CHAPTER 1

GENERAL INTRODUCTION

In medicinal and pharmacological arena, the drug actions are very essential to understand the mechanisms of the cell damage or repair. The drug molecules are nothing but ligands, which bind to the various active sites of the macromolecules (DNA, protein, etc.) and inhibits the cell processes.

The mechanism of the drug action can be understood, provided its three dimensional molecular structure is known. X-ray crystallography is the most powerful method for the determination of the 3-dimensional molecular structure, conformation, structure stability by hydrogen bonds and packing of the molecules in the solid state. Once the crystal structures of the drug molecules are determined, structure-activity relationships (SAR) can be predicted based on the conformation and functional groups present in the molecule.

The thesis comprises of the crystallographic studies of acridinedione and triazolothienopyrimidine derivatives. Since both the groups of molecules are of biological and pharmacological interest, crystal and molecular structure determination of seven acridinedione and four triazolothienopyrimidine derivatives were carried out. This chapter gives a general introduction to acridine and triazolothienopyrimidine derivatives and their applications. A brief description of the procedure for crystal structure determination using X-ray diffraction is also presented in this chapter.
1.1 INTRODUCTION TO ACRIDINE

Acridine, $C_{15}H_9N$, is a planar heterocyclic aromatic molecule derived from anthracene by the replacement of one meso CH group by nitrogen and it is shown in Figure 1.1. It was prepared by Graebe and Cairo in 1871. Eventhough the molecule was prepared in the 19th century, its importance was realised only in 1950's. Several researchers were more specific and threw light on acridine molecule, since it possesses various medicinal properties and is predominant over anticancer drugs.

DNA (Deoxyribo Nucleic Acid) binding drugs are usually more effective, as it involves directly in the cell process. The modes of binding of the ligand molecules to DNA are groove binding (major or minor) and intercalation. Acridine molecules bind reversibly to double helical DNA by sliding between the adjacent base pairs (intercalation). Local helical distortions like helix unwinding takes place in order to accommodate the inserted ligand molecule (Neidle and Abraham 1984). The mode of non-covalent interaction or stacking interaction of acridine with DNA leads to various biological applications.

1.2 BIOLOGICAL APPLICATIONS OF ACRIDINE DERIVATIVES

Acridine and its derivatives exhibit various biological activities, related to frameshift mutation, antitumor, antimalarial, antimicrobial, hypotensive, anti-inflammatory, anti-implantation, antiameobic and photophysical properties.

1.2.1 Frameshift Mutagens

9-amino acridines are classical frameshift mutagens in viruses and bacteria (Acheson 1956). Amino acridines binds to DNA by intercalation (Ferguson and Denny 1990; Baguley et al 1982; Wilson et al 1981;
Karle et al. 1980; Nasim and Brychcy 1979; Sakore et al. 1977, 1979; Reddy et al. 1979; Lerman 1961; Peacocke and Skerret 1956) resulting in increase of the spacing between the adjacent base pairs to approximately 6.8 Å (Berman et al. 1979; Pritchard et al. 1966). Streisinger and his colleagues (Streisinger et al. 1966) proposed a model for frameshift mutagenesis in which, DNA strand breakage occur with or without subsequent gap formation can lead to transient local melting and reannealing of DNA that can lead to mispaired configuration (looped out single-stranded DNA regions) that are then stabilized by DNA repair. Subsequent DNA replication can give rise to addition or deletion of base pairs, so called frameshift mutations. The addition or deletion usually is of the +1 or -1 base pair, occasionally larger additions and deletions occur with reasonable frequency (Ocada et al. 1970; Imada et al. 1970; Okada et al. 1969; Terzaghi et al. 1966).

Benzacridines, derivatives of acridine with added benzene rings, are found to be mutagenic and carcinogenic in nature. They were detected to be environmental mutagens (Lehr et al. 1988) with low water solubility. 3,6-diamino substituted acridine derivatives (Proflavine) are substrates for metabolic activation (Fugunaga et al. 1987) and they can be activated to mutagenic products by exposure to light (Nasim and Brychcy 1979; Uggla 1990).

1.2.2 Antitumor activity

In addition to the mutagenic effect of the 9-amino acridine derivatives, they also possess antitumor activity. A series of 9-acridinyl amino derivatives (quinacrine) namely, ICR-170, ICR-171, ICR-191 and ICR-449 are mutagens as well as antitumor agents. ICR-170 is a powerful antitumor agent against ascites tumors and a mutagen for neurospora (Glusker et al. 1972; Berman and Glusker 1972; Peck et al. 1961).
ICR-171, ICR-191 and ICR-449 are mutagens for salmonella, but not an active antitumor agent (Glusker et al 1972a; Carrell 1972; Glusker et al 1973). Certain anilo acridine derivatives (Amsacrine) namely, m-AMSA and 2-meO AMSA or O-AMSA bind to DNA by intercalation with slightly higher unwinding angles, both 20.5° (Waring 1976) than that of 9-amino acridine. Both the structures have the same conformation but the former one is an active antitumor agent than the latter one (Karle et al 1980).

Nitroacridines, in particular 1-nitro acridine derivatives, nitracrine or ledacrine have been widely used as anticancer drugs (Gniazdowski et al 1978). These 1-nitro substituted nitracrine derivatives have been registered as antitumor drugs (C-283, C-684 and C-829) in Poland (Hempel et al 1979; Stezowski et al 1985). The conformation of the 2-nitro nitracrine differs slightly from the 1-nitro nitracrine, which are inactive antitumor agents (Hempel et al 1979a).

1.2.3 Antimicrobial activity

Recently, the antimicrobial activities like bactericidal and fungicidal were tested with 9-acridinones and 9-thioalkylacridines towards E.coli, Staphylococcus aureus, Mycobacterium smegmatis and Candida albicans. It was found to be the inhibitors of RNA synthesis more than the DNA and protein synthesis in the antimicrobial activity of the drugs (Cremieux et al 1995). In earlier days, 9-amino acridine was combined with sulfa drugs (sulfonamides) by salt bridges and found to possess synergistic antimicrobial activity (Ghose et al 1988, 1987).

Apart from the bactericidal and fungicidal activities, few acridine derivatives are said to possess antiamebic (Prasad et al 1984), hypotensive, anti-inflammatory and anti-implantation (Jain et al 1991; Pratibha et al 1991) activities.
1.2.4 Miscellaneous

Acridine molecules bind to DNA by intercalation. A mere intercalation alone does not play a crucial role in pharmacological properties, but strongly depends upon the nature and the positions of the different ring substituents. Similarly, when p-nitrobenzoyl is linked with acridine moiety by hexamethylene spacer, it behaves as a DNA photocleaving agent (Kuroda et al 1995; Kuroda and Shinomiya 1992; Buchardt et al 1987). In addition to it, the cyclo-bis and tris acridines are also effective DNA photocleaving agents (Lorente et al 1995).

If the binding constants or affinity of the intercalators is to be increased, the acridine molecule (ligand) has to be linked with a positive ion to form metal complexes, which increases the binding constants of acridine to DNA, since DNA is a negatively charged polymer (Ceci et al 1993).

Methylation of the amine group of proflavine (3,6-diaminoacridine) provides acridine orange, which is a basic dye for leather and widely used in biochemistry as a stain for nucleic acids (Ferguson and Denny 1991). Acridine yellow is the 2,7-dimethyl derivative of proflavine and was formerly used as a dye for leather.

Intramolecular charge transfer is the basic requirement for the biological, photophysical and electrochemical properties of acridinium dyes. Nearly 16 crystal structures of acridinium dyes were determined by Goubitz K., Reiss C.A., Heijdenrijk D. and their groups (Goubitz et al 1989; Haming et al 1990).

1.3 PRESENT STUDY OF ACRIDINEDIONES

So far, crystal structures of a number of acridine derivatives have been solved and their biological activities (DNA intercalation, frameshift...
mutation, antitumor, antiameobic, antimalarial, anti-implantation, hypotensive, antiseptic and anti-inflammatory), photophysical and electrochemical properties were correlated with the conformation of the molecules.

Acridinediones, the acridine derivatives having two keto functional groups at the 1\textsuperscript{st} and 8\textsuperscript{th} positions are found to be good antimalarial agents. A series of 3-aryl-7-chloro-3,4-dihydro-1,9(2H,10H)-acridinediones have been tested in mice, monkey and parasites and notified as very good antimalarial agents. The substitution of alkyl at N10 and C2 positions, introduction of imino side chain at C9 position and the imines of the N-H acridinediones are found to be antimalarial agents (Werbel \textit{et al} 1985; Raether \textit{et al} 1989; Kesten \textit{et al} 1992). Substituted hexahydro acridine-1,8-dione, a novel dihydropyridine molecule resembles K-channel openers, which relaxes KCl precontracted urinary-bladder smooth muscle \textit{in vitro} (Li \textit{et al} 1996; Trivedi \textit{et al} 1995). These acridinediones were also found to be efficient laser dyes, lasing around 475-495 nm (Shanmuga Sundaram \textit{et al} 1993; Prabahar \textit{et al} 1991). Apart from the above applications, acridinedione also possesses photophysical and electrochemical properties (Mohan \textit{et al} 1996).

The present study of acridinediones, whose outer rings are hydrogenated and their basic skeleton structure is shown in Figure 1.1. Till 1990, more than 2000 publications related to acridines were published. Even then, less number of acridinedione (lack of conjugation and lack of planarity) crystal structures have been solved. Informations related to structure-activity relationships of acridinediones are vague. Keeping this in mind, Prof.V.T.Ramakrishnan and his co-workers (University of Madras) have synthesized a number of acridinedione derivatives in order to study their thermodynamic, photophysical and electrochemical properties. We have carried out the crystal structure determination for a series of acridinedione molecules of the above mentioned. The molecules are of monomeric, dimeric
(bis) and trimeric (tris) in nature. Our studies describe the conformation, hydrogen bonding nature and molecular packing in solid state.

Of the seven acridinediones presented in this thesis, three are monomers, two are dimers (bis), one trimer and the other is a sulphur analogue (thiapyranedione derivative).

The acridinedione compounds studied in the thesis are given below with the molecular formula and their code name used in the thesis.

1. 9-Propyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8 (2H,5H) acridinedione, \( \text{C}_{20}\text{H}_{29}\text{NO}_{2} \) (MADN-I)

2. 10-Benzyl-9-propyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8(2H,5H)acridinedione monohydrate, \( \text{C}_{27}\text{H}_{37}\text{NO}_{2}\text{H}_{2}\text{O} \) (MADN-II)

3. 10-Butyl-3,3,6,6,9-pentamethyl-3,4,6,7,9,10-hexahydro-1,8 (2H,5H) acridinedione, \( \text{C}_{22}\text{H}_{33}\text{N}_{2}\text{O}_{2} \) (MADN-III)

4. 1,5-Bis-[3,3,6,6,9-pentamethyl-3,4,6,7,9,10-hexahydro-1,8 (2H,5H)acridinedione-10-yl]pentane dihydrate, \( \text{C}_{41}\text{H}_{60}\text{N}_{2}\text{O}_{4}\text{H}_{2}\text{O} \) (BADN-I)

5. 1,3-Bis-[3,3,6,6,10-pentamethyl-3,4,6,7,9,10- hexahydro-1,8 (2H,5H) acridinedione-9-yl]propane, \( \text{C}_{39}\text{H}_{54}\text{N}_{2}\text{O}_{4} \) (BADN-II)

6. 1,3,5-Tris-[3,3,6,6,9-tetramethyl-3,4,6,7,9,10-hexahydro-1,8 (2H,5H) acridinedione-10-yl]-benzene, \( \text{C}_{60}\text{H}_{75}\text{N}_{3}\text{O}_{6} \) (TADN)

7. 3,3,7,7-Tetramethyl-3,4,7,8-tetrahydrodibenzo[b,e]4H-thiapyrane-1,9(2H,6H)ridione, \( \text{C}_{17}\text{H}_{22}\text{O}_{2}\text{S} \) (TPDN)
Chapter 2 describes the crystal structures of three acridinedione monomers MADN-I, MADN-II and MADN-III and chapter 3 gives the crystal structures of two acridinedione dimers (bis) BADN-I and BAND-II. The crystal structure of the trimer (TADN) is presented in chapter 4, which shows a greater crystallographic interest, having a twinned lattice. Apart from the acridinedione, a thiapyranedione (nitrogen atom replaced by sulphur) derivative’s crystal and molecular structure (TPDN) is presented in chapter 5.

Acridine molecules are well known DNA intercalators. In order to understand the interaction between the acridinediones and DNA, spectroscopic studies of a dimer (BADN-I) and a sulphur substituted (TPDN) compound with ct-DNA were carried out and presented in chapter 6.

1.4 TRIAZOLOTHIENOPYRIMIDINE DERIVATIVES

Triazolothienopyrimidine molecules are planar molecules consisting of fused thiene, pyrimidine and triazo rings and its schematic diagram is shown in Figure 1.1. They are the new series of compounds whose crystal structures have been solved and presented in this thesis. Condensed [1,2,4] triazoles compounds are biologically important (Francis and Gelotte 1988; Kottke et al 1983) and pharmacologically active drug molecules.

1.5 PHARMACOLOGICAL APPLICATIONS OF TRIAZOLOTHIENOPYRIMIDINE DERIVATIVES

A series of triazolothienopyrimidine derivatives were synthesized by Prof. U.S. Pathak and his co-workers (L.M. College of Pharmacy, Ahmedabad) and tested them for pharmacological activities. These compounds were found to possess CNS (Central Nervous System) depressant, analgesic, and skeletal muscle relaxant properties.
Figure 1.1 Molecular diagrams of (a) acridine (b) acridinedione and (c) triazolothieno pyrimidine.
CNS drugs acting on the synthesis, storage, metabolism and release of neurotransmitters fall into the presynaptic category. Synaptic transmission can be depressed by blockade of transmitter synthesis or storage. For eg. p-chlorophenylalanine blocks the synthesis of serotonin (neurotransmitter). Choline acetylase, an enzyme which is responsible for the synthesis of acetylcholine (neurotransmitter) near the presynaptic end of axons by the transfer of acetyl group from acetyl CoA. The arrival of a nerve impulse at the presynaptic membrane leads to the diffusion of acetylcholine to the post synaptic membrane (Stryer 1986). Triazolothienopyrimidine molecules bind at the active sites of the enzymes and inhibit the enzymatic action. The synthesis and transmission of acetylcholine is inactivated by enzymatic degradation. Thus the molecular mechanism of CNS depressant is activated.

If the neurotransmitter has been released into the synaptic cleft, its action is terminated either by uptake or degradation. In few cases, the transmitter receptors provides the primary site of drug action in the post synaptic region. Drugs can act either as neurotransmitter agonists or they can block the receptor function (Katzung 1989).

1.6 PRESENT STUDY OF TRIAZOLOTHIENOPYRIMIDINES

A total of four triazolothienopyrimidine derivatives are studied and presented in this thesis, two of them are substituted pyrimidine structures, one is a substituted pyrimidone and the fourth one is pyrazolo pyrimidone derivative. The names of these compounds with code names are given below.

1. 2-(4-Chlorophenylamino)-6,7,8,9-tetrahydro-[1]benzothieno[3,2-e][1,2,4]triazolo[1,5-clpyrimidine, C\textsubscript{17}H\textsubscript{14}N\textsubscript{5}SCI (TTPN-I)
2. 2-(4-Chlorophenyl)amino-4-methyl-6,7,8,9-tetrahydro-[1]benzo-
thieno[3,2-e] [1,2,4]-triazolo[1,5-c]pyrimidine, C_{18}H_{15}N_{5}SCl
(TTPN-II)

3. 4-Phenyl-6,7,8,9-tetrahydro-[1]benzothieno[3,2-e] [1,2,4]
triazolo[4,3-alpyrimidin-5(4H)-one, C_{17}H_{14}N_{4}OS (TTPN-III)

4. 5-[4-Methylphenyl]-6-[4-methylphenyl]amino-1-phenylpyrazolo
[3,4-d]pyrimidin-4(5H)-one, C_{25}H_{21}N_{5}0 (PPDN)

Chapter 7 deals with the crystal structures of TTPN-I and TTPN-II.
Crystal structure determination and other details of TTPN-III and PPDN
are given in chapter 8.

The last chapter (ie.chapter 9) bears the overall conclusion of the
thesis in an explicit manner.

1.7 PROCEDURE FOR CRYSTAL STRUCTURE
DETERMINATION

The major part of the thesis deals with the crystallographic studies
of organic molecules and hence it is essential to give a brief summary of the
crystal structure determination. X-ray crystallography is the most powerful
method for determining relative atomic positions in a molecular structure
by noting the electron density maxima in the unit cell. The electron density
is represented as

\[
\rho(x,y,z) = \frac{1}{V} \sum \sum F_{hkl} \exp \left[-2\pi i (hx+ky+lz)\right]
\]  (1.1)

where \(\rho(x,y,z)\) is the electron density at position (x,y,z). V is the volume of
the unit cell. \(F_{hkl}\) is the structure factor for a reflection hkl.
1.7.1 Crystallisation

Crystallisation is nothing but the existence of dynamic equilibrium between the particles in fluid phase and solid phase from the saturated solution. Several techniques are involved for crystallisation of small molecules. Among them slow evaporation, slow cooling and diffusion method are different types, of which slow evaporation is the simplest technique to obtain crystals of diffraction quality. Single crystals of all compounds presented in the thesis were obtained from slow evaporation technique. After careful examination under polarising microscope, a good quality crystal can be selected for diffraction studies.

1.7.2 Unit cell parameters determination and intensity data collection

Determination of unit cell parameters and the intensity data collection were carried out using a four circle diffractometer (Siemens P4 or Enraf-Nonius CAD4) with θ/2θ scan mode and monochromatic radiation (MoKα or CuKα). In order to check the intensity deterioration due to radiation damage or by crystal decomposition, three standard reflections were monitored for every one hour or for every hundred reflections.

1.7.3 Data Reduction

The raw data collected from diffractometer suffers from physical and geometrical factors and hence could not be used for structure elucidation immediately. The intensity data have to be treated for Lorentz, polarisation and absorption effects. The Lorentz and polarisation corrections are essential for every case, but the absorption correction is to be applied depending on the nature of the compound and radiation used, i.e., depending on the linear absorption coefficient value.
The space group of the crystals were determined from the systematic absences of the reflections and the intensity statistics. If a space group ambiguity arises then the content of the unit cell i.e., the number of formula units present in the unit cell is analysed.

1.7.4 Structure solution

In general, the structure factor is represented as

\[ F_{hkl} = \sum_{j=1}^{N} f_j \exp \left[ 2\pi i (hx_j + ky_j + lz_j) \right] \]  \hspace{1cm} (1.2)

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

\[ F_{hkl} = |F_{hkl}| \exp^{i\phi_{hkl}} \]  \hspace{1cm} (1.3)

\(|F_{hkl}|\) is the structure amplitude and \( \phi_{hkl} \) is the associated phase. The structure amplitude can be obtained directly from the observed intensity as its square root; but there is no way to experimentally get the associated phase values. In order to compute the electron density as in equation 1.1, one needs both the structure amplitudes and phases. The nonavailability 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 method
The above methods can be successfully used to trace out the approximate positions of all the atoms (trial structure of a molecule) in an unit cell. This process is known as structure solution. If the molecule consists of limited number of light atoms, then direct methods can be used for the structure determination. We have used only direct methods to solve all the structures presented in this thesis.

1.7.5 Direct methods

Direct methods are used to calculate the phases directly by simple mathematical means from a single set of X-ray intensities. The basic postulates of direct methods are positivity (the electron density is positive everywhere) and atomicity (the atoms are spherically symmetric). The structure amplitudes and phases are linked through a knowledge of electron density by Fourier transformation. A mathematical constraint on the function \( \rho(x) \) impose corresponding constraint on the structure factor. This constraint is sufficient to evaluate \( \phi_{hk\ell} \) directly. Various steps involved in direct methods are:

Step I Conversion of observed structure factors \( |F_{hk\ell}| \) to normalised structure factors \( |E_{hk\ell}| \) 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 apriori.

Step IV Phase propagation and refinement using tangent formula (Karle and Hauptman 1950).
Step V Calculation of best phase sets and express 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.

After computing for the electron density map, the electron density maxima shows a sensible molecular fragments and it can be compared with the expected molecular structure. The computer program used for the structure solution is SHELXS86 (Sheldrick 1990).

1.7.6 Structure refinement

Structure refinement consists in obtaining the best fit between a set of observed measurements and quantities calculated from a model postulated to explain them. Differences between the observed and the calculated values can arise from 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. Several structure refinement processes are used in structure determination. They are

1) Least-squares method
   i) Full matrix
   ii) Block diagonal
2) Rigid-body
3) Energy minimisation
4) Simulated annealing
5) Maximum entropy method
6) Maximum likelihood
Among them, full matrix least-squares refinement technique is the conventional one and widely used in small molecular structure determination. We have used SHELXL93 (Sheldrick 1993) computer program for full-matrix refinement. The least squares refinement consists in using the squares of the difference between the observed and calculated values as a measure of their disagreement, and adjusting the parameters so that the total disagreement is a minimum. The refinement is based on $F_0^2$ because it is impossible to refine on $F$ using all the data which would involve taking the square root of a negative number for 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

$$ R_1 = \frac{\Sigma | |F_o| - |F_c| |}{\Sigma |F_o|} \quad (1.4) $$

where the summation is made over all observed reflections [$F_o > 4\sigma(F_o)$]. Lower the R value, 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

$$ wR_2 = \left( \frac{\Sigma w_i (|F_o| - |F_c|)^2}{\Sigma w_i |F_o|^2} \right)^{1/2} \quad (1.5) $$

where

$$ w = 1/ [\sigma(F_o^2) + (K1^*P)^2 + K2^*P] $$

$K1$ and $K2$ are the constants and $P = (F_0^2 + 2F_c^2) / 3$.
1.7.7 Calculation of geometrical parameters

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

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

\[
1 = \left( (\Delta x)^2 + (\Delta y)^2 + (\Delta z)^2 - 2ab \Delta x \Delta y \cos \gamma - 2ac \Delta x \Delta z \cos \beta - 2bc \Delta y \Delta z \cos \alpha \right)^{1/2}
\]

(1.6)

where \(a, b, c, \alpha, \beta, \gamma\) are the unit cell parameters. The above equation can be applied for any crystal system to calculate the bond lengths. This parameter helps to identify the nature of chemical bonds (triple, double, partially double and single bond nature) involved in a molecule.

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

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

(1.7)

Bond angles are useful to find the type of hybridisation of a particular atom.

Torsion angle is the angle between the two planes designated as 123 and 234 of the four atoms 1, 2, 3 and 4. Torsion angles are calculated as
\[ \chi = \frac{\mathbf{N}_1 \times \mathbf{N}_2}{|\mathbf{N}_1| \cdot |\mathbf{N}_2|} \] (1.8)

where \( \mathbf{N}_1 \) and \( \mathbf{N}_2 \) are normals to the 123 and 124 planes respectively.

\[ \chi = 0, \text{ the configuration is } \text{cis or syn periplanar} \]
\[ \chi = \pm 60, \text{ the configuration is } \text{gauche (+g or -g)} \]
\[ \chi = 180, \text{ the configuration is } \text{trans or anti periplanar} \]

where configuration is the spatial arrangements of the atoms.

1.7.8 Ring conformation

Ring conformation can be determined with the help of mirror symmetry lying perpendicular to the ring plane and the two-fold symmetry lying in the ring plane as depicted in Figure 1.2. The maximum symmetry i.e., six two-fold and six mirror symmetries are present for a planar six membered ring and for a chair conformation, three mirror and three two-fold symmetries are present. In case of boat conformation, two mirror symmetries and for twist boat, two two-fold symmetries are present. The other two are the sofa and half-chair conformations. The former one possesses only one mirror and the latter one possesses only one two-fold symmetry. 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 (Duax 1976 and Nardelli 1983). Program PARST (Nardelli 1983a) was used for the calculation of geometrical parameters.

1.7.9 Molecular interactions

In crystalline state, the molecules are stabilised by intramolecular and intermolecular interactions like hydrogen bonds, short contacts between the two atoms and van der Waals forces. Hydrogen bonds play a crucial role
Figure 1.2  The most commonly observed conformations of six membered rings. The mirror and twofold rotational symmetries are indicated on the right.
in determining the structure of water, the folding of proteins and the pairing of bases in DNA etc. For this reason, crystal packing studies are essential to understand the laws governing the intramolecular and intermolecular H-bonding in a molecular crystal.

Hydrogen bond is the specific interaction between the 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 H-bonding donor and A is the acceptor. To be more accurate, hydrogen bond is nothing but electrostatic interaction. After the hydrogen bond formation, the D...A distance is shortened, whereas the D-H distance is elongated and the proton of the donor is moved to the middle position of D...A (Giacovazzo et al 1992).

The crystal structures presented in this thesis are governed by O-H...O, N-H...O, N-H...N and C-H...O types of hydrogen bonds. For this reason, the different types of hydrogen bonds are discussed here.

An O-H...O interaction is a hydrogen bond, if the H...O distance is significantly less than the sum of their van der Waals radii (2.6Å) and the angle O-H...O > 170° (Olovsson and Jonsson 1976). At present, even the long range electrostatic interactions are considered to be weak hydrogen bonds with H...O distance < 3.0Å and the angle O-H...O > 90° (Steiner and Saenger 1993).

The formation of base pairs in DNA and folding of proteins are mainly due to the presence of N-H...O and N-H...N hydrogen bonds. The H...O distance is 2.05Å and N-H...O distance is 2.9Å with an angle of 170° (Legros and Kvick 1980; Berkovitch-Yellin and Leiserowitz 1984). Regarding N-H...N hydrogen bonds the distance criteria is 3.10Å.

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The formation of base pairs in DNA and folding of proteins are mainly due to the presence of N-H...O and N-H...N hydrogen bonds. The H...O distance is 2.05Å and N-H...O distance is 2.9Å with an angle of 170° (Legros and Kvick 1980; Berkovitch-Yellin and Leiserowitz 1984). Regarding N-H...N hydrogen bonds the distance criteria is 3.10Å.
The concept of C-H...O hydrogen bond was not accepted in earlier days. After the conclusive evidence of the existence of C-H...O bonds in crystals provided by Taylor and Kennard in 1982, the C-H...O hydrogen bond was paid more attention. It is also an electrostatic interaction with C...O distance 3.0-4.0Å and angle 90-180° (Desiaraju 1991). The ability of a C-H group to act as a proton donor depends on the hybridisation [C(sp)-H > C(sp²)-H > C(sp³)-H], and increases with the number of adjacent electron withdrawing groups (Steiner 1996).

In addition to the above hydrogen bonds there are various other hydrogen bonds like C-H...N, C-H...Cl, C-H...S and N-H...S which are pronounced in crystal structural chemistry. Apart from them, there is also a possibility of interactions like C-H...π interactions in molecular crystals, where the delocalised electrons in an unsaturated terminal alkynes (C \equiv C) are ready to interact with the C-H group (Steiner 1996). The π...π interactions are also present in planar molecules, where the planar rings stack one over the other.