CHAPTER II

PHYSICO-CHEMICAL PROPERTIES OF HETEROCYCLIC COMPOUNDS
Five (or) six membered ring with hetero atoms, such as Oxygen (or) Nitrogen (or) Sulphur impart special biological activity to the compound. It is also known that fusion of heterocyclic nuclei enhances the pharmacological activities [1-7] more than their parent nucleus.

Oxazoles have been the subject of many reviews [8] and textbooks[9]. Oxazoles are azoles containing nitrogen and oxygen. This group of heterocyclic compounds posses five membered rings [10-11] which is composed of three carbon, one nitrogen and one oxygen atoms. The azoles are planar molecules with conjugated electron sextets in cyclic system as in parent oxazole molecule is shown below:

![Oxazole Structure]

The lone pair of electrons on nitrogen which is coplanar with heterocyclic and not involved in the delocalization confirms weakly basic properties. The method of preparation of oxazoles was first reported by Cornforth [12] and was subsequently modified. Since then many new substituted oxazoles have been developed.

Oxazoles are prepared by reaction between an acid amide and a α-halo ketone [13].

**Reaction I-1**

\[
\text{C}_6\text{H}_5\text{C}=\text{O} + \text{N} - \text{H}_2 \rightarrow \text{C}_6\text{H}_5 - \text{C} = \text{N} + \text{H}_2\text{O} + \text{HBr}
\]

A group of synthseses, which utilize amino-, imino- and amidonitriles gave a wide range of 5-substituted oxazoles on reaction with aldehydes. Nitrilium salts condense with α-halo ketones in high yields [14].

**Reaction I-2**

\[
\text{R}^1\text{C} = \text{N} - \text{SnCl}_4 + \text{Ph.CO.CH.CR} \rightarrow \text{R}^1\text{C} = \text{N} - \text{SnCl}_4 + \text{Ph.CO.CH.CR}
\]
Nitrilium methyldes give 1,3-cycloaddition [15].

\[
\text{Reaction I-3.} \quad R-C=\text{N} \xrightarrow{\text{Et}_3\text{N}} \quad \xrightarrow{\text{R}^2\text{CHO}} \quad \begin{array}{c}
\text{N} \\
\text{CHR}^1
\end{array} \\
\text{N} \\
\text{CHR}^1
\]

1,3-Dipolar cycloaddition reaction have been employed carbonyl carbenes affording low yields of oxazoles. [16].

**Reaction I-4**

\[
\begin{array}{c}
\text{N}_2 \\
\text{R- CO - C - R}^1
\end{array} \xrightarrow{\Delta \text{R}^2\text{CN} \text{ Metal. Cat}} \quad \begin{array}{c}
\text{O} \\
\text{C R}^1
\end{array} \\
\text{C R}^1
\]

Carboxyl nitrenes offer a third variant on 1,3- cycloadditions [17-20].

**Reaction I-5**

\[
\text{R- CO - N}_3 \xrightarrow{\text{pph}_3} \quad \begin{array}{c}
\text{N} \\
\text{C}
\end{array} \\n\text{R-C}
\]

\[
\text{R}^1\text{C} \equiv \text{CR}^1
\]

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2
\end{array}
\]

\[
\text{R} = \text{alkyl/aryl/alkoxy}
\]

Oxazolin-5 ones under kinetic controlled conditions give 5-acyloxy-derivatives [21].

**Reaction I-6**
Oxazoles may also be synthesized by the acid catalyzed reaction of propargyl derivatives with amides (or) nitriles, as in the synthesis of 2, 4, 5-trimethyl oxazole [22].

**Reaction 1-7**

\[
\text{HC}≡\text{C}−\text{Me} + \text{Me CONH}_2 \xrightarrow{\text{ACOH}, \text{H}_2\text{SO}_4} \text{Me} \begin{array}{c} \text{Me} \\ \text{O} \\ \text{N} \end{array} \begin{array}{c} \text{Me} \\ \text{Me} \end{array}
\]

Diagnostically useful spectroscopic characteristics of oxazoles have been reviewed including chemical shifts "J" values and \(^{14}\text{N}\) spectroscopy [23]. The UV spectra are similar to the related azoles.

Oxazoles absorb at 250 nm (log\(^{E}\- 3.59) where as monophenyl derivatives absorb in the 245-270 nm region, alkyl substituents do not affect parent chromophore significantly. In the IR spectrum a strong band at 1555-1585 cm\(^{-1}\) is attributed to an \(\cdot\text{N}=\text{C}-\text{O}\) ring stretching mode. The mass spectral fragmentation have been extensively studied with the aid of deuterium labeling techniques and high resolution mass spectrometry [24]. In certain cases interesting correlations with photochemical behavior were observed. The general observations are recorded in chapter-3 (Experimental section).

Oxazoles do not readily undergo Electrophilic substitution reaction although many are stable in acidic conditions [25]. Oxazole is a weak base, and in contrast to furan are stable to concentrated acids at moderate temperatures.

Methyl oxazole [26] (P\(^k\) BH\(^+\)= -1.07) is approximately 100 time less basic than 4- methyl Imidazole. 2-methyl substituent increases the pka value more than a 4-methyl substituent, presumably because of hyper conjugative effect.
The presence of pyridine like nitrogen in the azole ring [27] considerably deactivates the system. A consideration of the transition states in electrophilic substitution at C-2, C-4 and C-5 positions indicate that the C-2 intermediate is highly unfavourable.

Oxazoles when heated with 2, 4-dintro-phenyl hydrazine [28] in acid solution get cleaved with the formation of bisnitrophenyl hydrazones of 1,2-dicarbonyl compounds.

Nucleophilic substitution reactions on the oxazole ring are relatively uncommon. In the case of nucleophilic displacement of halogens is halogen-2 > halogen-4 > halogen-5 [29].

The reaction of α-amino acids with acid chlorides lead to oxazolones synthesis [30]. Photochemistry, photoisomerisation of oxazole ring [31] and photochemical interconversions with isoxazoles are typical processes. The hydroxy derivatives are capable of tautomerisation and four ketonic forms are possible, the are 2 - oxazolin - 5- ones, 3- oxazolin - 5- ones, 4 - oxazolin -2- ones and 2-oxazolin-4 - ones [32].

Oxazole is a stable ring towards a range of reductive conditions but reduction of the ring to oxazoledienes may get affected with sodium in ethanol [33]. A range of reductive cleavage is known but Raney Nickel was ineffective. Reductive ring cleavage was inhibited by base enhanced by acid.

The oxazole ring is normally stable to oxidative conditions[34-35]. Cold permanganate, chromic acid, sodium hypobromite, fuming nitric acid and ozone cleave most oxazole derivatives. Oxazole are normally stable to hydrogen peroxide, but 4-(2-oxaryl) pyridine with H₂O₂-HOAC gives the pyridine N-oxide.

Present investigation deals with the synthesis of four compounds, three are; 2-amino-4-/methyl/ ethyl and phenyl oxazoles and one 2-amino (N, N-diphenyl)-4- phenyl oxazoles from urea/ diphenyl urea and an appropriate ketone using bromine as condensing agent. Details are given in experimental section (Chapter-III).
Physico-Chemical properties of Isoxazoles

Isoxazoles [36] is a five membered heterocyclic compound containing two adjacent hetero atoms oxygen and nitrogen. The labile five membered ring undergoes electrophilic substitution reaction, owing to the high instability of ring towards the nucleophilic reagents.

Isoxazole was first synthesized in 1903 [37]. It resembles pyridine in odor. The dimension and resonance energies of isoxazoles have not been measured, but chemical properties showed that the compounds are best considered as resonance hybrid to which the charged structures contribute.

II

Isoxazole is a colorless weak basic liquid and boils at 96° C. It is a 1,2- dihetero compound [38-43]. Isoxazoles are not soluble in dilute mineral acids and in general don’t give definite salts that can be isolated by treatment with acid. Quaternary salts have been obtained from derivatives of both ring system with alkylating agents. The isoxazole ring [44] is opens easily under these condition; the direction and ease of opening depends on the substituents\(^{1,2}\).

\[
\text{[1]} \quad \text{hot} \quad \text{NaOH} \quad \text{Me} \quad \xrightarrow{\text{MeC}} \quad \text{I} \quad \text{MeCO}_2\text{H} + \text{MeC} \quad \text{[2]} \quad \text{Cold} \quad \text{NaOH} \quad \text{MeN} \quad \text{I} \quad \text{MeCO}_2\text{N}
\]

Opening of the 3, 4, 5-triphenyl isoxazole ring (3, synthesis below) was first observed by Meisenheimer by ozonolysis [45-48]. On the assumption that the remaining double bond of the isoxazole ring between carbon and nitrogen atoms does not isomerise, (unlikely to occur under the mild
condition used), the product has the structure as shown below. It is the benzoyl derivative of an oxime of known stereo chemical configuration. Meisenheimer showed that this derivative correspond to an oxime which on treatment with \text{PCI}_5 in ether underwent the Beckman rearrangement [49] to give and there by proved for the first time that the trans groups interchanged.

![Chemical Structure Image]

Phenyl isoxazoles [50-51] nitrated preferentially in the phenyl ring, these showing that the deactivating effect of the (Pyridine) nitrogen atom overcomes the activating properties of the (furan) oxygen atom. Electrophilic substitution can take place at position 4 of isoxazoles.

Isoxazole ring [52] have so far always been built up from compounds usually (usually hydroxylamine) already possessing a nitrogen-oxygen bond. Isoxazole itself is obtainable from propargyl aldehyde and hydroxyl amine; Similarly 1,3-dicabonyl compounds also give isoxazoles with hydroxyl amine in a very general synthesis [53].

**Reaction II-1**

\[
\begin{align*}
\text{C} &\equiv \text{CHO} \\
\text{HC} &\quad + \quad \text{HO} \text{-NH}_2 \\
&\rightarrow \\
\text{HC} &\equiv \text{CHO} \\
\text{HC} &\equiv \text{CHO} \\
&\rightarrow \\
\end{align*}
\]

A number of 2-isoxazoles have been obtained by synthesis [54].

**Reaction II-2**

\[
\begin{align*}
\text{HC}=\text{C}\text{Hph} &\quad + \quad \text{phc}=\text{O} \\
\text{HC}=\text{C}\text{Hph} &\quad + \quad \text{NH}_2 \\
&\rightarrow \\
\end{align*}
\]
Little is known about isoxazolidine, which can be considered as a N,O-dialkyl hydroxylamine[55].

**Reaction II-3**

\[
\begin{align*}
\text{CH} &= \text{CH}_2\text{Br} & \text{CH}_2\text{Br} + H & \xrightarrow{\text{hydrolyse}} \xrightarrow{\text{heat}} \text{NH} \\
\text{CHO} & & \text{HOCO}_2\text{Et} & & \text{O} & \text{NCO}_2\text{Et} & \text{O} & \text{O} \\
\end{align*}
\]

The antibiotic oxamycin, or cycloserine, are infact of D-4-amino-3-isoxazolidone [56].

**Reaction II-4**

![Diagram of Reaction II-4]

<table>
<thead>
<tr>
<th>benzisoxazole</th>
<th>isoxazolone</th>
</tr>
</thead>
</table>

Benzisoxazole is a very feeble base and nitrates at position-5: Anthranil is readily obtained from 2-nitrobenzaldehyde [57].

**Reaction II-5**

![Diagram of Reaction II-5]

Reactivity of isoxazoles and its derivatives [58] may be explained by the dissymmetry of its nucleus having two hetero atoms located in a conjugative system which allows displacement of electrons from oxygen to nitrogen. A differentiation of three carbon atoms lead to marked differences in physical and chemical properties of the isoxazole derivatives.

During the recent past, considerable attention has been paid to the synthesis of isoxazoles(Chapter-III) fused to heterocycles and their synthesis of by ring transformations. Fairly good number of compounds have been isolated from natural sources.
Physico-Chemical properties of 1,3-Benzoxazines

Oxazines [59] are compounds containing six membered ring with two hetero atoms, (one oxygen and one nitrogen), in their least hydrogenated forms. According to position of oxygen and nitrogen atoms in the ring, three kinds of oxazines (I-III) are possible which are 1,2-oxazine, 1,3-oxazine and 1,4-oxazine.

Due to the divalency of oxygen, only two double bonds are present in the oxazines and an extra hydrogen atom to be disposed of, which may be attached to carbon in a methylene group or to nitrogen in an imino group. Consequently isomeric forms of each kind of oxazine are possible.

In 1,3-oxazines (IV) two hetero atoms one oxygen and one nitrogen atom lie in 1,3-position in the six membered ring of 4 carbon atoms.

1,3-oxazine derivatives with two double bonds can exist in three isomeric forms. (V-VII).

Of these isomers only 1,3-4H oxazines are well known which were first obtained by Wohl [60] in 1901. General method for the preparation of 1,3-4H-oxazines was given by Gabriel, [61] Karrer and Miyamichi. [62] The
compounds having one double bond are known as dihydro compounds of 1,3-oxazines. The structures (VIII-XI) of the possible oxazines are.

![Structures](image)

(VIII) 5,6-dihydro-1,3-2H-oxazine  
(IX) 5,6-dihydro-1,3-4H-oxazine  
(X) 3,4-dihydro-1,3-2H-oxazine  
(XI) 2,3-dihydro-1,3-6H-oxazine

Among these 5,6-dihydro-1, 3-4H-oxazines are well known 1,3-oxazines. First it was obtained by Gabriel and Elfeldt [63] in 1891 by benzylation of γ-bromopropyl amine in the presence of sodium hydroxide N-benzyol-γ-bromopropyl amine forms as an intermediate product(I), which on heating gives 5,6-dihydro-1,3-4H-oxazine hydro bromide.

![Chemical Reaction](image)

The fully saturated ring is tetrahydro 1,3-oxazine. This method for their preparation was first described by Kohn [64]. It can be obtained by cyclizing 3-amino propan-1-ol derivatives with aldehyde.

**Reaction III-1**

![Reaction Scheme](image)

Later number of authors obtained these derivatives in similar way using both aldehyde and ketone as cyclizing agents [65-67]. Earlier kohler, Bruce [68], Hicks [69] and Fischer et. al.,[70] reported the method for preparation of benzo derivative of 1,3-oxazine.
Dihydro derivatives of 1,3-benzoxazine can be prepared [71] by the reaction of P-substituted phenols with formaldehyde (2 moles) and primary aliphatic amines (1 mole).

**Reaction III-2**

![Chemical Reaction](image)

The dihydro derivatives are more stable than the 1,3-benzoxazines themselves towards hydrolyzing agents. The 1,3-oxazines lack the stability of the oxazoles and are readily hydrolyzed by dilute acid. In the presence of dilute acid (preferably methanolic or ethanolic), the tetra hydro derivatives of 1,3-oxazines can readily be hydrolysed with ring opening [72]. Stability of 1,3-oxazine varies oxazines prepared by cyclization using aliphatic aldehydes are more stable than those formed from aromatic aldehydes.

Besides some other methods [73] these compounds can also be prepared (Chapter-III) by Mannich reaction of a primary amine with the appropriate phenol (i.e. salicylaldehyde) in presence of an excess of formaldehyde.

**Changes in polarizability and Aromaticity of Oxazoles, Isoxazoles and 1,3-Benzoxazine derivatives.**

Ring transformations of five membered heterocycles [74-77] and their benzologues for the recent 10 years are discussed and reviewed. These transformations are classified in to four groups:

(a) "Classical ring transformations", where the starting and resulting system is of the same size, but the hetero atoms and or their position have changed;

(b) "Degenerate ring transformations", where during the course of the transformation the starting compounds and product have the same ring system, but the reaction proceeds by a ring opening and subsequent ring closure process;
(c) "Ring contraction" and "ring enlargements", where the sizes of the product rings are smaller (or) larger respectively than those of the starting compound;

(d) "Pseudo ring transformation" (or) "ring chain transfer", where the process is formally a ring transformation, but is realized by a ring closure of a side chain of the starting heterocyclic and opening of the original ring.

The quantitative aromaticity indices focused on structure, magnetic, and energetic criteria. The best polarizability-based index of aromaticity[78] have been finding as the polarizability-anisotropy of the π electrons. However, none of the indices constructed from polarizabilities seen to be entirely suitable as measures of aromaticity. The compounds of the structural critical tests that can be used to eliminate quickly unsuitable aromaticity scales for the present set to heterocycles.

Ab-initio electron correlate calculations of the equilibrium geometries, dipole moments and static dipole-polarizabilities are derived for the hetero aromatic five and six membered rings [79]. The geometries and dipole moments agree well with available experimental microwave determinations. The polarizabilities are expected to be accurate within 5% limits. Structural isomerism affects the dipole moments strongly but the polarizabilities are rather insensitive to it. Uncoupled Hartree-Fock calculations indicate that as much as half the polarizability comes from the π-electrons. Simple empirical formulas based upon atom-and bond-additive models correlate the calculated polarizabilities of five-and six-membered heteroaromatic rings quite well.

Planar conformations are stable minima for all about five-and six-membered rings. Lower level calculation [80] are unreliable in predicting which molecules are planar.

The polarizabilities along with earlier results for the Oxazoles, Isoxazoles and 1, 3-Benzoxazines, constitute a uniform quality data set for 120 hetero aromatic rings. Additive atom and bond polarizability models which are accurate to within few percent are constructed for the 104 planar molecules.
MOLECULAR MODELING

Molecular modeling [81-83] has become a well established research area during the last decade due to advances in computer hardware and software that have brought high performance computing and graphics within the reach of most academic and industrial laboratories. A growing number of Journals now focus on Molecular Modeling: Journal of Computational Chemistry, Computers in Chemistry, Journal of Computers-Aided Molecular Design, Journal of Molecular Graphics, Molecular Simulations and Tetrahedron computer methodology. Several recent texts and reviews describe progress in molecular modeling research and applications.

It is the important to realize what is really meant by "Computer-assisted drug designing". Molecular modeling systems provide powerful tools for building visualizing, analyzing, and storing models of complex molecular systems that can interpret structure-activity relationship [84-85].

The aspect of molecular architecture [86-87] means that a molecule which has freely rotating bonds can take up many shapes (conformations) without breaking any of its bonds. To visualize these various types of molecular shapes and evaluate their dynamics is molecular modeling. It was possible to design a force field [88-90] to calculation a value for molecular mechanics energy (E_{MM}) for a molecular, bonds and co-ordinates for the molecule. It is more common, however simple to sketch that molecular on a computer screen to get an approximate geometry and then to minimize it for its energy.

Individual atoms without a molecular are not electrically neutral but the molecular as a whole may be. There are, therefore, cumbic forces [91] pushing and pulling the atoms close to and away from each other. This electrical force is a long range effect, and unlike the Vander wall's interaction they are very influential.

This can be simulated in a molecular model. The energy can be removed from a molecule, driving it to a low energy conformation.
In the recent years it has been shown that ab-initio quantum chemical methods [92-94] utilize the SCF (Self consistent field) approach within the Hartree Fock-Roothan approximation are limited in their practical approach as they are restricted to very small molecules and require calculation of a very large number of many center integrals, hence require high CPU time and large storage on the disk. Therefore, semi-empirical methods were introduced that retain characteristics of quantum chemical approach in the calculation of wave function from which electronic and other properties may be obtained.

These method are based on the Hartree Fock approach whose matrix elements expressed as integral over atomic basic function.

**MOLECULAR MECHANICS**

Molecular mechanics methods [95] are based on a pragmatic view of the molecular structure that is considered as a set of balls and springs with series of potential energy functions expressing the molecular force field [96] as a sum of these functions. A typical energy equation is as follows.

\[ E_{\text{total}} = E_{\text{stretching}} + E_{\text{bending}} + E_{\text{vanderwaals}} + E_{\text{electrostatic}} + E_{\text{hydrogen bond}} \]

Each of the individual energy terms have preferential equilibrium positions (bond lengths, bond angles, dihedral angles, vander waal interaction distances, etc) and force constants that are either experimentally known or theoretically estimated.

A "Force Field" [97] therefore consists of a set of analytical energy functions and their associate sets of numerical parameters.

**Minimization:**

Molecular mechanics energy minimization (E\text{MM}) [98] involves successive iterative computation, where initial information is submitted to full geometry optimization. All parameters defining the geometry of the system, modified by small increments until the overall structural energy reaches a local minimum. The goal is to reach a local minimum on the potential surface within the minimum amount of time. No method
guarantee finding the absolute lowest energy structure the global minimum. Energy minimization stop at the first local minimization encountered without realizing that, more stable minima may be possible.

Energy minimization [99] can proceed either in internal co-ordinates (the variables explicitly considered are the bond lengths, bond angles and dihedral angles) or, as is more often the case, in Cartesian co-ordinates (each atom is characterized with x, y, z co-ordinates, and the atom moves with small increments along these axes).

Molecular energies [100] are calculated by using the Schrodinger equation of a given molecular system either with / or without approximations. Semi empirical treatment such as AM1, MNDO, CNDO, INDO, MINDO, PRDDO and PCIL0 are some of the most semi empirical programs, where as the GUASSIAN and HONDO series are typical ab- initio programs. AMPAC and MOPAC are QCPE packages that include the AM1, MNDO, and MINDO programs. Along with GUASSIAN series, these are among the most popular programs for quantum mechanical calculations.

Theoretical calculation can provide a number of indices that may not be directly related to experimental data but that can be very useful because they carry high physical information content (molecular, location and frontierorbitals, electronegative, polarization, demoralization, atomic and bond population etc.)

Cramer et. Al.,[101] recently described a promising new 3D-QSAR method based on calculating the interaction of each molecule in a set of super imposed active structures with a variety of probe atoms on a three-dimensional lattice.

**Force Fields**

**Energy Calculation of Physico-Chemical Parameters**

A molecular mechanics model [102-104] will readily give a value for energy simple by adding up the strain in all of the bonds and the Vander Walls and columbic interactions of all of the atoms. This quantity can be called $E_{MM}$, the molecular mechanics energy (it is also called the steric
energy). The property that $E_{MM}$ most closely mirrors is the internal energy of a molecule, which is given the symbol $U$.

The standard equations of thermodynamics relate 'U' to other quantities: Enthalpy, $H$, is defined as:

$$
H = U + PV
$$

(1)

Here 'P' refers to pressure and 'V' to volume, neither of which are easy to define in a molecular mechanics model. Considering only changes in enthalpy simplifies at constant pressure ($\Delta P = 0$):

$$
\Delta H = \Delta U + P \Delta V
$$

(2)

For a simple molecular mechanics model there is no pressure, so:

$$
\Delta H \approx \Delta U \approx \Delta E_{MM}
$$

(3)

A change in free energy, $\Delta G$, is related to a change in enthalpy, $\Delta H$, by the equation which was represented as

$$
\Delta G = \Delta H - T \Delta S
$$

(4)

In this equation, $T$ is the absolute temperature (measure in Kelvin), and $\Delta S$ is a change in entropy. In there is reason to be live that the change in entropy for a process is likely to be small ($\Delta S \approx 0$) then a change in molecular mechanics energy, $\Delta E_{MM}$, may be a reasonable approximation for a change in free energy.

The molecular mechanics energy, $E_{MM}$, is made up of the energy in every bond, $E_{bonds}$, is added to the energy in every angle, $E_{angles}$, and to the energy of all the Vander walls interaction $E_{vdw}$, torsion angles, $E_{torsion}$, charge interaction, $E_{charge}$ must also be included. Different groups have developed force fields and they all follow this scheme, equation -(5), although most have additional terms as well, which will be referred to as miscellaneous.

$$
E_{MM} = E_{bonds} + E_{angles} + E_{vdw} + E_{torsion} + E_{charge} + E_{miscellaneous}
$$

(5)
**Bond energy: E bonds**

$E_{MM}$ is considered to be bond stretching. The energy of a bond is simply a constant multiplied by the square of the displacement from the equilibrium position which is a simple spring, as described by Hook’s law, and gives an harmonic energy curve.

$$E_{\text{Bonds}} = K_1 (1-l_0)^2$$  \hspace{1cm} (6)

Since covalent bond are very weak as compared with the other forces affecting molecules, they rarely change much from their equilibrium bond length. This also mean that extreme displacements are actually favored.

**Bond angle Energy: E angles**

Bond angles are the energy of bending a bond angle taken to be proportional to the square of the displacement from equilibrium.

$$E_{\text{angles}} = K_0 (\theta - \theta_0)^2$$  \hspace{1cm} (7)

As with bond lengths, this expression is only realistic for small displacements from equilibrium, but this is not too bad, because bond angles can not change much.

**Vander Walls interaction: E vdw:**

Atoms can't get close together if they approach beyond a particular distance, and if a bond does not form, the energy of interaction goes up very rapidly. Although atoms are just clouds of electrons surrounding a tiny nucleus, they behave as if they have a quite definite size and measure of this is the Vander Walls radius.

These interaction induce a dipole on any near by atom, and the net effect of attraction. This is some times called the London Force (or) a dispersion interaction. Thc net is proportional to $1/r^2$. This makes a calculation of Leonard Jones 6, 12 potential rather easy to carry out since $1/r^{12} = (1/r^6)^2$.

**Torsion angle Energy: E torsion:**

Molecules rotate around single bonds, and there is energy barrier for such rotation. This energy barrier is implicit in the contribution to $E_{MM}$. It
is not easy to simply add a spring truncated Fourier series has been used based on the torsion angle defined by the four atoms involved, designed '0' in equation -(8)

\[ E_{\text{Torsion}} = \frac{V_1}{2} (1+\cos0) + \frac{V_2}{2} (1-\cos2\theta) + \frac{V_3}{3} (1+\cos3\theta) \]  

Torsion terms introduce a further element of choice in to the force field design. The balance between the torsion barrier due to Vander walls interaction and the torsion barrier due to expressions such as (eqn-8) there appears to be partial redundancy in the parameters.

**Charge-charge interactions: \( E_{\text{charge}} \)**

Aligning the groups bring two partial negative charges close to each other, which is unfavorable as compared to the opposite arrangement, which pairs partial positive charge and partial negative charges. The simplest way to quantify this effect is to assign a partial charge to every atom and to use Coulomb's law. (equation-9) to calculate the energy of interaction.

\[ E_{\text{Charge}} = \frac{1}{4\pi\epsilon} \sum q_1 q_2 / r \]  

The force between charged particles is proportional to \( 1/r^2 \) and so the energy of interaction is proportional to \( 1/r \). The partial charges on two different atoms are represented by \( q_1 \) and \( q_2 \). The total value of \( E_{\text{charge}} \) can only be found by adding up the results of eqn-9 for all pairs of atoms.

**Miscellaneous Interactions: \( E_{\text{miscellaneous}} \):**

Most force fields also have some other terms called 'Cross terms'. If a bond is stretched, it may be easier to bend the associated bond angles. If a bond angle is opened out, the barrier for torsion rotation may be reduced. These effects can be incorporated in to force field, by including expressions depending on the pairs of terms which might interact. Such extra terms however, help the molecular mechanics models which were not included in the parameterization data.

**Determination of partial Charges :**

An alternative approach is to calculate partial charges by consideration of the electro negativity of atoms. Electro negativity, the
power of an atom to attract electrons was introduced by Pauling. The
electro negativity of an atom will naturally depend on its charge. This
suggests a way of calculating the charges on atoms in a molecule; the
charges on all the atoms in a molecule are varied until they all have the
same electro negativity. This should give charge distribution which reflects
the electro negativity of the elements. This idea has implemented by
Gasteiger.

Formulae used for the calculation of partial charge [105] on ligand
donor atoms, is as follows:

\[ q = \frac{[SR \text{ of the molecule} - SR \text{ of the atom}]}{\sqrt{2.08 \times SR \text{ of atom}}} \]

Where SR of molecule = Stability of Ratio of the molecule is given by

\[ SR \text{ Molecule} = \left[ \frac{[SR \text{ of C}]^{n_1} \times [SR \text{ of H}]^{n_2} \times [SR \text{ of N}]^{n_3} \times [SR \text{ of O}]^{n_4}}{n_1 + n_2 + n_3} \right]^{1/2} \]

Where C, H, N and O represent the atoms involved in the formation
of a molecule and n1, n2 and n3 and n4 represent their respective
numbers in a molecule viz., (Cn1Hn2Nn3On4)

\[ SR \text{ of C} = 2.47; \text{ SR of H} = 2.31 \]
\[ SR \text{ of N} = 2.93; \text{ SR of O} = 3.46 \]

**Z - MATRICES**

It is convenient to describe a molecule in terms of internal
coordinates, using a z matrix [106-107], as Cartesian coordinates. This
means that the position of each atom is expressed in terms of the positions
of atoms which have already been defined. Thus a typical line in a z-
matrix is a description of a molecule how it looks like in 3D space.

Atom type r atom 1 \( \theta \) atom 2 \( \Phi \) atom 3

The first item is the sort of atom that is being described. The second
item r is the distance from this new atom to another atom 1. this atom
must have already described in the z-matrix next is angle \( \theta \), which is the
angle created by the atom, atom 1 and atom 2. A second angle \( \Phi \), describes
the torsion angle between the new atom and atoms 1-3.
This description depends on there being three atoms that are already defined, so the beginning of the z-matrix is slightly different. The first atom is usually just given an atom type, and no information about its position. The second atom will be defined simply by its distance from the first atom. The third atom by its angle and so on.

**Dipole Moment**

In terms of the wave mechanical picture, a molecule may be looked upon as an assembly of positively charged nuclei surrounded by a negatively charged 'cloud' which is made up of contributions from electrons in various Orbitals. The nuclei and the electron cloud are, to some extent mobile and so when the molecule, whether it is polar or monopolar is subjected to a constant electric field, the electron cloud will be attracted by the positive plate and the nuclei will be attracted by the positive plate and the nuclei will be attracted by the negative plate with the result that there will occur a small displacement of the center of gravity of negative charge relative to that of positive charge. This separation of the centers of positive and negative charges in the molecule in the presence of an electric field is described by the statement that the field has induced an electric dipole in the molecule; and the molecule is said to have suffered a distortion polarization [108].

(or)

\[ 1d = 1 \times e. s. u. \text{ cm} \]

It should be noted that the Electric dipole moment is a vector quantity and its direction is conventionally taken to be the direction from the positive charge to the negative charge.

The average dipole moment, \( m_i \), induced in a molecule is directly proportional to the local intensity \( F \) of the electric field acting on the molecule; thus,

\[ m_i = a_d F \]

The constant of proportionally \( a_d \) is a molecular property and is called the distortion polarizability; it is induce dipole moment per unit field strength and is a measure of the ease with which the molecule is or polarized.
Polarizability \( a_0 \), as \( a_0 = \mu^2/3KT \).

Hence for polar molecules the total polarizability, \( a_t \), is given by

\[
a_t = a_d + a_o = a_d + \mu^2/3KT
\]

and the total average dipole moment per molecule in the electric field is then

\[
m_t = a_t F = F (a_d + \mu^2/3KT).
\]

As before, \( F \) is the intensity of the electric field actually acting in the molecule. For nonpolar molecules, \( \mu = 0 \) and thus distortion polarizability is the only kind of polarizability.

**Structural information from dipole moment**

Since the dipole moment arises from the separation of charges due to the difference in electro negativity of the two atoms connected by a chemical bond it should be possible to associate a dipole moment with every bond in the molecule. This discrepancy or so called may be to either or both following reasons: (1). The angle between dipole vectors may be increased due to metal repulsion of the adjacent groups (or) (ii). The magnitudes of the bond moments may be altered by mutual interaction due to their proximity.

Dipole moments measurements [109] for aromatic compounds have given a number of interesting results. The dipole moment of paradinitro benzene is evidently zero.

It should be noted that the dipole moment of a para-substituted benzene molecule with identical groups at the para-position can be zero only if the dipole vector of the two groups lie along the bonds by which groups are linked to the ring.

In the present studies it is assumed that since dipole moment appears to be a factor dependent of asymmetry and asymmetry on its turn control the hydrophobicity. Which a parameter responsible for lipophilicity, and lipophilicity [110-111] is the sole criteria for the selection of molecule by biological organism, it is therefore correlated that the biological activity
as the lipophilicity are dipole governed parameters. The studies attempt to
derive a relationship between two.

Hydrophobic interactions usually provide the major driving force for
binding, while hydrogen-bonding and electrostatic interactions primarily
provide specificity and often add little to the free energy of binding. The
hydrophobicity is related to molecular asymmetry.

A major problem with all design approach is our current lack of
ability to calculate even a qualitatively accurate estimate of the free energy
of binding between two molecules in aqueous solution. An important
advance in modeling ligand-receptor interactions is the recent application
of free energy perturbation methods. This takes advantage of the properties
of a thermodynamic cycle to stimulate a physical process which is very
difficult to calculate (the transfer of a drug from solution in to a receptor
binding site, compared with the transfer of its analogue) by an equivalent
non physical process. (the mutation of a drug in to its analogue, performed
both in solution and binding site) which is relatively is to calculate. This
mutation is easily carried out by gradually changing the parameters of the
initial drug molecule to the parameters of the final drug molecule during a
molecule dynamics simulation, which is performed once in "solution",
usually in a box of several hundred water molecules, and again in the
macromolecule.

**Biological studies and its significance**

For the development in the field of chemotherapy, it is necessary to
test new for their curative properties against various diseases. Microbes
[112] play an immense positive role in our day to day life. They are
responsible not only for important life processes. However, there are
numerous bacteria, which cause diseases and spoil food products. Drug
[113], which kill or resist the growth of these microbes are known as
antimicrobial agents. Antimicrobial drugs played a very significant role in
the history of medicine. So it was though worthwhile to study oxazole,
Isoxazole and 1,3-benzoazaine derivatives for their antimicrobial studies
against
Rhizoctonia bataticola, Fusarium oxysporum, Aspergillus niger for (fungi) and Shigella dysenteriae, Bacillus subtilis, Escherisia coli for (bacteria).

Antimicrobial Activity.

The invention of microscope in the 17th century gave vision to the hitherto unknown world of microorganisms. These organisms are closely associated with the health and welfare of human beings and plants. Some are beneficial and others cause diseases to human and plants. The theory of spontaneous of diseases was finally buried by Pasteur and Koch in 1876, when they convinced one and all that the anthrax disease was incited by a bacterium. In 1878 Burill of Illinois reported that the fire blight diseases of peas and apple was caused by bacterium. Arthur (1885) proved that the diseases could be incited by bacterium obtained from a pure culture. By 1900 E.F. smith firmly established the best method of study in animal bacteriology. Agastino Bassi in early 1800's proved that muscardin is a fungal disease [114-115], which is more common in silkworms. The common diseases of human and animals, which are caused by fungi, include actinomycosis, sporotrichosis and epidermophytosis. Joseph Hinsten in 1878 was the first scientist who developed pure culture technique to the germs outside the body and proved by experiments that the germs can grow outside the body are also susceptible to produce same symptoms, when it is inoculated into the body as the same pattern. Fungi and bacteria are culture and a number of chemicals are tested in vitro for their activity on microbes.

The microbial is measured in vitro in order to determine.

(i). The potency of antimicrobial agent.

(ii). Sensitivity of the germ microorganism to the known concentration of the drug.
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