Preface

This thesis entitled "Crystal Structure and Conformational Studies of Some Organic Compounds of Medicinal Interest" presents the results of the crystallographic investigations carried out by the candidate in the Department of Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai-600 025, India under the guidance of Prof. M. N. Ponnsawamy during the period 2000-2005.

Studies on the structure, symmetry and conformation of molecules of medicinal and biological interest form the basis of major part of investigations from this laboratory during the past five decades. Crystallographic studies on biological molecules have revolutionized our insights into the way the biological systems operate. The knowledge of stereochemistry of the molecules is also derived from single crystal X-ray diffraction studies. The double-helical structure of DNA, the planarity of peptide bond, the triple helical structure of collagen, the globular conformation of enzymes and antibodies – all owe their discoveries to X-ray diffraction studies. Practically all the drugs known today are the result of either accidental discoveries or from trial and error processes. The X-ray studies thus play an important role in the design of appropriate drugs.

The thesis consists of nine chapters, dealing with the crystal structures of organic compounds which possess medicinal and pharmaceutical values. The crystal structure of a Zn complex is added as an Appendix. The relevant references cited in the text are listed in alphabetical order at the end of the thesis.
Chapter 1 presents the crystal structures of three phenyl derivatives, namely (i) 4 - (isobutyrylamino) - 2 - (trifluoro methyl) benzoic acid [IBTBA], (ii) 2-Chlorophenyl) (3,4-dimethoxy phenyl) methanone [CDMPM] and (iii) 1,2-Bis (2-Chlorophenyl) -1,2-bis (3,4-dimethyl phenyl) ethane-1, 2-diol [BCBDE]. All the structures were solved by direct methods and refined to final R-values of 0.0443, 0.0463 and 0.0578 respectively. The phenyl rings in all the three molecules are planar. In CDMPM, the phenyl rings orient at an angle of 73.9(8)° to each other. The isobutyrylamide group in IBTBA adopts an extended conformation. In BCBDE, the 3,4-dimethyl phenyl groups stack one over the other with little sliding. Both the hydroxyl groups of ethane moiety show trans configuration. C-H...O, N-H...O and C-H...Cl types of intra and intermolecular hydrogen bondings stabilize the molecules in the unit cell in addition to van der Waals forces.

Chapter 2 deals with the crystal structures of (i) 5-(4-Chlorophenyl)-6-ethyl pyrimidine –2,4-diamine + 2-(acetyl amino) benzoic acid [CPEPD + AABA] and (ii) 5-(4-Chlorophenyl) -6- ethyl pyrimidine –2, 4-diamine + 2- (propionyl amino) benzoic acid [CPEPD + PABA]. Both the structures were solved by direct methods and refined to final R-values of 0.0494 and 0.1026 respectively. In both the molecules, the benzene and pyrimidine rings are planar. The pyrimidine and phenyl rings orient similar to the biphenyl ring systems. C-H...O, C-H...N, N-H...N, N-H...O, N-H...Cl and C-H...Cl types of intra and intermolecular hydrogen bondings play vital roles to stabilize the molecules in the unit cell.

Chapter 3 presents the crystal structures of (i) 3,3,6,6-Tetramethyl-3, 4, 6,7,9,10-hexahydro-1, 8 (2H, 5H) acridinedione (TMHA) and (ii) 10-(2-Methoxyphenyl)-3,4,6,7,9,10-hexahydro-1, 8(2H, 5H) acridinedione (MPHA). Both the structures were solved by direct methods and refined to final R-values of 0.0672 and 0.0965, respectively. The central pyridine ring of the acridinedione moiety tends
to be in planar conformation due to electron delocalization effects around the ring. The fused rings on either sides of the central ring show sofa conformation in both the molecules TMHA and MPHA. Packing of the molecules in the unit cell are due to C-H...O and N-H...O types of hydrogen bondings in addition to van der Waals forces.

Chapter 4 describes the crystal structure of 4-\{E-[(1- Allyl-2-butyl-4-mercapto-4,5-dihydro-imidazole-5-yl) imino] methyl\} -5-phenyl-1,3,4-triazole-2-thiol [ABMIPT]. The structure was solved by direct methods and refined to a final R-value of 0.0582. The imidazole, triazole and phenyl rings are planar and the n-butyl group attached to imidazole moiety adopts an extended conformation. The phenyl ring is oriented at an angle of 24.1(2)° to the imidazole moiety. The triazole and imidazole rings are oriented at an angle of 39.8(2)° to each other. N-H...N, C-H...N, C-H...S and S-H...N types of hydrogen bondings stabilize the molecules in the unit cell.

Chapter 5 deals with the crystal structure of 5-Benzyl-8-E-benzylidene-6, 7,7a, 10a-tetrahydro-5H- cis- cyclopenta- [5,6] pyrano [3,3- c] quinolin-6-one [BBTCPQ]. The structure was solved by direct methods and refined to a final R-value of 0.0565. In this molecule, the pyran ring adopts half-chair conformation whereas the cyclopentene takes up envelope conformation. The other rings present in the molecule are planar. The molecules are stabilized by C-H...N and C-H...O types of intra and intermolecular hydrogen bondings in addition to van der Waals forces.

Chapter 6 presents the crystal structure of 1-Phenyl sulfonyl-2-methyl-3-cyano indole [PSMCI]. The structure was solved by direct methods and refined to a final R-value of 0.0891. The indole and benzene rings are planar and the cyano
group in pyrrolidine ring shows linear conformation. The C-H...N and C-H...O types of hydrogen bondings are involved in stabilizing the molecules in the unit cell in addition to van der Waals forces.

Chapter 7 describes the crystal structures of (i) Methyl-4-oxo-r-2, c-6-diphenyl piperidine-3-carboxylate [MODPC] and (ii) N-Methyl-3-t-isopropyl r-2, c-6-diphenyl piperdin -4-one [NMIDPPO]. Both the structures were solved by direct methods and refined to final R-values of 0.0458 and 0.0570, respectively. The piperidine rings in both the molecules adopt chair conformation with the planar phenyl rings substituted equatorially at 2, 6-positions. C-H...O type of intermolecular hydrogen bondings are useful in crystal packing.

Chapter 8 deals with the crystal structure of 1, 6-Dtaoa [6.5] orthocyclophane-13, 16-diene-15-one [DOCD]. The structure was solved by direct methods and refined to a final R-value of 0.0466. The whole moiety of cyclophane derivative is almost planar except the n-butyl group which is in zigzag conformation. The planarity is due to electron delocalization, which is reflected in bond length values. The packing of the molecules in the unit cell is through van der Waals forces.

Chapter 9 presents the crystal structure of 2,4-Bis(pyridine-2-carbonyl)-1-(2-pyridyl)-3,5-di-p-tolylcyclohex-1-ol [PPTCH]. The structure was solved by direct methods and refined to a final R-value of 0.062. The central cyclohexane ring adopts chair conformation. Three pyridine and two toluene rings are planar. O-H...N, C-H...N and C-H...O types of hydrogen bondings stabilize the molecules in the unit cell in addition to van der Waals forces.

The crystal structure of tris (1, 2-Diaminoethane) zinc (II) perchlorate [Zn(en)_3]^2ClO_4^-] is dealt at the end as an Appendix. The structure was solved by direct
methods and refined to a final R-value of 0.0769. The environment around Zn atom is octahedral and the three five membered rings present in the molecule take up half-chair conformation. The N-H...O, C-H...O and O-H...N types of hydrogen bondings stabilize the molecules in the unit cell in addition to van der Waals forces.

The overall details pertaining to crystallization, crystal data, intensity data collection, data reduction, the corrections applied, structure solution, structure refinement, the formulae used in calculating the geometrical parameters and ring conformations are explained at the beginning of the thesis itself in the experimental section while the specific details of each structure is presented in tabular form in the respective chapters.

All computations involved in this thesis were carried out using various Pentium-PC computing systems available in the department.

The figures and tables are numbered serially chapter wise. The figures are given at the appropriate places in the text while the tables are given collectively at the end of each chapter.

The structure factor (h,k,l,Fo²,Fe²) tables are given in the CD as a zip file (SFT.ZIP) enclosed in a pouch at the back cover of the thesis.

Based on the above studies, the following papers have been published / communicated.


4. 1, 2-Bis (2-Chlorophenyl)-1, 2-bis (3, 4-dimethylphenyl) ethane-1, 2-diol. N. Sampath, S. Aravindhan, M. N. Ponnuwamy, H. S. Yathirajan and M. Nethaji. *Acta Cryst.* (2005) E61, o886-o888


6. Crystal structure of N-Methyl-3-t-isopropyl-r-2, c-6-diphenyl piperidin-4-one; N. Sampath, S. Aravindhan, M. N. Ponnuwamy and M. Nethaji. *Analytical Sciences.* (2004) VOL.21, x67-x68


Experimental

Introduction

The crystal structure and conformation of some medicinally important organic compounds are presented in this thesis. Crystal structure analysis consists of several important stages, such as crystallization, intensity data collection, data reduction, structure solution and finally structure refinement. Since the techniques involved in conducting the experiments and the procedure adopted for the structure determination are common for all the chapters, a brief summary of the details is given in this section.

Crystallization

Crystallization is to create a dynamic equilibrium between the particles in fluid phase and solid phase from saturated solutions. Several techniques are available for crystallization of small molecules such as slow evaporation, slow cooling and diffusion methods. Among them the slow evaporation method is the simplest technique adopted to obtain good diffracting quality crystals. Single crystals of all the compounds presented in this thesis are obtained from slow evaporation technique.

Intensity Data Collection

In practice there are three different methods available to determine the structure of a compound, namely X-ray diffraction technique in solid state, NMR studies in liquid state and quantum chemical or molecular mechanics calculations in isolated state.
Of these, X-ray diffraction is the most powerful technique used to elucidate the three-dimensional structure of molecules. In the present study, Intensity data were collected using either of the two different types of diffractometers, namely Enraf-Nonius CAD4 diffractometer (Enraf-Nonius, 1994) or SMART CCD area detector (Siemens, 1996). Brief details of these instruments are given below.

**CAD-4 Diffractometer**

In CAD-4 diffractometer, the crystal can be rotated around three axes (χ,θ,ω) independently, and the detector can be rotated about a fourth angle (2θ, centric with ω); this gives rise to the name “four-circle diffractometer” (Enraf-Nonius, 1994). Values of the four corresponding angles may be computed for all possible reflections, once a few reflections have been located and identified. The angles for a particular reflection were set automatically under computer control, the intensity of the reflection was measured with detector and recorded, together with measurements of the background intensity near the reflection. One normally advances incrementally through the miller indices h,k,l and a systematic scan of all desired reflections are done completely automatically.

**SMART CCD System for Single Crystal Diffraction**

SMART (Simens Molecular Analysis Research Tool) possesses all the components needed to collect X-ray diffraction data from single crystals.

SMART (Siemens, 1996) uses similar diffraction geometry as in Siemens P4 diffractometer, where the direct beam propagates from −XL to +XL; +ZL is up; and +YL makes a right-handed set (at ω = 0°, χ = 270°, the goniometer head is at +YL). These axes are called the laboratory axes.
The goniometer setting angles $2\theta$ and $\omega$ are right-handed rotations about ZL and $\phi$ is a left-handed rotation about ZL. A PLATFORM three circle goniometer has $\chi$ fixed at 54.7°. The goniometer setting $2\theta$ angle is identical to the detector "swing" angle. The detector axes are referred to as X and Y, as opposed to XL, YL and ZL for the laboratory axes. When an area detector frame is displayed, the origin of the frame is at its lower left, at $X = Y = 0$. When the goniometer setting angles are all zero, the detector X axis parallel to $-Y$ and the detector Y axis is parallel to ZL.

Orientation matrices determined by SMART follow the same convention as the XSCANS scintillation counter program. The matrix itself is independent of the setting angles of the frames used to determine it.

**Unit Cell Parameters and Data Collection**

Unit cell parameters were obtained from a least-squares fit of the angular settings of 25 accurately determined reflections (see crystal data tables). The three dimensional intensity data were collected using graphite monochromated Mo Kα / Cu Kα radiations. Two or three standard reflections were monitored periodically and their variations are used for the necessary corrections to be applied. All the intensities were corrected for variable scan speed, background and attenuation using the relation

$$I_{raw} = f [N_c - 2(L_b + R_b)] NPI$$

where, $I_{raw}$ is the relative intensity

- $N_c$ is the peak count
- $L_b$ & $R_b$ are the left and right background counts
- NPI is the scan speed, and
- $f$ is the attenuation factor.
The observed structure factor for each reflection is obtained through the equation

$$F_0 = k \left[ I_{raw}/Lp \right]^{\frac{1}{2}}$$

where, $k$ is the scale factor relating the arbitrary intensity counts to structure amplitude

$L$ is the Lorentz factor defined as $= 1/\sin2\theta$, and

$p$ is the polarization factor given by

$$p = \frac{[\cos2\theta_m + \cos^22\theta]}{[1+\cos2\theta_m]}$$

where, $\theta$ is the Bragg angle, and $\theta_m$ is the monochromator setting angle.

Siemens SMART CCD area detector (Siemens, 1996) is equipped with graphite monochromated Mo K$\alpha$ radiation. The data collection was covered over a hemisphere of reciprocal space by a combination of three sets of exposures and each set had a different $\phi$ angle (0, 88 and 180°) for the crystal and each exposure of 30s covered 0.3° in $\omega$. The coverage of the unique set is 99% complete. The crystal-to-detector distance was 4cm and the detector swing angle was -35°. Crystal decay was monitored by repeating thirty initial frames at the end the data collection.

Data Reduction

The raw data collected from the diffractometer suffers from physical and geometrical error factors and hence cannot be used for structure elucidation straightaway. Therefore the intensity data have to be corrected for Lorentz, polarization and absorption effects. The Lorentz and polarization corrections are must for every case, since the reflection efficiency varies with the reflection angle, whereas the absorption correction has to be applied depending upon the nature of the
compound and the radiation used, i.e. depending on the linear absorption coefficient value (Stout and Jensen, 1968).

The space groups of the crystal are determined from the systematic absences of the reflections and by intensity statistics. If space group ambiguity arises then the contents of the unit cell, the number of molecules present in the cell, the distribution of intensity and other relevant details are analyzed in depth.

Structure Solution

In general, the structure factor is represented as

\[ F_{hkl} = \sum f_j \exp [2\pi i(hx_j + ky_j + lz_j)] \]

where \( f_j \) is the atomic scattering factor or form factor for the \( j^{th} \) atom. In other words

\[ F_{hkl} = |F_{hkl}| e^{i\phi_{hkl}} \]

Here, \( F_{hkl} \) is the structure amplitude and \( \phi_{hkl} \) is the associated phase. The structure amplitude can be obtained directly from the square root of the observed intensity. But there is no direct means to get the associated phase values experimentally. In order to compute the electron density,

\[ \rho(x,y,z) = (1/V) \sum \sum F_{hkl} \exp [-2\pi i(hx_j + ky_j + lz_j)] \]

where, \( V = \) Volume of the unit cell.

One needs both the structure amplitudes and phases. The non-availability of the phases to compute the electron density is called the phase problem in
crystallography. Several methods are used to solve the phase problem, and some of them are

i) Direct methods

ii) Heavy atom method

iii) Isomorphous replacement method and

iv) Anomalous dispersion methods

The above methods can be successfully applied to locate the approximate positions of all the atoms (trial structure of a molecule) in the unit cell. Direct methods have been used to solve the structures presented in this thesis. A brief summary of the stepwise procedure involved in the above methods is given below.

**Direct Methods**

Direct methods is used to calculate the phases directly by simple mathematical procedure from a single set of X-ray intensities. The basic postulates of direct methods are the positivty (the electron density is positive everywhere) and the atomicity (the atoms are spherically symmetric). The structure amplitudes and phases are linked with electron density through Fourier transformation. A mathematical constraint on the function $\rho(x)$ imposes a corresponding constraint on the structure factor. This constraint however does not hamper the evaluation of $\phi_{hkl}$ directly. The various steps involved in the direct methods are

**Step I** Conversion of observed structure factors $|F_{hkl}|$ to normalized structure factors $|E_{hkl}|$ which are independent of $\theta$.

**Step II** Setting up of phase relations using triple phase relations (triplets) and four phase relations (quartets).
Step III  Selection of a few reflections, the phases of which are assigned \textit{apriori}.

Step IV  Phase propagation and refinement using tangent formula (Karle and Hauptman, 1950).

Step V  Calculation of best phase sets and expressing the reliability of the phases in terms of Combined Figure of Merit (CFOM).

Step VI  Calculation of electron density map (E-map) with $|E_{hkl}|$ as the Fourier Coefficient.

\textbf{Structure Refinement}

Structure refinement consists of obtaining the best fit between a set of observed measurements and the quantities calculated from a model postulated to explain them. Differences between the observed and the calculated values can arise due to random errors (statistical fluctuations) in the observations and defects in the model (systematic errors). The trial structure obtained from the structure solution is refined in order to get the accurate atomic positions and the associated thermal parameters. Though several structure refinement process are in vogue, the full-matrix least-squares refinement technique is the conventional one and more widely used in small molecular structure determination. We have used SHELXL93 (Sheldrick, 1993) computer program for the refinement. The least-squares refinement consists of using the squares of the differences between the observed and calculated values as a measure of their disagreement, and adjusting the parameters so that the total disagreement tends to a minimum. The refinement is based on $F_0$ which would involve taking the square root of a negative number of reflections with negative $F_0^2$ (i.e. background higher than the peak as a result of statistical
fluctuation). The refinement on $F_0^2$ using all the data provides a good result for weakly diffracting crystals and in particular for pseudosymmetry problems. The residual factor or reliability index $R_1$ is given as

$$R_1 = \frac{\Sigma |F_0| - |F_e|}{\Sigma |F_0|}$$

where the summation is made over all the observed reflections [$F_0 > 4\sigma(F_0)$]. Lower the $R_1$ value is greater the accuracy of the molecular model. A suitable weighting scheme is applied at the end of the refinement procedure, the weighted $R$-factor $wR_2$ (intensity based) is given as

$$wR_2 = \left( \frac{\Sigma w(|F_0| - |F_e|)^2}{\Sigma w|F_0|^2} \right)^{1/2}$$

where

$$w = 1/[\sigma(F_0^2) + (K_1P)^2 + K_2P]$$

$K_1$ and $K_2$ are constants and $P = (F_0^2 + 2F_e^2)/3$

Goodness-of-fit (S) is defined as

$$S = \left( \frac{\Sigma w(|F_0| - |F_e|)^2}{(m-n)} \right)^{1/2}$$

where $m$ is the number of reflections and $n$ is the total number of parameters or variables.
Calculation of Geometrical Parameters

Crystal and molecular structure determination provide us the unit cell parameters and fractional atomic co-ordinates of all the atoms and their associated thermal parameters. The geometrical parameters such as bond lengths, bond angles and torsion angles can be derived from the coordinates of the relevant atoms.

For a triclinic lattice, the distance between the two points in fractional atomic coordinates \((x_1, y_1, z_1)\) and \((x_2, y_2, z_2)\) is given by the law of cosines in three dimensions

\[
L = \sqrt{(\Delta x)^2 + (\Delta y)^2 + (\Delta z)^2 - 2ab\Delta x\Delta y\cos\gamma - 2ac\Delta x\Delta z\cos\beta - 2bc\Delta y\Delta z\cos\alpha}
\]

where \(a, b, c, \alpha, \beta, \gamma\) are the unit cell parameters and \(\Delta x = x_1 - x_2\), \(\Delta y = y_1 - y_2\) and \(\Delta z = z_1 - z_2\). The above equation can be applied for any crystal system to calculate the bond lengths. A knowledge on the bond length values helps to identify the nature of chemical bonds (triple, double, partially double or single bond) involved in the molecule.

Bond angle formed by the three atoms A, B, C where the angle is subtended by the bonds AB and AC can be calculated using the formula

\[
\theta = \cos^{-1}\left(\frac{(AB)^2 + (AC)^2 - (BC)^2}{2(AB)(AC)}\right)
\]

Bond angles are useful to find the type of hybridization of a particular atom.
Torsion angle is the angle subtended between the two planes designated as PQR and QRS of the four atoms P, Q, R and S. Torsion angles are calculated as

$$\chi = \left( \begin{array}{c} \mathbf{N_1} \times \mathbf{N_2} \\ \mathbf{|N_1||N_2|} \end{array} \right)$$

where N1 and N2 are normals to the PQR and QRS planes, respectively. Torsion angles are useful to understand the orientation/conformation of one plane/ring with another plane/ring formed by the various groups of atoms in a molecule.

**Ring Conformation**

Ring conformation can be predicted with the help of a mirror plane lying perpendicular to the ring plane and the two-fold symmetry lying in the ring plane as depicted in Fig E.1. Three mirrors and three 2-fold symmetries (for a chair), two mirror symmetries (for a boat) and two-fold symmetries (for a twist boat) are the possible conformations in addition to sofa and half-chair for a six-membered ring. The sofa has only one mirror and the half-chair possess one two-fold symmetry. The three possible conformations of a five-membered ring are shown in Fig E.2. In five-membered rings, containing identical heteroatom, at the 1 and 3 positions, substitution at the 2nd position appears to affect the conformation a little when compared to the unsubstituted ring. Many rings are found to be distorted without having any defined conformations. In practice, conformations are described from the asymmetry parameters which give the extent of deviation of the ring from the ideal conformations (Cremer and Pople, 1975; Duax et al., 1976, Nardelli, 1983a). Program PARST (Nardelli, 1983b; 1995) is used for the calculation of geometrical parameters.
Fig E.1. Possible conformations of the six-membered ring.
Fig E.2. Possible conformations of the five-membered ring.
Molecular Interactions

In crystalline state, the molecules are stabilized by intramolecular and intermolecular interactions like hydrogen bonds, van der Waal’s forces and possibly some short contacts between the two atoms. Hydrogen bonding is the specific type of non-bonded interaction between two electronegative atoms (donor and acceptor) where the hydrogen atom is bonded to them. The schematic representation of the hydrogen bond is D-H...A where D is the donor and A is the acceptor. The crystal structures presented in this thesis are found to have C-H...O, C-H...S, C-H...N, O-H...Cl, N-H...N, O-H...F, C-H...F and N-H...O types of hydrogen bonds.

The existence of C-H...O bonds in crystals is evident from the study of Taylor and Kennard (1982) and Desiraju (1991, 1996). The ability of a C-H group to act as a proton depends upon on the hybridization \([C(sp)-H > C(sp^2) – H > C(sp^3) – H]\), and increases with the number of adjacent electron withdrawing groups (Steiner, 1996).

Weak attractive forces between uncharged atoms or molecules are collectively referred to as van der Waal’s forces. These forces arise from the electrostatic attraction of the nuclei of one molecule by the electrons of a different molecule. The repulsion arising between the electrons of two molecules as well as the nuclei of two molecules counteract the electrostatic attractions, but there is always a small net attractive force. The van der Waal’s forces are range forces i.e., they are significant only when the molecules are very close to one another.
Computation

The graphics plots are obtained using programs PLUTON (Spek, 1997), ZORTEP (Zsolnai, 1997) and SHELX (Sheldrick, 1993; 1996; 1997). All calculations were performed using Indigo Silicon Graphics and various Pentium PC computing systems available in the department.