Chapter - 5

Summary and Conclusion
The observations made in the previous chapter and the extended explanation for the observations made on the complexation and their electronic spectral investigations Part-I and also the structure activity relationship for different 5a, 5b-substituted derivatives of barbiturates part-B, may help us to summarise the findings in following few conclusions.

- As regards the behaviour of 4f-shells in Sm(III) and Eu(III), drug and ligand bond formation, the study reveal that the [M(III) – L/drug] interaction exhibit predominantly ionic bonding.

- There are evidences of their intermediate behaviours, i.e. predominantly ionic interactions, with certain degree of covalency in it.

- The effective shielding and substantial screening thus restrict the direct involvement of the 4f orbitals from ligand interaction.

- The deformation of normal electronic wave function under the ligand field is evident.

- The variation in the spectral parameters in general follow a pattern based on ligand characteristics and the statistical factors viz. electrostatic, conformational and or thermo-dynamic parameters.

- The oscillator strength values in general followed the sequence of the basic strengths of the ligands. Certain
deviations in case of some ligands, may be on account of steric situations extended by the ligands/drugs, as a specific case.

- The oscillator strength values have shown a variation which are in good agreement with the general features of 4f-shells.
- The covalence representing parameters in the present cases are observed to be significant but small than the symmetry representing parameters.
- A relative variation in the oscillator strength values with respect to ligands showed increased relative binding affinity of the drug molecules than the simpler amino acid ligands. T
- The relative variations in $T_{\lambda \text{complex}}/T_{\lambda \text{aqua}}$ also exhibit greater changes in symmetry associated with the drug molecules than the simpler amino acid ligands.
- The observed sequence in the oscillator strength values with respect to amino acids and drugs, have been found to be:

$$\text{Sar} > \text{Pyrznm} > \text{Lysn} > \text{Hist}$$

which are in accordance with the ligand basicities and more precisely with the ligand softness values.

- The observed sequence in the oscillator strength values for various assignments of Sm(III) and Eu(III) in different ligand environments, in general, followed a sequence:

$$\text{Sm(III)} : \, ^6\text{P}_{3/2} > ^4\text{I}_{13/2} > ^4\text{I}_{13/2} \{^6\text{P}_{5/2}\} > ^4\text{M}_{15/2} \{^4\text{I}_{11/2}\}$$

$$\text{Eu(III)} : \, ^5\text{L}_6 > ^5\text{H}_6 > ^5\text{L}_7 > ^5\text{G}_6 > ^5\text{D}_2$$
Observations made on the quantitative predictive retention activity relationship using the PC model output on molecular mechanics have helped us to compile following observations.

The relative activity for the series of substituted derivative barbituric acid show highly dependent lipophilic character. The narcotic responses of drugs are proteins by the molecular interaction of drugs with Lipoprotein or Lipoprotein complexes.

The conformation changes due to various substitutions at the 5a, 5b position bring about the hydrophobic interaction influencing the lipophilicity of the drug and perhaps the perturbation of bioproteins by hydrophobic bonding is the cause of narcosis.

The increasing lipophilic character facilitate the movement of drug through lipophilic biophases and direct it on to the sites of action.

The steric modification/arrangement accelerate or retard the motion of the molecule in the biophases toward the site of interaction.

The different variety of compounds (allyl, alkyl, aromatic) has almost nothing in common except the lipophilic character.

Among the two position, 5a position have appeared to be more vulnerable than the 5b position.

The alkyl substitutents are found to be more effective than the aryl substitutents.

The allyl substitutents are highly favoured than alkyl substitutents.
• In case of allyl derivatives a bulky constituent seems to favour the drug action than the long chain substituents.

• A small dose of allyl – allyl with larger dose of alkyl-alkyl may work the patient for a long active situation.

\[ \text{Diagram: Allyl derivatives structure} \]

• The observed sequences for the lipophilicity with respect to be 5a and 5b positions have been found to be Ak-Ak > Al- Ak> H-H in case of thio barbituric acids.

• Amongst the 3-methyl barbituric acid the observed sequence with respect to 5a and 5b positions have been found to be:

\[ \text{Al – Ak} > \text{H – H} > \text{Ak – Ak} > \text{Al – Ak} \]

• In case of barbituric acids the lipophilicity for the compounds with respect to 5a and 5b positions have been found to be:

\[ \text{Al – Ak} > \text{Ak – Ak} > \text{Ak – Ak} > \text{Ak – Ar} > \text{H – H} \]

• The furfuryl derivatives however have shown some deviations.
The observed sequence for 3-position substituted barbituric acid and thio barbituric acid for lipophilicity has been found to be:

\[
\text{Meth-Barb} > \text{Thio-barb} > \text{Barb}
\]

which is the sequence for their \(\pi\)-electron densities for the trienol ring.

The observed sequence for the overall susceptibility of 5b position over 5a (keeping 5a positions as constant) has been observed to be:

\[
\text{H} - \text{H} > \text{H} - \text{Ar} > \text{H} - \text{Ak}
\]

but for Al, Ak and Ar groups at 5a positions, the observed lipophilicity sequence is:

\[
\text{Ar} - \text{H} > \text{Al} - \text{H} > \text{Ak} - \text{H}
\]

where as keeping Ak group constant at 5b-position the observed sequence of groups with respect to lipophilicity is:

\[
\text{Al} - \text{Ak} > \text{Ak} - \text{Ak} > \text{Ar} - \text{Ak}
\]

These sequences are in agreement with the lipophilicity of the drug molecules.

The larger molar volume have shown greater drug influence than the smaller volumes.
The larger negative $\pi$-values with non-ionic functions have been found to be more potent hypnotics.

The $\pi$-electron distribution over the trienol ring help the molecule for its bonding on the site of interaction.

It has been observed that the aromatic ring with polar functions of side chain have produced lower values of lipophilicity.

The $\pi$-electron of the aromatic ring result a more compact molecule there by increasing the water solubility or decreasing lipophilicity of the drug. This may help in regulating the drug with noble doses and timing low lipophilic highly water soluble compound and to be more rapidly excreted in the urine. These highly water soluble functions permit the largest possible apolar moiety to be incorporated into the drug without influencing lipophilicity.

It may be stated that for the difference in the intrinsic activity of the barbituric acid and its different derivatives, that a more specific interaction of these physico-chemical functions with polar counterparts and their interaction with lipoprotein would give leverage to the hydrophobic interactions, so that greater conformational changes would be produced with very little or almost zero hydrophobic bonding power in the drugs. The studies may help in designing long acting drugs for withdrawal actions.