(2)
α (°)	90	90	90	89.897(2)
β (°)	116.541(2)	96.490(3)	94.48(3)	85.809(2)
γ (°)	90	90	90	85.225(2)
Z	4	4	4	2
V (Å^3)	836.83(17)	844.34(7)	895.4(3)	365.63(10)
D_{calc} (g/cm^3)	1.398	1.386	1.589	1.491
F (000)	368	368	432	168
μ (mm^{-1})	0.104	0.103	0.151	0.119
2θ range	4.68–52.18	4.28–56.56	5.94–49.84	2.60–52.14
Index ranges	$-8\leq h\leq 9$	$-11\leq h\leq 11$	$-16\leq h\leq 16$	$-4\leq h\leq 4$
	$-21\leq k\leq 13$	$-6\leq k\leq 6$	$-9\leq k\leq 0$	$-7\leq k\leq 7$
	$-8\leq l\leq 8$	$-25\leq l\leq 25$	$0\leq l\leq 9$	$-19\leq l\leq 19$
R_1	0.0431	0.0403	0.0374	0.0686
wR_2	0.1023	0.1064	0.0749	0.1338
GOF	1.081	1.032	1.104	1.314
N-total[b]	5241	8545	1747	4024
N-indep.[c]	1663	2103	1569	1450
N-obsd.[d]	1431	1593	1206	1376
Variable	127	121	141	115

Table 1. *Continued…*

Chapter 2				
	2b	**2c**	**2d**	**2e**
Empirical formula	$C_9H_5ClO_2$	$C_9H_5BrO_2$	$C_9H_5IO_2$	$C_{10}H_8O_2$
Formula. wt.	180.58	225.04	272.03	160.16
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic
T (K)[a]	223(2)	100(2)	223(2)	298(2)
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/n$
a (Å)	4.891(4)	4.7185(10)	10.2226(7)	9.611(2)
b (Å)	9.862(8)	10.078(2)	4.7960(3)	5.0139(12)
c (Å)	16.881(15)	10.039 (4)	18.4340(12)	17.987(4)
α (°)	90	90	90	90
β (°)	96.29(2)	94.373(4)	105.6790(10)	104.678(4)
γ (°)	90	90	90	90
Z	4	4	4	4
V (Å^3)	809.4(12)	807.9(3)	870.15(10)	838.5(3)
D_{calc} (g/cm^3)	1.482	1.850	2.077	1.269
F (000)	368	440	512	336
μ (mm^{-1})	0.420	5.036	3.632	0.088
2θ range	4.80–45.00	4.70–52.86	4.14–56.60	4.41–51.90
Index ranges	$-4\leq h\leq 4$	$-5\leq h\leq 4$	$-13\leq h\leq 13$	$-11\leq h\leq 11$
	$-10\leq k\leq 10$	$-12\leq k\leq 11$	$-4\leq k\leq 6$	$-6\leq k\leq 6$
	$-18\leq l\leq 18$	$-20\leq l\leq 21$	$-24\leq l\leq 24$	$-22\leq l\leq 22$
R_1	0.0834	0.0498	0.0444	0.0515
wR_2	0.1880	0.1224	0.1193	0.1222
GOF	1.171	1.118	1.062	1.027
N-total[b]	3081	4267	7217	8065
N-indep.[c]	1013	1639	2171	1631
N-obsd.[d]	766	1482	1750	1109
Variable	109	113	109	115

Table 1. *Continued…*

Chapter 3					
	1a	**1b**	**1e**	**1f**	**1g**
Empirical formula	$C_9H_6O_2$	$C_9H_5FO_2$	$C_9H_5IO_2$	$C_{10}H_8O_2$	$C_9H_5NO_4$
Formula. wt.	146.14	164.13	272.03	160.16	191.14
Crystal system	monoclinic	monoclinic	monoclinic	orthorhombic	monoclinic
T (K)[a]	203(2)	203(2)	183(2)	203(2)	223(2)
Space group	$P2_1/n$	$P2_1/c$	$P2_1$	$P2_12_12_1$	$P2_1/n$
a (Å)	5.091(3)	3.849(8)	4.1162(14)	6.862(2)	3.726(2)
b (Å)	14.988(9)	6.349(13)	6.013(2)	12.442(4)	7.511(5)
c (Å)	9.886(6)	31.47(7)	35.398(12)	19.621(7)	29.983(18)
α (°)	90	90	90	90	90
β (°)	90.180(11)	92.83(4)	90.958(6)	90	91.937(12)
γ (°)	90	90	90	90	90
Z	4	4	4	8	4
V (Å^3)	754.3(8)	768(3)	876.1(5)	1675.1(10)	838.6(9)
D_{calc} (g/cm^3)	1.287	1.419	2.063	1.270	1.514
F (000)	304	336	512	672	392
μ (mm^{-1})	0.091	0.116	3.608	0.088	0.122
2θ range	4.94–56.80	5.18–57.74	6.88–56.92	3.88–57.18	5.44–56.72
Index ranges	$-6\leq h\leq 6$	$-5\leq h\leq 4$	$-5\leq h\leq 5$	$-9\leq h\leq 9$	$-4\leq h\leq 4$
	$-19\leq k\leq 19$	$-8\leq k\leq 8$	$-7\leq k\leq 8$	$-13\leq k\leq 16$	$-10\leq k\leq 9$
	$-13\leq l\leq 13$	$-42\leq l\leq 39$	$-47\leq l\leq 47$	$-26\leq l\leq 17$	$-21\leq l\leq 40$
R_1	0.0714	0.0585	0.0570	0.0709	0.0584
wR_2	0.1863	0.1267	0.1560	0.1635	0.1405
GOF	1.037	0.919	1.449	1.069	1.025
N-total[b]	9198	3286	9460	10514	5168
N-indep.[c]	1872	1764	4136	4129	2065
N-obsd.[d]	1178	1028	3861	3193	1200
Variable	100	117	219	217	134

Table 1. *Continued…*

Chapter 3			
	2b	**2c (redetermined)**	**2f**
Empirical formula	$C_9H_7FO_2$	$C_9H_7ClO_2$	$C_{10}H_{10}O_2$
Formula wt.	166.15	182.60	162.18
Crystal system	monoclinic	orthorhombic	orthorhombic
T (K)[a]	173(2)	100(2)	293(2)
Space group	$P2_1/c$	*Pbcn*	*Pbcn*
a (Å)	9.529(2)	7.146(3)	7.3167(12)
b (Å)	6.0556(15)	8.232(3)	8.5089(12)
c (Å)	12.861(3)	25.032(9)	25.704(3)
α (deg)	90	90	90
β (deg)	105.810(4)	90	90
γ (deg)	90	90	90
Z	4	8	8
V (Å^3)	714.0(3)	1472.4(9)	1600.3(4)
D_{calc} (g/cm^3)	1.546	1.647	1.346
F (000)	344	752	688
μ (mm^{-1})	0.126	0.462	0.093
2θ range	4.44–56.60	3.26–52.26	6.34–57.02
Index ranges	$-12 \le h \le 12$	$-6 \le h \le 6$	$-9 \le h \le 9$
	$-8 \le k \le 7$	$-3 \le k \le 10$	$-11 \le k \le 11$
	$-17 \le l \le 17$	$-24 \le l \le 30$	$-34 \le l \le 33$
R_1	0.0596	0.0650	0.0641
wR_2	0.1475	0.1552	0.1687
GOF	1.074	1.092	1.099
N-total[b]	8417	2588	5700
N-indep.[c]	1752	1167	2013
N-obsd.[d]	1300	1044	1715
Variable	109	109	110

Table 1. *Continued…*

Chapter 4					
	1a	**1b**	**1c**	**1d**	**1e**
Empirical formula	$C_9H_4F_2O_2$	$C_9H_4F_2O_2$	$C_9H_4F_2O_2$	$C_9H_4F_2O_2$	$C_9H_4F_2O_2$
Formula. wt.	182.12	182.12	182.12	182.12	182.12
Crystal system	monoclinic	monoclinic	triclinic	monoclinic	triclinic
T (K)[a]	293(2)	100(2)	293(2)	100(2)	100(2)
Space group	$P2_1/n$	$P2_1/n$	$P\bar{1}$	$C2/c$	$P\bar{1}$
a (Å)	3.8159(8)	3.7382(9)	3.8186(12)	12.4524(15)	3.7264(4)
b (Å)	6.3305(13)	6.3729(15)	11.043(3)	8.0516(10)	7.4178(9)
c (Å)	32.311(7)	31.479(7)	19.776(6)	31.015(4)	14.0071(16)
α (°)	90	90	81.295(5)	90	91.260(2)
β (°)	91.80(3)	93.399(4)	88.697(5)	101.362(2)	97.152(2)
γ (°)	90	90	83.603(5)	90	98.075(2)
Z	4	4	4	16	2
V (Å^3)	780.1(3)	748.6(3)	819.2(4)	3048.7(7)	380.05(8)
D_{calc} (g/cm^3)	1.551	1.616	1.477	1.587	1.591
F (000)	368	368	368	1472	184
μ (mm^{-1})	0.140	0.146	0.134	0.144	0.140
2θ range	2.52–49.94	6.52-52.80	2.08–52.12	5.36–52.82	2.94–52.26
Index ranges	$0\leq h\leq 4$	$-4\leq h\leq 4$	$-4\leq h\leq 4$	$-15\leq h\leq 15$	$-4\leq h\leq 4$
	$0\leq k\leq 7$	$-7\leq k\leq 7$	$-13\leq k\leq 13$	$-10\leq k\leq 9$	$-9\leq k\leq 9$
	$-38\leq l\leq 38$	$-36\leq l\leq 39$	$-24\leq l\leq 24$	$-25\leq l\leq 38$	$-17\leq l\leq 17$
R_1	0.0763	0.0724	0.0699	0.0474	0.0410
wR_2	0.2228	0.1524	0.1760	0.1149	0.1044
GOF	1.064	1.227	1.063	1.033	1.053
N-total[b]	1581	4447	8347	13792	3513
N-indep.[c]	1380	1523	3208	3119	1511
N-obsd.[d]	852	1270	1806	2765	1295
Variable	119	126	243	263	127

Table 1. *Continued…*

Chapter 4					
	1f	**2b**	**2c**	**2d**	**2f**
Empirical formula	$C_9H_4F_2O_2$	$C_9H_4Cl_2O_2$	$C_9H_4Cl_2O_2$	$C_9H_4Cl_2O_2$	$C_9H_4Cl_2O_2$
Formula. wt.	182.12	215.02	215.02	215.02	215.02
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
T (K)[a]	293(2)	100(2)	293(2)	100(2)	100(2)
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/n$
a (Å)	6.90(2)	3.813(3)	3.875(6)	3.7809(9)	3.7901(6)
b (Å)	16.16(6)	7.405(6)	17.75(2)	6.2252(15)	15.425(2)
c (Å)	18.01(6)	31.94(2)	13.627(19)	36.625(9)	15.483(2)
α (°)	90	90	90	90	90
β (°)	90	91.762(13)	90.14(2)	92.344(3)	92.098(2)
γ (°)	90	90	90	90	90
Z	8	4	4	4	4
V (Å^3)	2009(12)	901.4(12)	937(2)	861.3(3)	904.6(2)
D_{calc} (g/cm^3)	1.204	1.584	1.524	1.658	1.579
F (000)	736	432	432	432	432
μ (mm^{-1})	0.109	0.678	0.652	0.709	0.675
2θ range	3.38–52.46	2.56–52.10	3.76–51.58	4.46–52.06	3.72–51.84
Index ranges	$-8\leq h\leq 8$	$-4\leq h\leq 4$	$-4\leq h\leq 4$	$-4\leq h\leq 4$	$-4\leq h\leq 4$
	$-19\leq k\leq 19$	$-7\leq k\leq 9$	$-21\leq k\leq 21$	$-7\leq k\leq 7$	$-18\leq k\leq 18$
	$-22\leq l\leq 21$	$-39\leq l\leq 29$	$-16\leq l\leq 16$	$-45\leq l\leq 41$	$-19\leq l\leq 19$
R_1	0.1546	0.0619	0.0711	0.0396	0.0614
wR_2	0.3968	0.1053	0.1374	0.0907	0.1497
GOF	0.907	1.022	1.119	1.148	1.319
N-total[b]	11555	4809	8600	5683	8852
N-indep.[c]	3963	1775	1789	1682	1773
N-obsd.[d]	574	1119	1300	1552	1711
Variable	235	121	122	126	121

Table 1. *Continued…*

Chapter 5					
	3	**4**	**5**	**6**	**7**
Empirical formula	$C_9H_7FO_3$	$C_9H_7ClO_3$	$C_9H_7NO_5$	$C_{10}H_{10}O_3$	$C_{10}H_{10}O_4$
Formula. wt.	182.15	198.60	209.16	178.18	194.18
Crystal system	monoclinic	triclinic	monoclinic	monoclinic	monoclinic
T(K)[a]	293(2)	100(2)	100(2)	100(2)	100(2)
Space group	$P2_1/c$	$P\bar{1}$	$P2_1/c$	$P2_1/n$	$P2_1/c$
a (Å)	19.311(4)	6.6481(5)	6.2755(15)	5.4529(5)	6.6844(7)
b (Å)	5.5820(11)	7.2198(6)	9.774(2)	6.7501(7)	5.3844(6)
c (Å)	7.3202(15)	10.0508(8)	14.039(3)	23.474(2)	24.494(3)
α (°)	90.00	75.1780(10)	90.00	90.00	90.00
β (°)	90.73(3)	80.6960(10)	90.973(4)	94.411(2)	91.668(2)
γ (°)	90.00	63.0000(10)	90.00	90.00	90.00
Z	4	2	4	4	4
V (Å^3)	789.0(3)	414.95(6)	860.9(4)	861.46(15)	881.21(17)
D_{calc} (g/cm^3)	1.533	1.589	1.210	1.374	1.464
F (000)	376	204	324	376	408
μ (mm^{-1})	0.130	0.426	0.101	0.102	0.114
2θ range	7.60–44.98	4.20–56.48	5.08-56.58	3.48–52.08	3.32–52.10
Index ranges	$-20\leq h\leq 15$	$-8\leq h\leq 8$	$-8\leq h\leq 8$	$-2\leq h\leq 6$	$-8\leq h\leq 8$
	$-5\leq k\leq 6$	$-9\leq k\leq 9$	$-12\leq k\leq 12$	$-8\leq k\leq 8$	$-6\leq k\leq 5$
	$-7\leq l\leq 7$	$-13\leq l\leq 11$	$-11\leq l\leq 18$	$-28\leq l\leq 28$	$-26\leq l\leq 30$
R_1	0.0624	0.0355	0.0518	0.0385	0.0386
wR_2	0.01877	0.0860	0.1109	0.0963	0.0952
GOF	1.108	1.074	1.018	1.042	1.056
N-total[b]	1671	4868	6707	4701	4705
N-indep.[c]	884	1954	2068	1701	1740
N-obsd.[d]	713	1797	1498	1478	1466
Variable	127	126	164	127	136

Table 1. *Continued…*

Chapter 5					
	8	**9**	**10**	**11**	**12**
Empirical formula	$C_9H_7FO_3$	$C_9H_6F_2O_3$	$C_9H_6F_2O_3$	$C_9H_6F_2O_3$	$C_9H_6F_2O_3$
Formula. wt.	182.15	200.14	200.14	200.14	200.14
Crystal system	triclinic	triclinic	monoclinic	monoclinic	triclinic
T(K)[a]	298(2)	298(2)	298(2)	298(2)	100(2)
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$P\bar{1}$
a (Å)	3.7911(5)	3.7362(5)	3.7703(6)	3.7199(7)	3.6704(4)
b (Å)	6.6771(9)	6.6882(9)	6.6112(11)	6.6698(12)	6.7796(7)
c (Å)	16.248(2)	16.969(2)	33.142(6)	33.683(6)	16.3936(18)
α (°)	99.097(2)	100.263(2)	90.00	90.00	100.852(2)
β (°)	96.015(2)	93.340(2)	92.929(2)	92.396(3)	95.421(2)
γ (°)	96.624(2)	96.730(2)	90.00	90.00	93.797(2)
Z	2	2	4	4	2
V (Å^3)	400.22(9)	413.00(10)	825.0(2)	835.0(3)	397.37(7)
D_{calc} (g/cm^3)	1.511	1.609	1.611	1.592	1.673
F (000)	188	204	408	408	204
μ (mm^{-1})	0.128	0.149	0.149	0.147	0.155
2θ range	5.12–52.10	4.90–52.16	4.92–52.06	4.84–61.82	2.54–52.22
Index ranges	$-4\leq h\leq 4$	$-4\leq h\leq 4$	$-3\leq h\leq 4$	$-4\leq h\leq 4$	$-4\leq h\leq 4$
	$-8\leq k\leq 7$	$-8\leq k\leq 8$	$-7\leq k\leq 8$	$-7\leq k\leq 8$	$-8\leq k\leq 8$
	$-19\leq l\leq 19$	$-20\leq l\leq 20$	$-40\leq l\leq 40$	$-41\leq l\leq 41$	$-20\leq l\leq 20$
R_1	0.0536	0.0682	0.0445	0.0492	0.0352
wR_2	0.1453	0.1907	0.1136	0.1368	0.0943
GOF	1.092	1.121	1.074	1.126	1.101
N-total[b]	3409	4271	4411	5224	4163
N-indep.[c]	1565	1630	1631	1623	1586
N-obsd.[d]	1310	1291	1446	1446	1472
Variable	122	131	133	136	139

Table 2. Hydrogen bond geometries in the crystal structures described in this thesis

Chapter 2				
Acid	**Interaction**	***d* (Å)**	***D* (Å)**	***θ* (˚)**
1a	O–H···O	1.66	2.641(2)	172
	O–H···O	1.64	2.599(3)	164
	C–H···O	2.45	3.372(2)	142
	C–H···F	2.47	3.345(2)	137
1b	O–H···O	1.64	2.620(4	172.8
	O–H···O	1.65	2.626(3)	168.9
	C–H···O	2.52	3.371(4)	135.0
	C–H···O	2.63	3.475(4)	134.9
	C–H···Cl	2.72	3.785(4)	166.0
1c	O–H···O	1.68	2.634(3)	162
	O–H···O	1.68	2.656(3)	173
	C–H···O	2.66	3.483(4)	132
	C–H···O	2.70	3.643(4)	145
	C–H···Br	2.92	3.638(3)	124
	C–H···π	2.76	–	160
1d	O–H···O	1.68	2.656(5)	175
	O–H···O	1.67	2.651(5)	173
	C–H···O	2.69	3.720(6)	159
	C–H···O	2.46	3.227(6)	127
	I···O	–	3.303(4)	–
1e	O–H···O	1.66	2.634(3)	173.1
	O–H···O	1.66	2.638(3)	170.9
	O–H···O	1.69	2.633(4)	158.2
	O–H···O	1.83	2.640(4)	137.6
	C–H···O	2.62	3.489(4)	136.3
	C–H···O	2.62	3.488(5)	136.2
	C–H···O	2.64	3.603(4)	147.7
	C–H···O	2.70	3.652(4)	145.9
	C–H···π	2.78	–	140
	C–H···π	2.88	–	141

Table 2. *continued …*

Chapter 2				
Acid	**Interaction**	***d* (Å)**	***D* (Å)**	***θ* (˚)**
1f (catemer)	O–H···O	1.67	2.6461(16)	169.7
	O–H···O	1.74	2.7077(18)	169.4
	C–H···O	2.62	3.435(2)	131.5
	C–H···O	2.63	3.589(2)	146.8
	C–H···O	2.65	3.480(2)	133.0
1f (dimer)	O–H···O	1.71	2.6864(13)	176
	C–H···O	2.38	3.3840(14)	153
	C–H···O	2.55	3.3815(14)	133
	C–H···π	2.70	–	153
1g	O–H···O	1.80	2.701(2)	150
	C–H···O	2.50	3.550(3)	164
	C–H···O	2.58	3.318(3)	125
	C–H···F	2.56	3.382(3)	132
	C–H···F	2.68	3.407(3)	124
2a	O–H···O	1.64	2.616(3)	174
	O–H···O	1.65	2.626(3)	173
	C–H···O	2.52	3.394(3)	137
	C–H···F	2.48	3.500(3)	156
	C–H···F	2.57	3.468(3)	140
2b	O–H···O	1.68	2.661(7)	179.0
	C–H···O	2.71	3.459(9)	125
	Cl···O	–	3.402(7)	–
2c	O–H···O	1.69	2.674(6)	177
	C–H···O	2.68	3.435(7)	127
	C–H···O	2.76	3.705(6)	146
	Br···O	–	3.265(4)	–
2d	O–H···O	1.68	2.658(5)	175.3
	C–H···O	2.72	3.670(6)	146.8
	I···O	–	3.351(3)	–

Table 2. *Continued …*

Chapter 2				
Acid	**Interaction**	***d* (Å)**	***D* (Å)**	**θ (˚)**
2e	O–H···O	1.68	2.652(3)	171.7
	O–H···O	1.67	2.652(3)	172.1
	C–H···O	2.69	3.690(4)	152.8
Chapter 3				
1b	O–H···O	1.66	2.633(6)	171.6
	O–H···O	1.67	2.612(6)	159.3
	C–H···O	2.47	3.345(8)	136.6
	C–H···F	2.60	3.470(8)	136.5
	C–H···F	2.66	3.357(8)	121.7
1e	O–H···O	1.61	2.57(2)	165.6
	O–H···O	1.74	2.636(15)	150.6
	C–H···O	2.38	3.36(2)	150.0
	C–H···O	2.46	3.405(16)	145.3
1f	O–H···O	1.68	2.646(3)	167.6
	O–H···O	1.66	2.638(3)	177.0
	O–H···O	1.68	2.646(3)	166.8
	O–H···O	1.69	2.638(3)	161.9
	C–H···O	2.36	3.418(3)	165.9
	C–H···O	2.53	3.533(3)	153.5
1g	O–H···O	1.67	2.634(3)	164
	O–H···O	1.72	2.660(3)	158
	C–H···O	2.45	3.345(4)	139
	C–H···O	2.46	3.367(4)	141
	C–H···O	2.60	3.425(3)	132
2b	O–H···O	1.67	2.652(2)	178.3
	C–H···O	2.52	3.294(3)	127.4
	C–H···F	2.44	3.115(2)	119.2

Table 2. *Continued …*

Acid	Interaction	*d* (Å)	*D* (Å)	*θ* (˚)
		Chapter 3		
2f	O–H···O	1.75	2.6494(17)	150.3
	O–H···O	1.70	2.6546(18)	163.0
	C–H···O	2.57	3.5845(19)	154.9
		Chapter 4		
1a	O–H···O	1.90	2.602(5)	126
	O–H···O	1.74	2.639(5)	150
	C–H···O	2.50	3.431(6)	143
	C–H···F	2.53	3.526(6)	153
1b	O–H···O	1.68	2.630(4)	162.0
	O–H···O	1.68	2.604(4)	154.7
	C–H···O	2.44	3.340(5)	139.7
	C–H···F	2.49	3.354(4)	136.3
	C–H···F	2.76	3.666(4)	141.1
1c	O–H···O	1.70	2.668(4)	168
	O–H···O	1.70	2.682(4)	174
	C–H···O	2.37	3.363(5)	152
	C–H···O	2.39	3.447(4)	164
	C–H···F	2.41	3.389(4)	150
	C–H···F	2.46	3.369(4)	140
	C–H···F	2.48	3.518(4)	160
	C–H···F	2.48	3.492(4)	154
1d	O–H···O	1.62	2.6000(19)	177.22
	O–H···O	1.66	2.6407(18)	178
	C–H···O	2.51	3.408(2)	139.9
	C–H···O	2.57	3.518(2)	145.3
	C–H···F	2.67	3.557(2)	139.2

Table 2 *Continued …*

Acid	Interaction	*d* (Å)	*D* (Å)	*θ* (˚)
		Chapter 4		
1e	O–H···O	1.68	2.634(2)	161
	O–H···O	1.66	2.6180(19)	165
	C–H···O	2.59	3.573(2)	149
	C–H···F	2.50	3.541(3)	160
	C–H···F	2.68	3.573(2)	139
2b	O–H···O	1.77	2.722(6)	161
	C–H···O	2.62	3.399(7)	134
	C–H···O	2.72	3.559(7)	128
2c	O–H···O	1.77	2.722(6)	161
	C–H···O	2.62	3.399(7)	128
	C–H···O	2.72	3.559(7)	134
2d	O–H···O	1.62	2.568(4)	161.3
	O–H···O	1.64	2.621(3)	173.8
	C–H···O	2.40	3.327(3)	142.3
2f	O–H···O	1.64	2.619(4)	162
	C–H···O	2.41	3.262(4)	135
	C–H···O	2.61	3.355(5)	126
	C–H···O	2.76	3.417(5)	119
		Chapter 5		
3	O–H···O	1.69	2.672(5)	176
	O–H···O	1.96	2.639(4)	124
	C–H···O	2.41	3.135(4)	130
	C–H···O	2.45	3.508(4)	165
	C–H···F	2.66	3.341(4)	120
4	O–H···O	1.73	2.7117(16)	179
	O–H···O	2.13	2.6796(17)	113
	C–H···O	2.00	2.7564(16)	132
	C–H···O	2.16	2.8768(19)	122
	Cl···Cl	–	3.1960(7)	–

Table 2 *Continued ...*

Chapter 5				
Acid	**Interaction**	***d* (Å)**	***D* (Å)**	***θ* (˚)**
5	O–H···O	1.68	2.657(2)	171
	O–H···O	2.07	2.656(2)	116
	O–H···O	2.21	2.866(2)	123
	C–H···O	2.35	3.372(2)	156
	C–H···O	2.40	3.164(2)	127
	C–H···O	2.65	3.525(2)	138
6	O–H···O	1.64	2.6240(13)	178
	O–H···O	2.08	2.6279(14)	113
	O–H···O	2.27	3.0254(14)	132
	C–H···O	2.22	2.8945(18)	118
	C–H···O	2.46	3.4598(19)	153
7	O–H···O	1.63	2.6133(14)	177
	O–H···O	2.07	2.6327(14)	114
	O–H···O	2.29	3.0332(15)	132
	C–H···O	2.46	3.4197(19)	147
	C–H···O	2.59	3.6581(18)	169
	C–H···O	2.51	3.4115(18)	140
8	O–H···O	1.72	2.702(2)	174
	O–H···O	2.04	2.791(2)	132
	C–H···O	2.22	2.892(3)	118
	C–H···F	2.53	3.606(3)	173
9	O–H···O	1.72	2.701(3)	174
	O–H···O	2.05	2.786(3)	130
	C–H···F	2.71	3.297(4)	114
	C–H···F	2.53	3.556(5)	157
10	O–H···O	1.74	2.723(2)	177
	O–H···O	2.01	2.801(2)	135
	C–H···F	2.46	3.335(3)	137
	C–H···F	2.67	3.424(3)	126

Table 2. *Continued …*

Chapter 5				
Acid	**Interaction**	***d* (Å)**	***D* (Å)**	***θ* (˚)**
11	O–H···O	1.84	2.702(2)	176
	O–H···O	2.20	2.815(2)	138
	C–H···F	2.71	3.240(3)	117
	C–H···F	2.65	3.421(3)	140
12	O–H···O	1.72	2.6989(14)	177
	O–H···O	2.04	2.7898(14)	131
	C–H···F	2.46	3.4866(16)	158
	C–H···F	2.48	3.1660(16)	120
	C–H···F	2.49	3.2448(16)	125

ABOUT THE AUTHOR

Dinabandhu Das was born in Hafizgonj, a village in the Hooghly district of West Bengal, India, in 1976. He received his primary education in Hafizgonj Primary School and completed his secondary and higher secondary school education in Bali Dewanganj and Gaurhati Haradas Institution respectively. After the completion of his B.Sc. and M.Sc. from Burdwan University, he joined the School of Chemistry, University of Hyderabad to pursue the Ph.D. degree in 2001.

List of publications

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