SOLVATION CONSEQUENCES OF DIFFERENT AQUEOUS MEDIA ON SOME BIOLOGICALLY ACTIVE COMPOUNDS: A PHYSICO-CHEMICAL STUDY

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JUNE, 2021

Dedicated

to

All My Teachers

DECLARATION

I declare that the thesis entitled "**SOLVATION CONSEQUENCES OF DIFFERENT AQUEOUS MEDIA ON SOME BIOLOGICALLY ACTIVE COMPOUNDS: A PHYSICO-CHEMICAL STUDY**" has been prepared by me under the guidance of Prof. Biswajit Sinha (Principal Supervisor) and Prof. Mahendra Nath Roy (Co-Supervisor), Department of Chemistry, University of North Bengal. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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ABSTRACT

Chapter I expressed detail study about some biologically active compounds there importance on living body with special reference. This chapter throw a light on water activity, solvent effect and preferential solvation, solute-solvent and solute-solute interactions. The Objectives of the present research work on biologically active compounds have also been briefly discussed in this chapter.

Chapter II depicted a brief of theoretical background of the present works included in this thesis. In that chapter different type equation and parameters and their uses to understand the solute-solvent interaction phenomena are discussed.

In chapter III, Various experimental methods that have employed for the calculation of the numerous properties such as viscosity, ultrasonic sonic sound velocity, density, refractive index *etc*., have been mentioned. In this chapter working principle of some instrument that used to calculate the above said data are also discuss. Purity of chemicals and its source of purchasing are also discussed.

In Chapter IV, Apparent molar volumes (ϕ_V) and viscosity *B*-coefficients for L-Leucine and L-Proline in (0.001, 0.003, and 0.005) mol · kg^{-1} aqueous tetrabutyl phosphonium p-toluene sulphonate solutions have been determined from solution density, ρ, and viscosity,η, measurements at (298.15, 303.15, and 308.15) K as a function of the concentration of L-Leucine and L-Proline. The limiting apparent molar volume (ϕ_V^0) and experimental slopes (S_V^*) obtained from the Masson equation have been interpreted in terms of solute-solvent and solute-solute interactions, respectively. The viscosity data were analyzed using the Jones-Dole equation, and the derived parameters *A* and *B* have also been interpreted in terms of solute-solute and solute-solvent interactions, respectively, in the mixed solutions. The refractive index(nD), molar refraction (R_M), reported.

Chapter V, In this chapter solvation consequences of the caffeine and paracetamol in aqueous uracil solution is studied in terms of viscometric and volumetric property. The standard partial molar volume (ϕ_V^0) and the slope (S_V^*) were calculated from Masson equation and viscosity *B*-coefficient were measured from Jones-Dole equation and these employed to express the different type of

interactions found in the solutions mixture. The activation parameters of viscous flow for the solutions mixture were also measured and expressed by the transition state theory applications.

Chapter VI The inspection of molecular interaction widespread in Allopurinol and in aqueous solutions of α-, β- and HP-β-cyclodextrin have been probed by thermophysical properties. The established complexes obtained were found to be hold with 1:1 stoichiometry. Role of solvent (aqueous solution of α-CD, □-CD, HP-β-CD) and contribution of solute–solute and solute–solvent interactions to solution complexes, have also been analyzed via stability constant-NMR, UV, Steady state Fluorescence, FTIR, HRMS, SEM, PXRD, Cytotoxicity, Hydrophobic effect, Hydrogen-bonding, structural effects in creation of inclusion complexes.

Chapter VIII The apparent molar volume (ϕ_V) of salicylaldehyde anil zinc(II) (abbreviated as SAZ) in N,N-Dimethylformamide (DMF), Dimethyl sulphoxide (DMSO) have been calculated from the measured experimental data on density at temperature, T= (298.15, 303.15, 308.15, 313.15 and 318.15) K. The partial molar volumes at infinite dilution, ϕ_V^0 and viscosity *B*-coefficients were also calculated. Again, apparent molar volume and density data were used to determine isobaric partial molar expansibilities (ϕ_E^0) and temperature dependence of ϕ_E^0 at constant pressure, $(\partial\phi_E^0/\partial T)_P$ of experimental solutions to study the different types of interactions in different solvents. The overall results indicate strong solute-solvent interactions of SAZ in both the solvents and hence SAZ acts as a net structure breaker in both the solvents.

Finally this thesis is end up with the conclusion in chapter no VIII with some remarks of the present work.

PREFACE

I began this present research work that is entitled as "**SOLVATION CONSEQUENCES OF DIFFERENT AQUEOUS MEDIA ON SOME BIOLOGICALLY ACTIVE COMPOUNDS: A PHYSICO-CHEMICAL STUDY"** in 2014 under the supervision of Prof. Biswajit Sinha (principal supervisor) and Prof. Mahendra Nath Roy (Co-supervisor) at the Department of Chemistry, University of North Bengal, India with an aim to investigate on the solution properties of some biologically active compounds in various aqueous media.

Since majority of the biochemical processes occur in aqueous medium, physico-chemical studies on the solution properties of biologically active molecules such as amino acids, carbohydrates, drugs, vitamins, alkaloids, nitrogen bases, and few electrolytes in aqueous media are very valuable, interesting and informative. Various type of molecular interactions, non-covalent interactions like hydrogen bonding, electrostatic and hydrophobic interactions, *etc* taking place on the aqueous solutions where these biologically active compounds as solutes and cosolutes.

The mechanism of action of biologically active compounds is quite complex and may include different possible intra and inter-molecular interactions. It is also found that molecular conformations correlate with biological activity of certain biologically active compounds. Hence, the information about the molecular interactions of such compound in aqueous media is benefit for understanding this mechanism of their actions. Different volumetric and viscometric properties like standard partial molar volumes and viscosity B-coefficients, adiabatic expansibilities *etc*., are very much beneficial in exploring of solute-solvent and solute-solute interactions. Therefore, thermodynamic and transport properties of aqueous solutions of these solutes are very much useful to knowing their mechanism of actions. So, the present research work is mainly focused on the physicochemical studies of some biologically active compound in different solvent media prepared in aqueous medium.

Acknowledgement

At the first opportunity I express my most sincere gratitude to my supervisor Prof. Biswajit Sinha and my Co- supervisor (Prof.)Dr. Mahendra Nath Roy for their proficient supervision through the splendid path of my research with great endurance. Constant support both of them, fruitful discussions and valuable suggestions at different stages are really a great motivation. The support and encouragement of all the other faculty members of the Department of Chemistry, University of North Bengal in the whole episode of my research was of colossal help. I am grateful to all the non-teaching staff of this department for their help during the crucial stage of my research.

My thanks to my past and present lab mates for their selfless help at different stages of my work. I also express my heartfelt gratitude to my parents for their selfless dedication to make me what I am today. My special thanks to my beloved wife Gargi Roy Mondal and to my sister Sushmita Mondal for their love, affection, support and encouragement during this period. The inspiration, encouragement and whole-hearted cooperation that I received from my friends, is most elegantly acknowledged.

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CHAPTER I

Introduction

The compound that will exerts a direct physiological effect on any type of living organism is known as biologically active compound.There is a diverse world of biologically active compound found in our daily life. Which include almost everything that would impact on the health and other biological phenomena that occurs in the living organism body. Some these are like vitamins, antibiotics, plant growth regulator(auxin, ethylene, etc), drug, extra cellular soil enzyme, siderophores, Humic substances, Natural insecticides or herbicides , Surfactant, different type of drug, Salt, ionic liquid, carbohydrates, acid, base etc. [1,7]

1.1. Biologically active molecule and living organism:

So a biologically active compound may be a compound that has a control on a living system, tissue cell. In case of nutrition, biologically active compounds are different from the essential nutrients. It is well known fact that nutrients are very much essential to our body, but the biologically active compounds aren't essential since the body will operate properly without them. Bioactive compounds will shows an Associate in nursing influence on health.[2-4] The branch Biochemistry define the biological activity of a substance incontestable in the living organisms. The biologically active substances area unit often from biological origin. Biological activity characterizes the biological effectiveness of a substance and describes the changes caused by biological material like hormones, vitamins, Enzyme and coenzyme, different type of drug molecule, etc.[5-7]

1.2. Technique for study the different types of interaction:

Different type of molecular interaction taking place between biologically active molecule and the living cell is our area of interest. Biological activity or molecular structure and physical properties will be investigated by viscometric volumetric method in aqueous medium. Some spectroscopic properties also done like infrared analysis, spectrofluorimetry, colorimetrical check, thermal analysis, UV-VIS spectrophotometry, negatron magnet resonance, catalyst activity, etc., area unit suggested for the quantitative and qualitative determination of chemical and organic chemistry compounds, their metabolites, and degradation product.[8-16] Biological activity (e.g., mutagenicity, cancerogenicity, teratogenicity, inhibitionof catalyst activity,toxicity) Each compound possesses varied biological activities. All the

actions and its participation within the biological, physiological and metabolically pathways despite the distinction within the experimental conditions are included in the the biological activity spectrum of a compound.

Provided that the changes in the gender, age, categorical species, and also the participation within the metabolic processes and pathways etc. area tumble down. Biologically active compounds will impart a net remarkable effect on the body whether it is suitable or harmful to our body, so within the body that will impact on the physiological condition in living system. Some of these type of compound are taken into research in medicinal chemistry in order to curing of cancer, heart diseases, gout, scurvy and many other different type of diseases. Our area of interest is focused on some biologically active compound that we come contact in in our daily life. Like numerous drug molecules, some food additive, food color, food preservative, surfactant present in detergent or soap or in tooth paste etc.[14-16] Since the study of interaction protein molecule with the bio active molecule in the living body is very much complicate. So the study of viscometric and volumetric, acoustic property, spectroscopic property, refractive index, conductivity measurement, surface tension value, rheological property etc. of these bioactive molecules with such amino acid in Aqueous media is a simple way to understand the all type interaction taking in between them. Water is taken as the sovent media in such cases, the logic is that water has high dielectric constant and human body (contain roughly around 60% water) or plants body mostly made up of water. So it is more justifiable that the interaction may be taking place in the aqueous media in the body. These type of study is very reliable and give us the deeper insight about the solute- solute or ion-ion, solute- solvent or ion-solvent, or solute-cosulte interaction.[17-24] In addition to this, it is also helpful for knowing the which type of interaction will predominate in the solution like Hydrophilic-hydrophilic or hydrophilic-hydrophobic or hydrophobic-hydrophobic. So the introductory part of my thesis mainly deals with the different type of amino acid interactions with ionic liquid, surfactant ,drug molecule, antioxidant, food additive ,some mild stimulating alkaloid present on the drinking beverages etc. In addition to this some application part and the solvation phenomenon including various type of interactions occurring in solution phase like solute-solute or ion-ion interactions and solute-solvent or ion-solvent interactions is discussed. In order to understand the different interaction takes place between the protein molecules with this biologically active substance we have to know about the amino acid and its function in living

organism and there after some of the biologically active molecules function and importance will be discussed later in this introductory chapter.[25-32]

1.3. Amino acid as a building block of the protein:

Amino acid is one of the most important and crucial substances for the all living bodies which made up of protein. Protein molecules have complex structural arrangement that contain four type of structure primary, secondary, tertiary and quaternary structure. Primary structure made up of specific sequence of various α-amino acid making the polypeptide chain. α- amino acid amino acid obtained from the primary structure by the hydrolysis of protein with enzymes or mineral acid by the following sequence.[32-38]

$$\boldsymbol{protiens \rightarrow Proteoses \rightarrow peptones \rightarrow polypeptides \rightarrow simple\ peptide \rightarrow \alpha - amino\ acid}$$

The secondary structure is consist of polypeptide chain form the H-bonded α-helix structure and means of some subunits (consist of polypeptide chain)and their spatial arrangement with respect to each other in an aggregate protein molecule. Best known example of a protein having quaternary structure is hemoglobin which transport oxygen from the lungs to the cell and carbon dioxide from cell to the lungs. Following figure 1.1 shows all types of structure of amines.

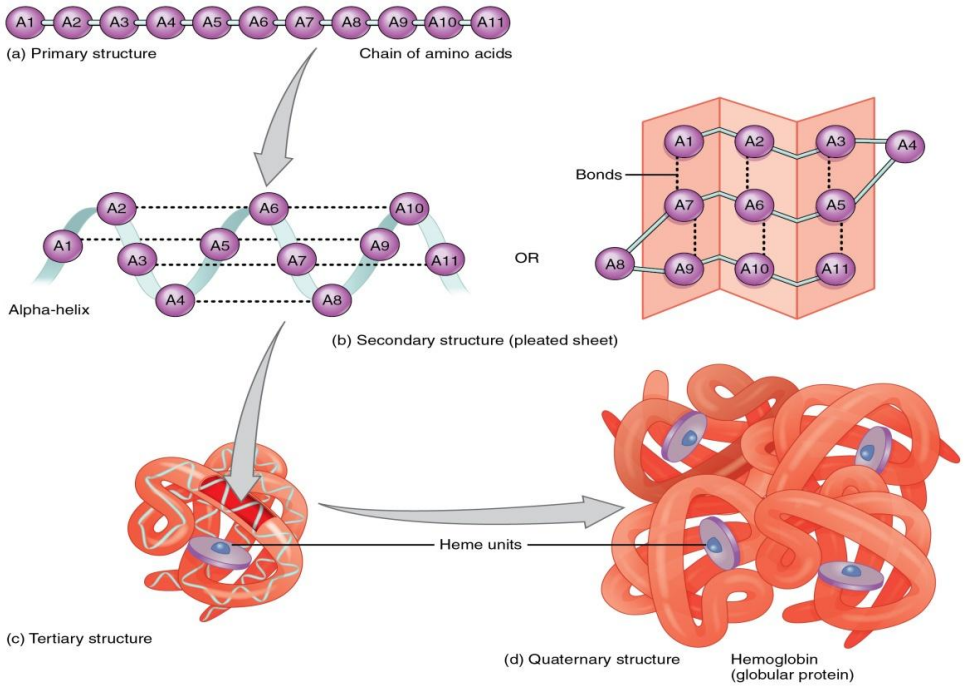

Figure 1.1. *3d view of four type of structure exist in the amino acid*

So it can understood from the above information that if we examine the interaction of amino acid in the aqueous solution with other cosolute of biologically active molecule it will provide us overall idea about the interaction taking place in between proteins with the such bioactive molecules in more simpler way . Because proteins are very much sensitive towards temperature and change in the *p*H which result into denaturation of protein. However in denaturation of protein all the structure collapsed but primary structure remain intact and protein lost it biological activity. This is reason why we take amino acid as a representative of the living organism and considered that the interaction taking place in between amino acid and bio active molecules are supposed to be same as like in living body. This is the main fundamental of the study.[33-40]

1.3.1. Types of amino acid and their need for living body

Our body desires as a net twenty completely different amino acids to grow and perform the biological activity. These all are square measure vital for our living human body, Among which only nine amino acids categories as essential amino acid. These are listed as leucine, isoleucine, valine, methionine, tryptophan, threonine, lysine, histidine and phenyl alanine. Non essential amino acids are produce in our body but the essential amino acids not produce by living body. So there should be only one option that it must consumed through our diet. Animal proteins like meat, eggs and poultry are the best sources of essential amino acids.[51,84]

Histidine: This essential amino acid is employed to provide aminoalkane, a neurochemical that's very important to response, digestion, sleep-wake cycles. It have a crucial role for maintaining the sheath, a protecting barrier that surrounds our nerve cells. Histidine metabolizes in Living body into histamine, which is play a vital role in case of body immunity build up, reproductive health, and digestion.

Valine: It is one amongst 3 branched-chain amino acids that helps to stimulate muscle growth and regeneration and is concerned in energy production.

Threonine: This essential amino acid may be a principal a part of structural proteins like albuminoid and scleroprotein, that square measure vital parts of the skin and animal tissue. It conjointly plays a task in metabolism and immune system . It metabolize fat of our body and may be beneficial for people who suffering from indigestion, anxiety, and mild depression.

Tryptophan: This essential amino acid has several alternative functions. It's required to keep up correct balance and may be a precursor to monoamine neurotransmitter, a neurochemical that regulates your appetence, sleep and mood.

Phenylalanine: This essential amino acid may be a precursor for the neurotransmitters amino acid, dopamine, adrenaline and monoamine neurotransmitter. It also plays vital role within the structure and performance of proteins and enzymes and also the production of alternative amino acids. Phenylalanine facilitate the body to use other amino acids as well as proteins and enzymes. The body converts phenylalanine to tyrosine, which is necessary for specific neuro-function.

Phenylalanine deficiency, though rare, can lead to poor weight gain in infants. It may also cause eczema, fatigue, and memory problems in adults. In diet sodas Phenylalanine is often used as artificial sweetener. If excess amount of aspartame consumed then it can increase the levels of phenylalanine in the brain which may results into anxiety and jitteriness and insomniac disorder .

Phenylketonuria (PKU) is genetic diseases where patient unable to metabolize phenylalanine. So they should avoid consuming diet that contain high levels of this amino acid.

Leucine: Leucine may be a branched-chain organic compound that is crucial for macromolecule synthesis and muscle repair. It conjointly helps regulate blood glucose levels, stimulates wound healing and produces growth hormones.

Methionine: essential amino acid plays a vital role in metabolism and detoxification. It's conjointly necessary for tissue growth and also the absorption of metallic element and chemical element, minerals that square measure very important to your health . Methionine keeps the nails strong of our body. It will help in absorption of selenium and zinc and the excretion of heavy metals, like lead and mercury.

Isoleucine: This branched-chain amino acids, is helps us in muscle metabolism and is heavily focused in muscle tissue. It's conjointly vital for immune system, hemoprotein production and energy regulation. It will shows it activity during healing of wound, blood sugar level maintain to optimum, and in hormone production. It is primarily present in muscle tissue and regulates energy levels. Older adults are found to be more isoleucine deficiency than younger people. This will results into muscle wasting and shaking.

Lysine: Lysine plays major roles in macromolecule synthesis, internal secretion and catalyst production and also the absorption of Calcium. It's conjointly vital for energy

production, immune system and also the production of albuminoid and scleroprotein.[31-34]

Though amino acids play versatile role in our body but moslty it recognized as a muscle developer and repairing the muscle in the body. That's why deficiencies of these amino acid will negatively impact our whole body as well as our central nervous system, procreative, immune and biological process systems. Tryptophan is required for the assembly of monoamine neurotransmitter, a chemical that acts as a neurochemical in living body.Serotonin is a vital regulator of mood, sleep and behaviors. Except thsese many other non essential amino are present which are contribute their role in order to sustain and growth of life in the living organism.

In this research work interaction of the drug molecules are also studied since without it living body can`t survive the diseases. So the Interaction as well as side effect and how to minimize the side effect by using some techniques so called "control drug realize" is very important. The net effect of the drug molecule on the living body can be understood by using some spectroscopic technique and conductometric or volumetric study can be done in aqueous media. So in order to understand that how the drug molecule impact on the living body, it obvious to know about the importance of the drug molecule.[41-48]

1.4. Necessity of Drug for sustaining the life:

Chemical substances that occurred naturally or produced by the synthetic way have the ability to curing the diseases and reducing pain are known as medicine or drug. However, there is a distinction between the term drug and medicine. Medicine is a chemical substance that cures diseases is safe to use and has negligible toxicity and does not cause addiction whereas drug is a chemical substance which also cures the diseases but it habits forming causes addiction and has the serious side effect[48-56]

1.4.1. Classification of drugs:

Drugs may be classified in several different ways some of these are discussed below.

1) Based on pharmacological effect 2) based on drug action 3) based on chemical structure.4) based on molecular targets.

1) Based on pharmacological effect: Every drug molecules have a specific effect on the human body. Like analgesic reduce or kill pain while antiseptic either kill or arrest the growth of microorganism. in this way different types of drugs are classified in this category.

2) Based on drug action: Drug molecules have a specific action on a particular biochemical process based upon this fact the drug molecules classified in this category. Like antacid reduces the acidity and antihistamine stop the secretion of histamine.

3) Based on chemical structure: Drugs that have some type of structure will show the same type of physiological effect.

4) Based on molecular targets: Drugs undergo interaction with the biomolecules for a biologically active compound like protein, carbohydrate, lipids, and nucleic acid. That is why are biologically active molecules are supposed to be targeted molecules for a drug.[57-60]

1.4.2. Drug interaction with biologically active molecules:

Drug molecules interact with the biologically active molecules by a different type of techniques and mechanisms. E.g. enzymes are made up of Amino acid is plays a crucial role to digest the food by a lock and key mechanism. Drug molecule Docking with the active site of the enzyme so the activity of such enzyme will be hindered. Some drugs do not bind to the active site of the enzyme but bind to a different site of the enzyme which is called the allosteric site. The binding of the drug at the allosteric site changes the shape of the active site of the enzyme in such a way that the natural substrate cannot recognize it and the function of the enzyme towards substrate will diminished. These are categorized as enzyme inhibitor drugs.[61-66]

Drug molecules are designed in such a way that they are combined with a specific target. Like there are two types of adrenergic receptors called Alpha-adrenergic receptors and beta-adrenergic receptors. These receptors differ slightly in the structure of their active site but still can bind epinephrine. Alpha-adrenergic receptors are present in large amounts in Tissue and beta-adrenergic present more in the heart. So a drug if designed for beta-adrenergic then it will cause more effect on the heart than tissue. Drugs show some side effect due to binding of it more than one type of receptors present in the body. Different type of drugs and their importance are discussed below.[66-72]

1) Antihistamine: Some people show hypersensitivity towards drugs dust pollen grains, far, fabric, it is known as an allergy that causes itching in the body and

sneezing by the release of histamine. Brompheniramine, terfenadine, promethazine, etc. use as an antihistamine drug to reduce allergic problems, vomiting, nausea, etc.

2) Tranquilizer: Iproniazid, phenelzine, Equanil, serotonin, etc are used for the treatment of stress fatigue coma mild and severe mental disease are considered as a tranquilizer. it is also known as an antidepressant drug.

3) Analgesic drug: Aspirin, Paracetamol is the most important example of a non-narcotic pain reliever. These drugs are quite effective in relieving skeletal pain such that due to arthritis.

Whereas morphine, Codeine, heroin are considered narcotic drug which may be addictive.

4) Antimicrobial: These types of drugs are used to cure a disease caused by microbes or microorganisms bacteria viruses fungi etc. Salvarsan, prontosil sulphanilamide are these types of drugs.

5) Antipyretic: Drugs that are used to reduce the body temperature during high fever are called antipyretics. This drug when applied to the patient, they get excess sweating. Paracetamol, Aspirin,novalgine are the well-known example of these type of the drug.

6) Antibiotics: This type of drugs in its low concentration either kill or inhibit the growth of microorganism by intervening their metabolic process. Penicillin Is a very effective drug for pneumonia, Bronchitis, sore throat. Another example is aminoglycoside ofloxacin.

7) Sulpha Drug: Those drugs which are derivatives of sulfanilamide are called sulfur drugs.

8) Antifertility drugs: Drugs that are used to stop the pregnancy in a woman are called antifertility drugs or oral contraceptives. this controls the female menstrual cycle and ovulation. Mifepristone is a synthetic steroid that blocks the effect of progesterone and is used as an antifertility drug. Others are Norethindrone,novestrol used for the same purpose.

9) Gastro-resistant: Rabeprazole, omeprazole, Lansoprazole, cimetidine, ranitidine are types of drugs that can restrict the secretion of pepsin and hydrochloric acid. The working function of these drugs is supposed to prevent the interaction of the histamine with the receptors present in the stomach wall.

10) Allopurinol is a remarkable drug that was used to cure gout of the mid of twentieth century to the present. It blocks the production of uric acid.[73-79]

1.5. Enzymes as biologically active substances:

A biological reaction like digestion takes that place in the stomach are catalyzed by some special catalyst these are known as enzymes. For every type of food, there is a specific enzyme are present in our body, e.g protease for protein, urease for urea, amylase for starch, etc. Chemically all the enzymes are found to be the globular type of protein. Some of the enzymes are also contained some non-protein components called cofactor for their activity. Factors are two types 1) inorganic ions such as Zn2+, Fe2+, Cu2+,Co2+, Mo3+, K+, Na+ ,etc.

2) organic molecules, these are again are also two types (i) coenzymes and (ii) prosthetic group. It can be easily separated from the enzyme by dialysis which is loosely bound to the protein molecules. Whereas prosthetic groups are tightly held to the protein by the covalent bond but can be separated by careful and controlled hydrolysis most of these are also derived from vitamins like biotin. Protein cofactor complex is called holoenzyme wilder inactive protein part that left after the removal of the cofactor is called apoenzyme. A small amount of the enzyme required for the body for perform specific functions in the body. For every biochemical reaction, there must be a certain specific enzyme required. A large number of enzymes functioning in the living system to sustain life.[67-69] A rough estimation of nearly about 3000 catalyzing different reactions present in a particular typical cell. Enzymes are also used in industry for the production of sweet syrup from corn starch, in the manufacture of wine from carbohydrate fermentation. The milk industry also uses enzymes to produce cheese from the milk. So the enzyme plays important role in our living system which cannot be ignored. The deficiency of different types of such enzymes causes diseases formed in the body in the human body. Like PKU(phenyl ketone urea) due to deficiency of an enzyme called phenylalanine hydroxylase which required for converting phenylalanine to tyrosine. Due to the deficiency of this enzyme, the other is ions present in the cell convert phenylalanine to phenylpyruvate in terms accumulated in the bloodstream can cause severe brain damage and mental retardation. Another type of deficiency is “albinism” due to the deficiency of the tyrosinase enzyme that Will impact the skin color of the human and animal. Because enough Melanine is not produced by the body in that time and the body turns into white.[80-86]

1.6. Vitamins and their importance for sustainable lives:

Vitamins are another type of biologically active compound that is required every day in our diet to sustain the biological process that takes place in the living body. Vitamins are biomolecules that cannot be produced by the body and must be intake through our diet to execute specific biological functions for the life growth and health of the Living Organism. Vitamins Never produced any type of energy in the cell nor build any tissue for the cell but still, it plays a key role to keep good health for living beings. Some of the vitamins like vitamin D vitamin A are produced in the human body but most of the vitamins cannot be synthesized by the body so they can be intake from the outside of the body through diet. But plants can synthesize all vitamins.[154]

vitamins are broadly classified into the following two categories one is called water-soluble (B1, B2, B3, nicotinic acid, Ascorbic acid or vitamin c, etc)and another as fat-soluble vitamins(A, D, K, E). Since our present work deals with water. So we take only water-soluble vitamins for investigation. some of the important vitamins are discussed below.[73-74]

1) Vitamin C: These water-soluble vitamins prevent different types of infections and contribute to a healthy immune system. It also helps the body to absorb the iron that a necessary component to carry oxygen through blood cells. Deficiency of these may cause scurvy diseases.

2) Vitamin D: This is fat-soluble vitamin promotes the absorption of calcium in the body and will make it important for bone health and development. It also helps to reduce inflammation and improve our immune system. Deficiency of it causes rickets diseases.

3) Biotin: It sustains health by increasing the absorption of carbohydrates with protein and fat from food. It helps to keeps our hair growing and makes bones healthy and strong.

4) Folic acid: It mainly helps us to produce fresh red blood cells, thus it stop the diseases called anemia.

5) Vitamin E: It has functioned as an antioxidant and helpful to protect the cells from different types of damage. Vitamin E plays a critical role in fights against critical diseases like cancer and Alzheimer's. It sustains the immune system by preventing different infections and fighting off viruses, bacteria.

6) Vitamin K: It is very much important for blood clotting. It also improves bone health. It can minimize the risk of osteoporosis and some heart diseases.

7) Vitamin A: This fat-soluble vitamin stimulates healthy eyesight and skin development. It also supports bone and tooth growth. In addition, vitamin A supports the immune system and is important in the reproductive process. It also enables the heart, lungs, kidneys, and other physiological organs to operate properly.

8) Vitamin B12: It improves the nervous system of the living body and thus helps our body to produce fresh cells. It also minimizes the risk of heart disease.[87-93]

1.7. The function of nucleic acid and its importance:

It is now an established fact that the nucleus of a living cell is primarily responsible for the transmission of genetic characteristics from one generation to the next . The chromosome that presents in the cell is responsible for heredity which is made up of protein and nucleic acid. Nucleic acid is two types deoxyribonucleic acid or DNA and ribonucleic acid or RNA. A nucleic acid that made up of a repeating monomeric unit of nucleic acid which is known as a nucleotide. nucleotides are consisting of three parts that are sugar molecule (heterocyclic nitrogenous base) and phosphoric acid.

Complete hydrolysis of DNA or RNA gives a mixture of three different compounds viz pentose sugar, nitrogen-containing pentose sugar heterocyclic compounds also called the nitrogenous bases, and phosphoric acid. Two pentose sugar have been isolated. In which DNA contains beta-2-D deoxyribose and RNA contains beta-D-ribose.In addition to this there are two different types of heterocyclic nitrogenous base isolated from the hydrolysis of the nucleic acid these are purine and pyrimidine. The most common Purines are adenine and guanine which is found in nucleic acid. The 3 most common pyrimidines are uracil, thiamine, and cytosine. Nucleoside contains only two basic components of nucleic acid that are a pentose sugar and a nitrogenous base. Nucleosides are classified into two categories depending upon the type of sugar present (i) ribonucleoside and (ii) deoxyribose nucleoside. There are five types of bases present in ribonuclease sites are Adenine, guanine, cytosine thymine, uracil. Whereas nucleotide contains all three basic components of nucleic acid, phosphoric acid group, a pentose sugar, and nitrogenous base.[94-100]

1.7.1. Structure of nucleic acid:

It has two levels of structure one is primary structure and the other is secondary structure. primary structures are the sequence of four nitrogen bases that are attached to the sugar-phosphate backbone of a nucleotides chain. secondary structure can be understood by the chargaff`s rule. It states that the base composition in DNA Varied from one species to other but in all cases, the amount of adenine was equal to that of

thiamine(A=T) and that of cytosine was equal to that of guanine(C=G). Watson et. al from their studies proposed a double-helical structure for DNA. According to this model, DNA consists of two right-handed polynucleotide strands or chains. These two helical chains are attached to each other by H-bonding taking place between adenine (A) with thymine(T) and guanine (G) with C(cytosine).

The biological function of nucleic acid: 1)Replication is the process by which a single DNA molecule produces two identical copies of itself,2) protein synthesis is another important function of DNA. Actually, proteins are synthesized by RNA molecules in the cell but the message for the synthesis of a particular protein is encoded in DNA there are three types of RNA molecules that take part in the protein synthesis. These are messenger RNA(m-RNA), ribosomal RNA (r-RNA), and transfer RNA (t-RNA).[131,101-103]

1.8. Carbohydrates and key role the as bioactive molecule :

I. Carbohydrates are considered as a main source of energy for functioning biochemical processes in the living system and act as a bio-fuel. Maintaining the blood sugar level is another important role of carbohydrate.

II. Since carbohydrates are present and act as the main source of energy it prevents the proteins not to burn for producing energy.

III. In the case of fat metabolism it shows its presence to metabolize the fat.

IV. Carbohydrates are also used as an artificial sweetening agent. Sucrose and Fructose are examples of such which used in our daily life.[4] Other examples are sucrose which the trichloro derivative of the sucrose is 600 times sweeter than sucrose. L- sugar is another type of carbohydrate that is sweet in taste. One Interesting fact is that they did not have any calorific value because our body does not have any such enzyme to metabolize these sugars.[50] So it is very much useful for or diabetes patient to maintain their blood sugar level. it is also used in making diet soda, diet food, diet sweet, etc. The role of carbohydrates as a dietary fiber cant be ignored.

VI. carbohydrates drive the biological process in the living body.[104-106]

1.9. Role and effects of Solvent on the physiochemical processes :

It was well known fact that most of the physiochemical and biological processes occur in solution phase. So the Solvation phenomenon plays a key factor in chemistry, biochemistry as well as in biology. The impact of the solvent in physiochemical reactions is very important and hence numerous researchers from

both experimental and theoretical grounds associated with chemistry or biochemistry has shown their interest from the last decade to present. The results of any chemical reaction is get altered by the addition of requisite amount of solvents through the different possible interaction taking place with the local surroundings. In addition to this this interaction also takes place with the individual reactants molecules that take part in the reaction. The physical barrier that associated with motion of such reactive species and the energy path that need to stabilize the energetic products yield in the respective reactions. These can be also understood by the interaction knowledge provided by the solvents. It was found that the solvent also distress the potential energy curves of these type of reactions. As the solvent species surrounding a solute molecule can form a solvated structure that can control the result of any biological or chemical phenomena, the solvent species play an key role in the chemical or biochemical reaction. In atmospheric phenomena and biological process the solvation has found to be a driving factor in diverse areas that is well established fact. In living body, solvated ions may also appear in larger amount where their absence or presence can fundamentally distorted the life functions.[107-109] Solvation of ions in aqueous mixtures or any organic solvents are also very common and the changing of solvent molecules which surrounded the ions in solutions is important to know about the reactivity of ions in related respective solution. Since conductivity of electrolytes is very much related to the ion-solvent interactions, so the solvated ions can govern the electrochemical applications ,such as in cell or battery industry, extraction of metal by electro chemical process, neuro chemical drug etc. It is obvious that maximum no. of the chemical reactions are proceeds in solution medium and so solvents can simply govern the reactions in a numerous way. In a reaction or any type of physiochemical process solvents can act as a reaction medium in which reactants molecules are solublize to proceed the reaction further. Solvent can act as one of the reactants and convey the dissoluted solutes to bring about the chemical components together in solution phase in the requisite amounts and make the reaction to becomes feasible.

In some thermo chemical process both in exothermic and endothermic case, the vital parameter i.e. temperatures, are also affected by the solvents selection. In an endothermic reactions, heat is supplied by a external heated inert solvent having high heat capacity, while in exothermic reactions boiling the solvent or absorbing heat can minimize the surplus heat. Most of the solid reactants do not react in the solid phase it requires medium which will provide homogenous reaction phase (*i.e.*, solution).

Solvent in such case plays the role homogeneous medium to bring the solid reactants come into contact with each other to yield the product. So, it is very much important to select an appropriate solvent to get most fruitful outcome or expected yield of the products. The characteristics of a ideal solvent is that it can fulfill all the required criteria. Such as for any type of reaction conditions it is necessary to remain its presence as an inert and must have an appropriate boiling point , thereafter at the completion of the reaction there should not occur any kind difficulties during its removal. It must have the ability to dissolve all the reactant species and reagents. The reaction rate are also govern by the differential solvation taking place in the the starting materials and transition states made by the sovent. When the reactant molecules proceed towards to the transition state, the solvent molecules may arrange themselves in such way to stabilize the respective transition state. The reaction rate is high and are found to proceed faster if the transition state is seen to be stabilized to a greater extent in respect of the starting material. On the other hand, the reaction rate will be smaller and reaction may be slower if the transition state is stabilized to a lesser extent than the starting materials. However, re-orientation and quick relaxation of solvent is needed for such differential salvation to came back in the ground from the transition state and the results of a reaction is found to be impact by the equilibrium solvent effects.[110-114]

1.10. Solvation consequences of solute molecules

Solvation of solute molecules is the process in which solute molecules are surrounded by the layer of solvent and form a wrapper over the every dissolved solute molecules. These wrapper or shell of solvent molecules are may be tightly bound or may be it loosely bound the solute molecules depending upon the nature of the both solute and the solvent. Intermolecular forces between the solute molecules and the solvent molecules responsible for such formation of solvent shell or solvent wrapper. During the solvation process only small fraction of solute get dissolved in comparatively excessive amount of solvent. So formation of a homogeneous phase takes place by different type of intermolecular interaction or attraction such as solute-solute, solute-cosolute and solvent-solvent interactions in the respective solvent medium. When the dissolution of the solute in the solution going on then with the increase in concentration of solvent, it was found that solute-solute interactions disappear slowly. So the solute-solvent interactions will dominate over the solute-solute interaction. The solute molecules agitate the solvent structure when they

dissolved into the solution and this will out-turn into the emergence of some solvation wrapper or salvation shell (moderate order in nature) around them formed by the solvent molecules. It was found thermodynamically that the dissolving process becomes spontaneous if the decreasing in the free energy obtained from the salvation process of the solute is higher than the rising in free energy due to demolition of the different type of interactions among the solute the solvent molecules.[115-118] When the lattice energy is greater than release solvation energy then the overall process of dissolution is supposed to be endothermic and but if the lattice energy is smaller than the solvation energy then the overall process must evolve as exothermic.

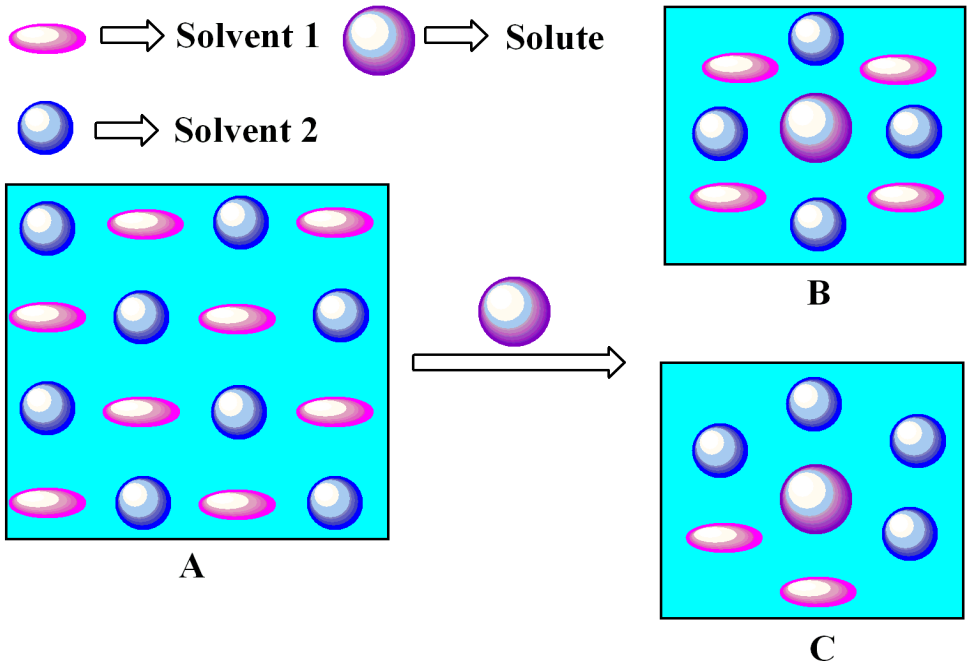

Fig. 1.2 Schematic representation of preferential solvation, A: binary solution mixture of solvent 1 and 2; B: ideal solvation; C: preferential solvation by solvent 1.

1.10.1. Preferential Solvation in solvent mixture:

The solvation mechanism for binary, ternary, etc, solvent mixtures is very much complicate in nature than that when taking place in pure solvents. The different types of interactions takes place in the solvent mixtures plays a significant role in the solvation phenomena, In addition to the different types of solute-solvent interactions. As a result there is a large deviation is perceived from the ideality according to the Raoult's law. Solute makes an remarkable difference in the composition of solvent mixture in sovaltion shell than that of the bulk composition.[119-122] This may referred as preferential solvation or selective solvation which diagrammatically represent on

the in Figure 1.2. Preferential solvation mostly found due to two type of solute-solvent interactions one is nonspecific (dielectric enrichment) and specific (hydrogen-bonding). It may be expressed as a outcome of solvent-solvent interactions in a solvent mixture.

1.11. Ion-Solvent or Solute-Solvent Interaction takes place in salvation process

In the present day various branches of chemistry basically deal with the solvation process of a solute by solvent molecules like formation of complex or synthetic chemical processes, *etc*. Solute-solvent or ion-solvent interactions is playing a vital role to regulate the chemical equilibrium and the rate of chemical reaction, *etc*., So that a portion of chemistry get involved with the solvation of ions or solutes and its origin may explained in terms of solute-solvent or ion-solvent and solvent-solvent interactions. In order to understand more clearly that if the structure of the solvent molecule is distorted or changed by the added solute it is very much important to know their interactions in the solution. It was found that the reactivity of a chemical reaction is mostly increase by the preferential absorption of solute particle of reactant molecule and the transition state through a specific or non-specific solute-solvent or ion-solvent interactions. During the solvation process altering in energy of the transition states are very much important. In order to know the solute-solvent or ion-solvent interactions more appropriately, research on the nature non-electrolytes solution and electrolytes solution in their binary mixtures of solvents and pure solvents have drawn attention in nowdays.[123-129]

During the solvation of the electrolytic molecules having neutral charge, the Ionic Solute and solvent interactions can be expressed more appropriately by knowing the interactions between the solute (ion) and the solvent molecules. Solvent having a ability to govern the inter-ionic forces in the ionic crystals. The inter ionic forces may be decrease to a extent that the moving ions are formed in the mixture due to independent transnational motion and considerable energy of these interactions that are summarily termed as ion-solvent interactions. Figure 1.3 represents the solvation of an ionic crystal by the exertion of a solvent.

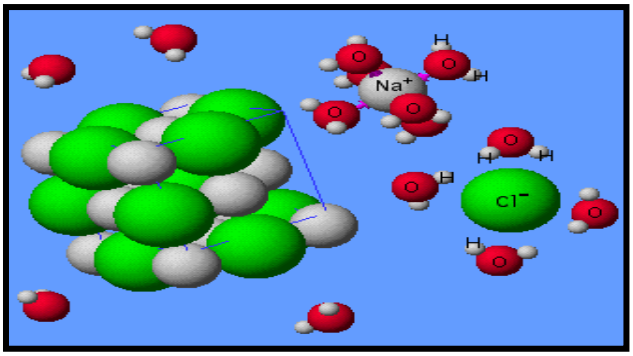

Fig. 1.3. Ionic crystal dissoluted by a solvent.

Ions can have the ability to orientate of the dipoles of respective solvent. Dipoles of the solvent may be rip up by the spherically symmetrical electric field of the ion from the solvent lattice and rearranged themselves with a specific charged end in direction of the central ion. For that cause ion-dipole interaction are considered as one of the main origin of the ion-solvent interactions takes place in the solution. In such cases the solvent molecules considered as electric dipoles and the ions are as point charge. Maximum no of reactions found in solutions are physiochemical or chemical or biochemical in nature. In past century it was considered that the solvent was behave as inert medium in any type of chemical reactions practically having no participation in reaction. But recent research work in aqueous medium found that non-aqueous and mixed solvents media can impart an affect on the ion-solvent interactions.[128]

Based on the association by the hydrogen bonding or acid base properties, numerous no of organic solvents can be differentiated from each other. Other properties like donor-acceptor properties, dielectric constants, organic group types, hard and soft acid-base(HSAB) principles, *etc* may be imply to differentiate organic solvent. Hence it is expected that thermodynamic the transport, acoustic properties, volumetric, viscometric properties of such solvents are very much affected by the existence of numerous electrolytes and non-electrolytes. Therefore the study of the affect of different electrolytes or non-electrolytes on the salvation process and also in their above said respective properties may give valuable information considering the numerous solute-solvent and solute-solvent/ion-solvent interactions.[130-135]

1.12. Ion-Ion or Solute-Solute Interaction in solution

The interactions between solvent and ions are usually associated with the vicinity of the ions in the mixture. It is here mentioned here that in addition to solvent

molecules the other ions are also studied through their surrounding environment. So mutual interaction taking place in between ion-solvent produce a key part of the "ion-ion interaction" between these ions. Ion-ion interactions can affect the properties of the whole solution to different degrees and are determined by the character of the electrolyte being examined. generally, ion-ion interactions are predominant over ion-solvent interactions.[135-138] In aqueous solutions of any electrolyte, ion-ion interactions are can be easily realized theoretically, but the interaction taking place between ion-solvent or ion-solvation very complex for study, and sometimes the small addition of a solute can remarkably changed the structural conformation of the solvent (e.g Water) .

1.13. Objective and application of the Research work

In present days researchers shows much more interest in the the study of physico-chemical properties of solute-solvent systems. In order to understand the miscellaneous intermolecular interactions taking place between components present in the mixture, the physico-chemical properties will provide a valuable information. So Endeavour to explore such behaviors through different type macroscopic and microscopic properties of the solution systems is investigated. Viscometric, acoustic ,volumetric, Thermodynamic, and transport studies are very much precise technique in this regard. Since maximum no. of the chemical and biological reactions found to takes place in solution medium, so the chemical reactions is depending on the behaviors of reactant present in the solutions mixture. Density, viscosity , dielectric constant, refractive index, etc are helpful solvent parameters in order to realization of different type of solvent properties to expressed the solvent effects in the chemical processes. The foundation model of solution is little bit a hard task due to complex nature of intermolecular interactions taking place in solution mixture. Therefore the main models centered on non-directional solute-solvent interactions (like Vander Waals interactions) are mainly applied. Various biological phenomena such as metabolism, transporting, signaling, *etc*., are also affected by the solvation process. Many theoretical considerations were also used to explore influence of the solvent effects on the bulk solvent properties. Onsager and Kirkwood have derived a simple model among all those treatments. There Several theories were proposed in the previous year for calculating the number molecules of solvents associated with respective ions and the number of those solvent molecules liberated to the bulk from the solvation shell during ion-pair development. At the beginning cations of transition

metal have geometrically well-defined first solvation shells. But they live through further solvation into a next concentric solvation sphere with no apparent solvation numbers or solvation sphere and geometries. However due to non-directional electrostatic ion-induced dipole or ion-dipole interactions maximum no. of the ions are get solvated in a marginally well-defined manner beyond the nearest surroundings of the ions. The theory of explaining the affect of the solvent quantitatively and the extent of ion-solvent interactions in solvent phase is needed to properly understand the different type of phenomena in solution thermodynamic chemistry. Partial molar volumes, isentropic compressibility, viscosity *B*-coefficient, refractive index and limiting ionic conductivities, *etc*., are basically used to calculate and realize the ion-solvent interactions takes place in solution thermodynamically.

The solute-solvent and solute-solute interactions have been found to influence in various fields of chemistry. Such type of solute-solvent interactions may guide the sufficient alteration in various chemical reactions accompanied with ions.[139-146] These type of change in ionic solvation are very helpful in various practical problems found in organic and inorganic compound synthesis, waterless battery technology, studies of reaction mechanisms and extraction of metal. Knowledge of such solute-solvent or ion-solvent interactions accompanied with the aqueous solutions have widest utility in diverse areas, such as energy transport, heat transport, mass transport, flow of fluid and the reaction kinetics, *etc*. Hence during the period from past to present a lot of attention has been drawn on the behavior of important biologically active compounds in various aqueous media under various experimental environment to study solute-solvent and solute-solute interactions.

Solution thermodynamics Studies on different types of important biologically active compounds like amino acids, alkaloids, drugs, vitamins, carbohydrates, *etc*., in various aqueous solution can proposed enriched information on various type of interactions in the solution, behavior of Solution and lifespan of numerous biological components. Solution thermodynamic parameters of such biological compounds in various aqueous medium help to understand the solvation process of solute. Researchers are chosen various type of aqueous media that will increase the net effect on these biologically active compounds and their solubility from their physico-chemical properties.[116-122] So the thermodynamic parameters and transport properties studied for such compounds would give us enriched information about different molecular interactions takes place in their respective solutions. Actually it can be said

that features covered a numerous topics but the main focus given towards on the viscometric, volumetric, spectrophotometric, and refractometric studies to explore the physico-chemical behavior of the solvent systems like aqueous media, Structures of solute and cosolute and their specific or mutual interactions in aqueous media or any other liquid phase.

1.14. Significance and span of the Physico-Chemical Parameters

Solvation process of a solute or ion in such a solvent plays an important role in proving solution character and thus solvation phenomena which complex nature, is influenced by the nature of the solvent and solute, *i.e*., their hydrophilic-hydrophobic behavior and molecular structure. Thermodynamic parameter and thermophysical properties are very much useful to know about the non-ideal behavior various complex solution systems. Because the physiochemical consequences evolve from the interplay of numerous molecular interactions or molecular forces amongst the different molecules.[146-148] In order to depict the intermolecular interactions between the different molecule through a study of some physical properties like, refractive index, density, viscosity and conductance, *etc*, helps us to investigate of the physiochemical behavior of the solution mixture. Regarding the practical point of view, these characteristics are very much important for the petrochemical ,pharmaceutical, and food industries chemical industries. Solution viscosity, densities and other related volumetric properties are important for physical and theoretical strands. The density is very much important for the changing of the concentration units and also for the study of the molecular interactions taking place in solute-solvent systems. Density measurement is applied in various fields; it found to be helpful to maintain quality in the production of industrial liquids, it helps in concentration determination in the beverage, soda and food industries, *etc*. Limiting Apparent molar volumes and the limiting partial molar volumes at infinite dilution can also be obtained for the solute-solvent systems provided densities of the mixtures are known. In addition to this the density data is very much important for the explain the properties like viscosity, and molar refractions, *etc*.

Chemical engineering calculations are required for gathering the knowledge of viscosity of the solution mixture where fluid flow, heat transport, mass transport, are the monitoring factors. Viscosity mainly provide info about the flow behavior of any gas and any liquid and it generally alter with the alteration of temperature. In case of solvent system it decreases as the temperature rises and *vice-versa*. Viscosity data helps to know about the nature and strength and extent of forces operating among the different type of molecules in a mixed solution system. Calculation of the viscosity data is very robust tools for a physiochemical researchers, since viscosity or the viscosity coefficient are dependent on the shape & size of molecule and also on the orientation of the molecules in solution phase. So it helps us to explain the ion-solvent or solute-solvent interactions through the measurement of free energy and the related thermodynamic parameters of transfer (like transfer of apparent molar volume) from one solvent to another for a ion or a solute.

Acoustic properties is another important valuable tool for gathering the knowledge about the behavior of various solutes like vitamins, carbohydrates, amino acids, and drugs, *etc*., in aqueous and non aqueous mixtures. At macroscopic level the changes can be understood from the propagation of ultrasonic sound measurement in solutions help to explore the changes in various physical properties. Since the structure and interactions between molecules present in the solution are highly affected by sound velocity, so molecular interactions can be determine quantitatively in the solution with the help of ultrasonic speed of sound.

Refractive index is another vital parameter for determination of the various physico-chemical phenomena of solutes in solution. Solute-solute or ion-ion, solute-solvent or ion-solvent as well as solvent-solvent interactions can be easily derived from the refractive index studies. Refractive index is supposed to be one of the key parameters of a solution and it can easily be measured somewhat more accurately. Molar refractivity helps us to know about electronic polarization of any ion present in solution that depends on the electronic shell arrangements of ions under the influence of the surrounding environment and neighboring ions.

In addition to this a solute-solvent system is more explained by the presence of different electronically excited states of the solvent molecule and solute molecule with considerable electronic interactions. When solvents of separate polarities are imply to record the absorption spectra Solvents found that it can changes the intensities, positions of absorption bands, shapes of the solutes. This effect arises due

to different types of intermolecular solute-solvent interactions present in the solutions, like ion-dipole, dipole-induced dipole, dipole-dipole and hydrogen bond, *etc*. These interactions/forces may lead to alter in the energy gap between excited and ground state of the absorbing species. Hence solute-solvent and the solvent-solvent interactions measured from the absorption spectra of the solutes present in the solutions. Due to this overall fact of discussion, research on the solution thermodynamics of some biologically active compounds in various aqueous medium have undertaken.[149-156]

1.15. Vital role of Solutes and Solvents used

The role of solutes and solvents in a solution mixture is included in this thesis is given below.

1.15.1 Solutes and cosolutes

L-Leucine performs numerous functions in the body. It helps to maintain blood sugar level, improves wound healing, and bring about the growth hormone. But leucine is best known for its role in the muscular system. It build up the muscle in the body and also supposed to repair it when required.

L-proline, is an amino acid. It is non-essential amino acid since body can synthesize it by the breakdown of L-glutamate. It is well known fact that Protein is disintegrate into amino acids the building blocks of protein. L-Proline is an important compound that responsible for repairing the damage tissue, collagen formation, arteriosclerosis prevention and blood maintenance pressure level of the body.

Paracetamol also known as N-acetyl-p-amino phenol or acetaminophen is an antipyretic, mild analgesic agent and also an anti-inflammatory non-steroidal drug.[156]

Allopurinol is a drug that is widely used for the treatment of the gout from mid of the last century to till now. It has shows accurate effectiveness towards the gout problem.

Uracil is an nucleobase found in nucleic acid of RNA. It is very useful to body in producing many necessary enzymes for proper functioning of cell in the living body. Uracil has also wide application as an allosteric regulator in the body. It is also found to operating in drug delivery.

Amino acids are the fundamental building blocks of proteins. Salt and some surfactant induced electrostatic forces often modify protein structure by changing the properties like denaturation, solubility and enzymes activity, *etc*. The physicochemical properties of certain salts and surfactant in aqueous solution of

amino acids thus provide valuable data on the solute-solvent and solute-solute interactions. These interactions are valuable to understand the stability of proteins and give information for several physiological and biochemical process that occur in a living body. Hence to get a deeper insight into the hydration of protein and various non-covalent forces that stabilizes the native structure of protein, it is important to detect the effect of such salts and surfactant on the model of proteins compound, simply the amino acids.[156-159]

Caffeine is a alkaloid which bitter in taste and state is white crystalline (purine). It occurs as odourless, glistening needles of fleecy masses. It is found in nature seeds, nuts, fruits and leaves of a number of plants like tea, beans, guarana, coffee, and cola, *etc*. Caffeine has put its role on vasoconstriction and other cardiovascular activities. It can have the ability to inhibit DNA reproduction and this can lead to serious complications for pregnant woman. It may be considered as one of the causes of cancer, ageing and heart diseases. In pharmacology this compound is often used as diet aids, analgesics, and flu/cold remedies.

Cyclodextrins found to protect the compounds from the effects of heat, and light, oxygen. It can be used to reduced volatility of compounds can be give rise the shelf life and reduced liberation of compounds into the environment. Cyclodextrins can be used to removal or isolation of specific compounds from their mixture.[160-162]

1.16. Solvents

Since water is considered as universal solvent system , so the aqueous systems draw the special attention. Such systems are comparatively very simple. Water is not an inert diluents. It possess a unique cluster structure through extensive hydrogen bonds in three-dimension, a large heat capacity and, a high boiling temperature, a high dielectric constant and found many anomalies in its specific volume. Due to its amazing properties it has been considered as a universal solvent in chemical, biochemical and cellular systems. Such as water ionizes and felicitate proton exchange between molecules to renders the affluence of ionic synergies in biological systems. In addition to this it's unique hydration properties towards various biological protein molecules afford the three-dimensional structure of such macromolecules and hence water can govern their functions in the solution.[145-150] Regarding that the preferential arrangement of water around the non-polar and polar parts of the biopolymers (preferential hydration) is very engrossing and informative. Except these interesting water properties, studies on its behavior as a solvent and its interactions

with different biologically active compounds draw extensive attention. Therefore, in this work different aqueous media were used as solvent systems. Cyclo dextrine, amino acids (*e.g.*, glycine and L-Alanine), RNA base like uracil were used as cosolutes for different aqueous solvent systems.[162-165]

1.17. Activity of water as a solvent

Water is universally present in biological systems and related materials and the surroundings. So the hydrophobic and hydrophilic interactions supposed to control the behavior of certain products in presence of water. Its thermodynamic parameter, *i.e.*, the water activity a_w depict that the equilibrium amount of water is available for the solvation of remaining solutes or for their degradation reactions which may be chemical or biochemical. Pure water is depicted by $a_w = 1$, but $a_w = 0$ means total skiving of 'free' water molecule. In order to understand comparison of stability of certain products have the similar water activity (a_w) in such cases knowledge of the water structure is important. Thus hydrophobic and hydrophilic interactions takes place between water and the bioactive molecule like drugs, foodstuff, amino acids, *etc*., and the influence of such soluble molecules on the hydrogen bonds present in the water are very valuable in order to preservation and storage of them. If water activity (a_w) value found to be lower then it stop the growth of the microbes. So by monitoring the water activity (a_w) in packaging food and its related industries is giving more life time to the food. Such effect of water activity (a_w) on the stability of bio-systems, protein, amino acid, carbohydrates, and nucleic acids are well defined.

The gradient of the chemical potential of water (μ_w) in a solution is related to its activity (a_w) through the expression:

$$\mu_w = \mu_w^* + RT \ln a_w \approx \mu_w^* - RTV_w^*(c/M + Bc^2 + \mathrm{K}) \qquad (1)$$

where μ_w^* = gradient of the chemical potential and V_w^* = the molar volume of pure water, respectively. R, T, c, M and B are the universal gas constant, the absolute temperature, the solute concentration, the solute molar mass and the so-called second virial coefficient, respectively. The second virial coefficient (B) shows the solute-solute and solute-solvent interactions because of non-ideal behavior of the mixture. From the above expression it is clear that why addition of a solute always minimize the water activity (a_w). By rearrangement of the above expression yields:

$$\ln a_w = -V_w^*(c/M + Bc^2 + \mathrm{K}) \leq 0$$
$$\text{or } B > -1/cM \qquad (2)$$

If $B < 0$, water behave as weak solvent and if $B \approx 0$, the solute will separated out as a precipitate from the solution. Hence the second virial coefficient (B) depends on pH of the solution. Biopolymers such biologically active molecules usually have lower value of B; so the large changes of a_w values produces minor effects on the B-values. But for existing biological systems, most of the food products and certain of polymers c is rather large and minor changes in the moisture content leads to a large drop in a_w -values. This type of a large drop in a_w -values affects the overall structure and arrangement of the solution taken under investigation.[163-165]

1.18. Method of Investigation

In order to investigate the solute-solute, solvent-solvent and solute-solvent interaction there are different experimental techniques are employed. Densitometry, Ultrasonic sound measurement, viscometry, volumetry, refractometry and UV-visible spectroscopy were used in the used in the present study and discussed in this thesis.Thermodynamic properties of solutions useful in determining the feasibility of chemical reactions in solution phase and also valuable to investigate theoretical phenomena of solution structure. Thermodynamic properties like apparent molar volume, limiting partial molar volume and partial molar volume of transfer, *etc*., obtained from density calculation which are more convenient parameters for depicting the solute-solvent and solute-solute interactions in the solution. The partial molar volumes and apparent molar volumes of electrolyte solutions are familiar tool in exploring structural interactions (*i.e*., ion-ion or solute-solute, ion-solvent or solute-solvent and solvent-solvent interactions) in solution mixture.[150-158] For electrolyte and non-electrolyte solutions, viscosities property explains their solution behavior. The compressibility factor, a second derivative of Gibbs energy, is reveal that it is very sensitive towards molecular interactions taking place in solution phase. So it can also provide valuable information regarding the partial molar volumes for such interactions. For the electrolyte and non-electrolyte solutions viscosity measure as function of concentration and temperature, in order to study solute-solvent or ion-solvent (solvation) interactions. In addition to this long-range ion-ion electrostatic interactions are also measured. Gradual addition of electrolytes may changes the

solvent viscosity due to inter-ionic and ion-solvent interaction. The viscosity *B*-coefficients will give appropriate explanation of ion-solvent or solute-solvent interactions, *i.e*., the net effects of salvation process, preferential solvation and long range structure-making or structure-breaking ability of the solutes. Refract metric studies also draw the attention on the different molecular interactions that taking place in solute-solvent systems of different compositions. Such studies useful in interpretation of the character of the solutes in various solvent systems. UV-visible spectroscopy also employed to of such solutions in order to explore the interaction and support the results obtained previously from viscosity, Acoustic, density, and refractive index measurements.

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CHAPTER II

Physico-Chemical Parameters Studied in Solution Chemistry

Solution chemistry is developed side by side with the growing of the fundamental chemistry. The alchemist's always try to find out universal solvent socalled "Alkahest".Chemists of the past era found the fundamental truth about the solvation, *i.e.* "like dissolves like".[1] Raoult in his study found systematically that freezing points and boiling point of any liquids are cery much influenced by the presence of dissolved nonionic solute particle and he found that the vapour pressure depend on the mole farction of solvent above the solution and is directly proportional to the mole fraction of pure solvent in solution which is familiar as Raoult's law.[2] In addition to this for electrolyte system Arrhenius's theory throw a light on the dissociation of ionic solutes into cations and anions in solution. Arrhenius established his theory on the basis of complete and incomplete dissociation takes place different type of electrolyte and by a comparing of the acquired results data from the calculation of osmotic pressure and specefic conductivity of dilute electrolyte solutions.[3] Except this many scintist of the solution chemistry feild share their valuable knowledge some of them are like Nernst ,Debye Huckel Ostwald, Lewis.[1]

Solution chemistry is a significant branch of chemistry that deal with the alter in particular solution parameters. This will happen while different type solute is dissolved in a solvent or in a mixture of different solvent. This branch will provide the valuable information about physio-chemical behaviour of both the solvent and the solute depends on the solubility of the solute in the solvent or in solution. Most of the solution mixtures formed from solute and the sovent do not obey the Raoults law i.e. behave as non-ideal solution. This type deviation from ideality can be explain by using different types thermodynamic parameters. In case of liquid-liquid systems various excess or deviated properties helpful for giving explanation of the deviation from Raoults law. But for solid-liquid systems apparent or partial molar properties can be helpful for the explanation of the same. Molecular arrangements and interactions present in any solution can be better understood with the help of these thermodynamic parameters. Significantly it shows the interaction taking place between the solute-solute, solute-cosolute and solvent-solvent molecules in the solution. The exact molecular structure however for a solvent in solution certainly

understood. The solvent structure gets reformed by the involving solute particle or an ion often to an certain extent that can also upset the solute molecules. The extent to which a solute or ion can get dissolute is depends on the degree of interactions amongst the solvent-solvent, solute-solute, solute-co solutes molecules or between the molecules if any present in the solution except solute and solvent molecule. Thermodynamic parameter enthalpy change and entropy changes, free energy change, *etc*., accompanied with a specific physiochemical reaction are evaluated by using different physico-chemical techniques like viscometry, densitometry, ultrasonic interferometry, conductometry, refractometry, *etc*.,. Then the data of different analysis performed in physico-chemical process utilisable to explore the factors that attached with the solute-solvent or ion-solvent interactions. Some Spectroscopic technique like IR spectroscopy, NMR spectroscopy, UV-Visible spectroscopy are also showing their presence in this regard. Therefore, the present dissertation dedicated to research works on some biologically active compounds in various aqueous media to know their solution behaviour.

2.1. Density measurement

Density data of solute-solvent and solvent-solvent systems very much informative in order to predict the interaction present in the solution mixture. In addition to this some valuable information about the nature and degree of the molecular interactions in such mixture of solution can be examined from different volumetric properties. The volumetric information derived from density data as a mass function, excess volumes of mixing and volume and mole fraction. Some fundamental properties such as entropy, enthalpy, and Gibbs free energy, etc., shows the macroscopic state as an average of various microscopic states of the system at a specific pressure and temperature. Proper explanation of these macroscopic properties through the molecular phenomena is found to be difficult. Sometimes higher derivatives of these properties found to explain more appropriately in terms of molecular interactions. Various type of molecular phenomena found in the solutions like micellization[6],hydrophobic hydration,[5] electrostriction,[4] and co-sphere overlap during the solute-solvent interactions[7] can be interpreted from their partial molar volumes of the various dissolved compound.

2.1.1. Partial Molar Volumes calculation

It is well-known from the phase rule: $F = C - P + 2$. For a one component and single phase system, F = 2. This suggests that at least two properties of a 'single phase one component' required to define its state. These parameters are generally atmospheric pressure and temperature. These variables can be easily guided or manipulated. The solution thermodynamic concern about the influence by the knowledge of partial properties that suggest in order to calculate each components effect and their concentration on thermodynamic state properties like entropy, volume, enthalpy, Gibb's free energy, *etc*. These all are extensive properties which depend upon the mass or the no of mole of solute present in the solution. These parameters being a state dependent function in a closed system, depending upon any two of the state variables, *viz.*, atmospheric pressure, temperature and volume of a system of definite composition. But in case of open system of variable composition (*e.g.*, liquid system) that contains two or even more components and the exchange of matter occurs with its surroundings gone through a change in composition (number of moles). So, the total extensive property is not considered only as a function of pressure and temperature but also as the actual number of mole of each component present in the system. Hence for a multi-component system a thermodynamic state function (Y) can be shown as follows:[8, 9]

$$Y = f(T, P, n_1, n_2, n_3, ...) \qquad (1)$$

The net change in this property (dY) at constant pressure and temperature is given by:

$$dY = \left(\frac{dY}{dn_1}\right)_{T,P,n_2,n_3,...} dn_1 + \left(\frac{dY}{dn_2}\right)_{T,P,n_1,n_3,...} dn_2 + \Lambda \qquad (2)$$

The term $(dY/dn_i)_{T,P,n_{j\neq i}}$ = partial molar parameter of the ith component and is denoted by $\bar{Y}_{m,i} = (dY/dn_1)_{T,P,n_2,n_3,...}$. Thus it denote rate at which the property Y alter with the extent of the ith species mixed to the mixture at constant temperature, atmospheric pressure and the quantity of all other species present in system. Partial molar quantities are intensive properties related to the changes in extensive properties of the solution (such as *V, G, H, S* and *A*) to the concentration changes. Among all the extensive thermodynamic properties, the volume is easiest to understand. Taking Y as volume rearrangement of Eq. (2) gives:

$$dV = \left(\frac{dV}{dn_1}\right)_{T,P,n_2,n_3,\ldots} dn_1 + \left(\frac{dV}{dn_2}\right)_{T,P,n_1,n_3,\ldots} dn_2 + \Lambda \qquad (3)$$

$$\text{or } dV = \bar{V}_{\mathrm{m},1} dn_1 + \bar{V}_{\mathrm{m},2} dn_2 + \Lambda \qquad (4)$$

where $\bar{V}_{\mathrm{m},1}$ and $\bar{V}_{\mathrm{m},2}$ are the partial molar volume of component 1 and 2, respectively. In the molecular level, the solute-solvent interaction or solvation has little bit affect on partial molar volume, like the partial molar volume of Li^+ ion is found to be negative and such unexpected negative value of volume is a proof of presence of electrostriction in the solution,[10] *i.e.*, strong electrostatic interaction takes place between Li^+ ion and the water molecules. Therefore, the partial molar volume give valuable informative data about the solute-solvent interactions takes place in the solution. The partial molar quantities are additive and integration of Eq. (4) yields:

$$V = \bar{V}_{\mathrm{m},1} n_1 + \bar{V}_{\mathrm{m},2} n_2 + \ldots\ldots \qquad (5)$$

For an ideal solution, the total volume is the sum of the molar volumes of the components in a mixture as given by:

$$V = V^*_{\mathrm{m},1} n_1 + V^*_{\mathrm{m},2} n_2 + \ldots\ldots \qquad (6)$$

where $V^*_{\mathrm{m},1}$ and $V^*_{\mathrm{m},2}$ are the molar volumes of components 1 and 2, respectively. In case of ideal solutions, the partial molar volume of each substance is same as their respective molar volumes. However, in case of non-ideal solutions the existence of the second component (i.e. solute) affect value of the molar volume of the first component and *vice versa*, *i.e.*, $\bar{V}_{\mathrm{m},1} \neq V^*_{\mathrm{m},1}$ and $\bar{V}_{\mathrm{m},2} \neq V^*_{\mathrm{m},2}$. So for non-ideal mixtures total volumes are either decreases i.e. volumetric contraction takes place or increases i.e volumetric inflation takes place than that for the ideal solution. This implies that partial molar volumes of the components do not equal to their molar volumes but can change with the composition of the mixture due to change in the molecular surrounding environment by packing or salvation of each molecule. This is shown below in Figure 2.1 for water-ethanol system[11] at 20 $^\circ$C at the overall composition range.

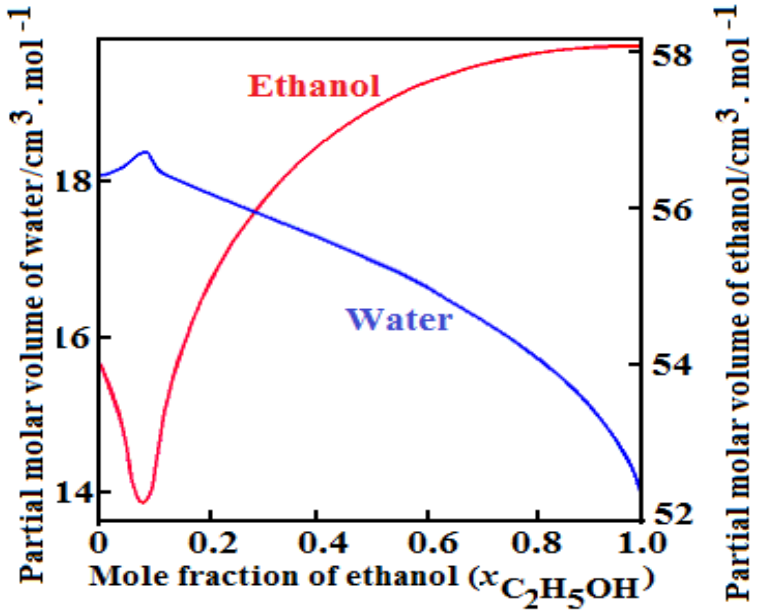

Fig 2.1. Partial molar volumes of ethanol and water in aqueous ethanol at 20 °C.

2.1.2. Apparent Molar Volume calculation

Partial molar volume evaluated carefully by calculating the solution densities of known concentrations. Apparent molar volume (ϕ_V) can be determine from the density data. It is the changes volume of the solution due to addition of the solute per mole.

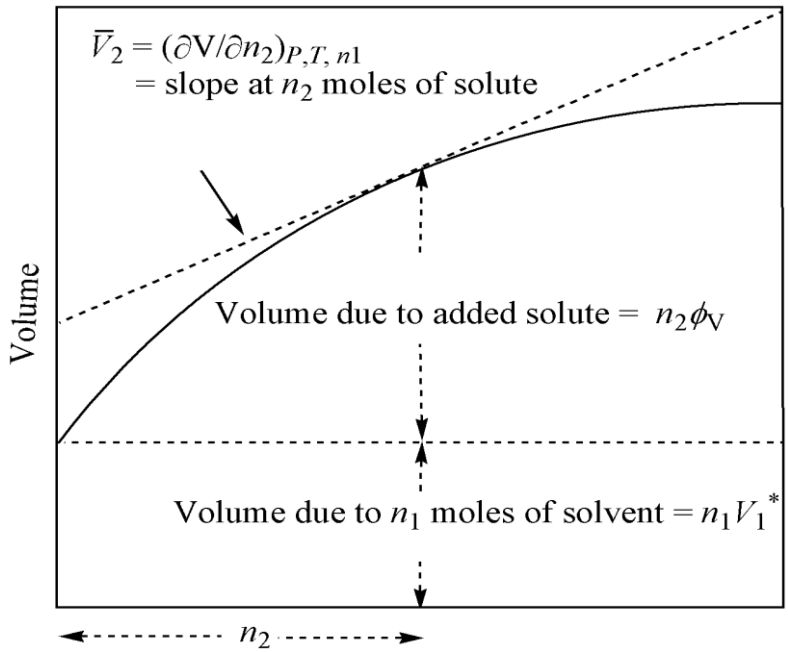

Fig 2.2. Realationship among the total solution volume, pure solvent volume and the apparent molar volume (ϕ_V) of the solute.

From **Figure 2.2** it can be realize the with the addition n_2 moles of a solute to a solution containing a fixed n_1 moles of a solvent, the volume of the solution changes and the apparent molar volume (ϕ_V) is shown below,

$$\phi_V = \frac{V_{\text{solution}} - V_{\text{solvent}}}{\text{molesof solute}} = \frac{V - n_1 V_1^*}{n_2} \tag{7}$$

and the solution volume when n_2 moles of the solute are added is given by:

$$V = n_1 V_1^* + n_2 \phi_V \tag{8}$$

Since number of moles of both the solute and solvent can't remain fixed simultaneously throughout the process, it does not have any importance to define apparent molar volume of the solvent. The apparent molar volume of solute and solvent can give the idea of the partial molar volumes of both the solute and solvent. Partial differentiation of Eq. (8) with respect to n_2 at constant n_1 provides the partial molar volume of the solute,

$$\overline{V}_2 = (\partial V / \partial n_2)_{n_1} = \phi_V + n_2 (\partial \phi_V / \partial n_2)_{n_1} \tag{9}$$

When determining the apparent molar volume (ϕ_V) from experimental data it is better to use the molarity scale (c) for the solute concentration[4] and densities (ρ). The apparent molar volumes (ϕ_V) of solutes can be had from the following relation:[4]

$$\phi_V = M/\rho_1 - 1000(\rho - \rho_1)/(c\rho_1) \tag{10}$$

where ρ_1 and ρ denotes the densities of solvent and solution, respectively and M denotes the molecular weight of the solute. If concentrations are expressed in molalities (m) of the solute, Eq. (10) converts into the following expression: [4]

$$\phi_V = M/\rho - 1000(\rho - \rho_1)/(m\rho\rho_1) \tag{11}$$

In order to extrapolate the apparent molar volume of an electrolyte or a solute at infinite dilution four major equations, *viz*., the Masson equation,[12] Owen-Brinkley equation[14] the Redlich-Meyer equation,[13] the and the Pitzer equation[15] are taken into consideration. In Masson equation give the apparent molar volume of electrolytes or ionic solutes (ϕ_V) follows a linear relation with the square root of the solute molarities (c) as given below:

$$\phi_V = \phi_V^0 + S_V^* \sqrt{c} \tag{12}$$

where ϕ_V^0 represents the apparent molar volume at infinite dilution or standard partial molar volume (equal to the partial molar volume at infinite dilution, $\overline{V}_2^0$) and S_V^* is the slope of the linear fit. Eq. (12) has been used for a majority of ϕ_V data in aqueous medium[16] and nearly all ϕ_V data in non-aqueous[17-21] solvents. But according to Redlich and Meyer,[13] Eq. (12) is a limiting law and for a specific solvent and temperature, the slope S_V^* should depend on the valence type. They suggested the following expression for deducing ϕ_V :

$$\phi_V = \phi_V^0 + A_V\sqrt{c} + b_V c \tag{13}$$

$$\text{where } A_V = kw^{3/2} \tag{14}$$

Here the theoretical slope (A_V), based on molar concentration, includes the valence factor:

$$w = 0.5\sum_i^j \nu_i z_i^2 \tag{15}$$

$$\text{and, } k = N_A^2 e^2 (8\pi/1000\varepsilon_r^3 RT)^{1/2}[(\partial \ln \varepsilon_r/\partial P)_T - \beta/3] \tag{16}$$

where β indicate the compressibility factor of the solvent. However, the variation of dielectric constant (ε_r) with pressure is remain unclear, even in water, to determine the theoretical limiting slope (A_V) accurately. Redlich-Meyer[13]equation adequately shows that the concentration dependence of many 1:1 and 2:1 electrolytes in dilute solutions. However it represents disagreement when applied for some 2:1, 3:1 and 4:1 electrolytes.[22-24] Actually, the volume provide to a solvent by the addition of 1 mole of an solute(ion) is very tough to determine. The reason for it is that when ion enter into the solvent the ion may disintegrate the solvent structure and thereby alter the volume of the solution and the compression of the solvent under the influence of the ion's electric field is called electrostriction.[25] It is very common event that may found whenever the electric fields is present in the order of 10^9-10^{10} V m^{-1}. But for polyvalent electrolytes, the Owen-Brinkley[14] equation is more precise for such extrapolation and to satisfactorily shown the concentration dependency of ϕ_V .The Owen-Brinkley equation includes the ion-size parameter (a) and is represented by:

$$\phi_V = \phi_V^0 + A_V\tau(\kappa a)\sqrt{c} + 0.5w_V\theta(\kappa a) + 0.5K_V c \tag{17}$$

where the symbols have their usual significance.[14] Pogue and Atkinson[26] used the Pitzer formalism to fit the apparent molar volumes. The Pitzer equation for the apparent molal volume of a single salt $M_{\nu_M} X_{\nu_X}$ is given by:

$$\phi_V = \phi_V^0 + V|z_M z_X|A_V|2b\mathrm{In}(I + bI^{1/2}) + 2\nu_M\nu_X RT[mB_{MX}^{\nu} + m^2(\gamma_M\gamma_X)^{1/2}C_{MX}^{\nu}] \quad (18)$$

where

$$B_{MX}^{\nu} = (\partial\beta^0/\partial P)_T + (\partial\beta^1/\partial P)_T(2/\alpha^2 I)[1-(1+\alpha I^{1/2})\exp(-\alpha I^{1/2})] \quad (19)$$

$$C_{MX}^{\nu} = (\partial C^{\phi}/\partial P)_T/2 \quad (20)$$

$$\nu = \nu_M + \nu_X \quad (21)$$

$$\alpha = 2.0(\mathrm{kg/mol})^{1/2} \quad (22)$$

$$b = 1.2(\mathrm{kg/mol})^{1/2} \quad (23)$$

and other symbols have their usual significance.[26]

2.1.3. Ionic Partial Molar Volume

The individual ionic partial molar volumes often provide information about the solution structure around an ion, *i.e.*, its solvation. Although it is difficult to calculate the ionic limiting partial molar volumes in non-aqueous electrolyte solutions, most of the existing ionic limiting partial molar volumes for such systems were calculated by the following methods actually created for aqueous solutions.[27] Most widely used technique was proposed by Conway *et al.*[27] These authors study the limiting partial molar volumes of the chlorides, bromides and iodides for a series of homologous tetraalkylammonium salts in aqueous solution and then plotted the limiting partial molar volume (ϕ_{V,R_4NX}^0) for such a series of salts with a common halide ion (X^-) as a function of the formula weight of the cation ($M_{R_4N^+}$) and obtained straight lines for each series as suggested by the following equation:

$$\phi_{V,R_4NX}^0 = \phi_{V,X^-}^0 + bM_{R_4N^+} \quad (24)$$

Eq. (24) when extrapolated to zero cationic formula weight provides the limiting partial molar volumes (ϕ_{V,X^-}^0) of the halide ions and ϕ_V^0 for an ion in a solution can be expressed as: [28]

$$\phi_{V,\mathrm{ion}}^0 = \phi_{V,\mathrm{int}}^0 + \Delta V \quad (25)$$

where $\phi_{V,\text{int}}^{0}$ = intrinsic volume of the ion and ΔV = volume change of the system due to ion-solvent interactions. Some other pioneer[29] supposed the anion solvation to be nullified for the electrolyte solutions and suggested the solvation number at infinite dilution to be associated with the extent of the cation solvation Therefore, Eq. (25) represented as:

$$\phi_{V,\text{ion}}^{0} = \phi_{V,\text{int}}^{0}(\text{R}_4\text{N}^+) + \Delta V \tag{26}$$

and the term $\phi_{V,\text{int}}^{0}(\text{R}_4\text{N}^+)$ can be had from the following relation:[30]

$$\phi_{V,\text{int}}^{0}(\text{R}_4\text{N}^+) = 2.52 r_{\text{R}_4\text{N}^+}^{3} \tag{27}$$

where $r_{\text{R}_4\text{N}^+}$ is the crystallographic radii of the R_4N^+ ion. Uosaki *et al.*[31] used this approach for separating $\phi_{V,\text{R}_4\text{NX}}^{0}$ values into ionic contributions in organic electrolyte solutions. Krumgalz[30] also applied the same method for a large set of partial molar volume data for non-aqueous electrolyte solutions. Based on Frank and Wen model,[32] Millero[33] has given the relation for the standard partial molar volume ($\phi_{V,\text{ion}}^{0}$) of an ion:

$$\phi_{V,\text{ion}}^{0} = \phi_{V,\text{int}}^{0} + \phi_{V,\text{elect}}^{0} + \phi_{V,\text{disord}}^{0} + \phi_{V,\text{caged}}^{0} \tag{28}$$

where $\phi_{V,\text{elect}}^{0}$ is the partial molar volume due to electrostriction, $\phi_{V,\text{disord}}^{0}$ is the partial molar volume due to void space and $\phi_{V,\text{caged}}^{0}$ is the caged partial molar volume for the caged water structure around ions. Although it is difficult to determine thevarious contributions to $\phi_{V,\text{ion}}^{0}$, Millero[33] has examined $\phi_{V,\text{ion}}^{0}$ values in water and methanol using the relations relations:[34]

$$\phi_{V,\text{ion}}^{0} = 2.52 r^3 + A' r^2 - B' z^2 / r \tag{29}$$

$$\phi_{V,\text{ion}}^{0} = 2.52 (r + a)^3 - B'' z^2 / r \tag{30}$$

where r is the crystallographic radii of the ion, z is ionic charge, a, A', B' and B'' are constants. The electrostriction of an ion can be estimated, when dielectric saturation is negligible, by the Drude-Nernst equation: [35]

$$\phi_{V,\text{elect}}^{0} = -\frac{N_A z^2 e^2}{2\varepsilon_r r}(\partial \ln \varepsilon_r / \partial P) = -\frac{B''' z^2}{r} \tag{31}$$

where ε_r = dielectric constant of the solvent and B''' = solvent dependent constant. Other symbols have their usual significance.[35] There is strong competition between ion and the solvent molecules for highly ordered solvents in order to increase the order. There will be a torque like situation arise where ions attempts to orient solvent molecules around themselves, whereas the solvent molecules try to keep the highly ordered bulk structure. Thus, a relatively large agitating region surround the solvated ions is produce that resulting into large values for $\phi_{V,\text{disord}}^0$ and S_{ion}^0 called partial molar entropy of the ion. In case of less structured solvents, the solvent molecules are get affected by ion-solvent interactions that results in to a smaller voids space around the ion with smaller $\phi_{V,\text{disord}}^0$, negative $\phi_{V,\text{elect}}^0$ and S_{ion}^0 values. Hence the degree of the solvent structure and the dielectric constant of the solvent have playing a crucial role for ion-solvent interactions.

2.1.4. Standard Partial Molar Volume of Transfer

Partial molar volume of solutes at infinite dilution can be employed to discover the solute (or ion)-solvent and solvent–solvent interactions in various solvent systems.[16,30,36,37] Transfer volume ($\Delta_t\phi_V^0$) is defined as the difference between the partial molar volumes of the solute in a particular solvent from that in a reference solvent present at infinite dilution. So $\Delta_t\phi_V^0$ is given by:

$$\Delta_t\phi_V^0 = \phi_V^0(\text{solute} + \text{cosolute} + \text{solvent}) - \phi_V^0(\text{solute} + \text{solvent}) \qquad (32)$$

The above equation shows the degrees and nature of solute-solvent or ion-solvent and solute-cosolute interactions, since at infinite dilution the solute-solute or ion-ion interactions are assumed to be negligible. Franks *et al.*[38] suggested that the partial molar volume of a non-electrolyte can be represented by a combination of it's intrinsic volume ($\phi_{V,\text{int}}^0$) and the volume ($\phi_{V,\text{solv}}^0$) for its interactions with the solvent. The intrinsic volume ($\phi_{V,\text{int}}^0$) is a sum of two types of contributions, *i.e.*, $\phi_{V,\text{int}}^0 = \phi_{V,\text{vw}} + \phi_{V,\text{void}}$; where $\phi_{V,\text{vw}}$ and $\phi_{V,\text{void}}$ denote the van der Waals volume and voids in the solution, respectively. According to Shahidi *et al.*[39] the intrinsic volume ($\phi_{V,\text{int}}^0$) of a non-electrolyte solute in solution is given by:

$$\phi_{V,\text{int}}^0 = \phi_{V,\text{vw}} + \phi_{V,\text{void}} - n\sigma_s \qquad (33)$$

where σ_s denotes the shrinkage volume due to the interactions of hydrogen bonding groups present in the solute with solvent molecules and n denotes the number of hydrogen bonding sites in the solute. For electrolytes and zwitterioninc solutes, the shrinkage arises from the electrostriction and Eq. (33) can be expressed as:

$$\phi^0_{V,\text{int}} = \phi_{V,\text{vw}} + \phi_{V,\text{void}} - \phi_{V,shrinkage} \tag{34}$$

Generally $\phi_{V,\text{vw}}$ and $\phi_{V,\text{void}}$ are assumed[40] to have same magnitude in water and in mixed solvent for the same type of solutes. Thus, $\phi^0_{V,\text{int}}$ depends on $\phi^0_{V,\text{shrinkage}}$, that is actually caused by the electrostriction in the solution. In this regard the cosphere overlap model[41,42] helps to analyze $\Delta_t\phi^0_V$ values in terms of solute-cosolute interactions. According to this model behaviour of water molecules in the hydration cosphere depend on the nature of the solute molecules present in the aqueous media. During the time of coshepre overlapping, when two solute particles come close enough so that their cospheres overlap, some of the molecules in the cosphere are override and thus the thermodynamic parameter of the solution may change. There are various types of interactions are taking place: (i) polar-ionic and polar-polar group interactions (*e.g.*, ion-dipole, ion-quadrupole, ion-induced dipole interactions), (ii) polar-non-polar and non-polar-non-polar group interactions (*e.g.*, hydrophobic-hydrophilic interactions, hydrophobic-hydrophobic interactions), *etc*., depending on the nature of the solvent and solute. Interactions of type (i) contribute positive values to transfer volumes ($\Delta_t\phi^0_V$), while the interactions of types (ii) and (iii) contribute negative values to transfer volumes ($\Delta_t\phi^0_V$). The overlap of hydration cospheres of charged species results into decrease in the electrostriction of the solute that leading to a lowering in $\phi^0_{V,\text{shrinkage}}$ and thus positive $\Delta_t\phi^0_V$ values obtained.[41] Kozak *et al.*[43] suggest a theory based on the McMillan-Mayer theory of solutions that allow the formal separation of the various type of effects due to pair-wise interactions of solute molecules as well as those due to interactions iamongst three or more solvent molecules. Friedman and Krishnan[44] as well as Franks and Evans[38] enterprete this consideration to incorporate the solute-cosolute interactions in the solvation sphere. Thus the transfer volume ($\Delta_t\phi^0_V$) is given by:

$$\Delta_t\phi^0_{V,} = 2Z_{12}m_2 + 3Z_{122}m_2^2 + 4Z_{1222}m_2^3 \tag{35}$$

where Z_{12}, Z_{122} and Z_{1222} are the pair, triplet and quartet interaction coefficients, respectively and m_2 = molality of the cosolute in the solution.

However, it is found to be very hard to get individual ionic transfer volumes ($\Delta_t\phi_V^0$) and the method used adopts some extra-thermodynamic assumptions (similar to the partial molar volume in section 2.1.3 above) in order to disintegrate the transfer volume ($\Delta_t\phi_V^0$) into ionic components. Maestre *et al.*[45] used the method of reference electrolyte (Ph_4AsBPh_4) for this purpose as reflected by the relations:

$$\Delta_t\phi_V^0(Ph_4AsBPh_4) = 2\Delta_t\phi_V^0(Ph_4As^+) = 2\Delta_t\phi_V^0(BPh_4^-) \quad (36)$$

$$\Delta_t\phi_V^0(Ph_4AsBPh_4) = \Delta_t\phi_V^0(Ph_4AsCl) + \Delta_t\phi_V^0(NaBPh_4) - \Delta_t\phi_V^0(NaCl) \quad (37)$$

Once $\Delta_t\phi_V^0(Ph_4As^+)$ or $\Delta_t\phi_V^0(BPh_4^-)$ has been determined, other single ion transfer volumes can be obtained from the transfer volume of the electrolyte. Conway[46] expressed the partial molar volume of an ion at infinite dilution as follows:

$$\phi_{V,\text{ion}}^0 = \phi_{V,\text{int}}^0 + \phi_{V,\text{elect}}^0 + \phi_{V,\text{struc}}^0 \quad (38)$$

where $\phi_{V,\text{int}}^0$, $\phi_{V,\text{elect}}^0$ and $\phi_{V,\text{struc}}^0$ denote the molar volume of the ion itself (a positive term), the partial molar volume due to electrostriction of the solvent (a negative term) and the structural contribution to the volume, respectively. The last term can be divided into two parts: one due to the accommodation of the ion in a cavity of the solvent (a negative term) and the other due to a local reinforcement of the solvent structure (a positive term). So Eq. (38) becomes:

$$\Delta_t\phi_{V,\text{ion}}^0 = \Delta_t\phi_{V,\text{elect}}^0 + \Delta_t\phi_{V,\text{struc}}^0 \quad (39)$$

The term $\Delta_t\phi_{V,\text{int}}^0$ diminishes because $\phi_{V,\text{int}}^0$ is the crystallographic volume of the ion and $\Delta_t\phi_{V,\text{ion}}^0$ will depend on a balance between the electrostriction and the structural contributions.

2.1.5. Apparent Molar Expansibility

The apparent molar expansibility (ϕ_E) of a solution is given by $\phi_E = (\partial\phi_V / \partial T)_P$ and therefore from Eq. (7):

$$\phi_E = \frac{\alpha V - \alpha_1 n_1 V_1^*}{n_2} \quad (40)$$

where α and α_1 are the thermal expansion coefficients of the solution and the solvent, respectively; *i.e.*, $\alpha = -\rho^{-1}(\partial\rho/\partial T)_P$ and $\alpha_1 = -\rho_1^{-1}(\partial\rho_1/\partial T)_P$. The apparent molar expansibility (ϕ_E) can be determined using the densities and their temperature coefficients as follows:

$$\phi_E = \alpha_1\phi_V + \frac{1000(\alpha - \alpha_1)}{c} \tag{41}$$

$$\phi_E = \alpha\phi_V + \frac{1000(\alpha - \alpha_1)}{m\rho_1} \tag{42}$$

2.1.6. Standard Partial Molar Expansibility

The standard partial molar expansibilities (ϕ_E^0) is represented by the following equation:[4]

$$\phi_E = \phi_E^0 + S_E\sqrt{c} \tag{43}$$

where solute concentrations are given in molalities (m), Eq. (43) becomes:

$$\phi_E = \phi_E^0 + S_E\sqrt{m} \tag{44}$$

and the value $(\partial\phi_E^0/\partial T)_P$ is obtained from the slope while ϕ_E^0 values are plotted linearly regressed against the experimental temperatures (T). Further, the temperature dependence of ϕ_V^0 for numerous solutes can be represent by :

$$\phi_V^0 = a_0 + a_1T + a_2T^2 \tag{45}$$

where a_0, a_1 and a_2 denotes the regression coefficients for the solute and T is the absolute temperature for a given solution. Eq. (45) when differentiated with respect to T at constant pressure P results into the partial molar expansibilities (ϕ_E^0) of the solute present in the mixture:

$$\phi_E^0 = (\partial\phi_V^0/\partial T)_P = a_1 + 2a_2T \tag{46}$$

The partial molar heat capacities of electrolytes found to be are negative and the fact that $(\partial C_P^0/\partial P)_T$ should be positive for the structure breaking solutes/electrolytes according to structural model[47] yields the following thermodynamic equation:

$$(\partial C_P^0/\partial P)_T = -T(\partial^2\phi_V^0/\partial T^2)_P \tag{47}$$

Therefore the structure breaking solutes have negative $(\partial^2\phi_V^0/\partial T^2)_P$ values. Similarly the structure-making solutes should have positive $(\partial^2\phi_V^0/\partial T^2)_P$ values. According to

Hepler[47] the sign of $(\partial\phi_E^0/\partial T)_P$ represents the long–range structure-making and breaking capacity of the electrolytes or solutes in various solvent systems. The general thermodynamic expression for $(\partial\phi_E^0/\partial T)_P$ is as follows:

$$(\partial\phi_E^0/\partial T)_P = (\partial^2\phi_V^0/\partial T^2)_P = 2a_2 \quad (48)$$

If the sign of $(\partial\phi_E^0/\partial T)_P$ is positive then electrolyte or solute is a structure maker and if the sign of $(\partial\phi_E^0/\partial T)_P$ is negative then it considered as structure breaker.

2.1.7. Ionic Partial Molar Expansibility

When $\phi_{V,\text{ion}}^0$ values are plotted against the experimental temperatures (T), the slope provides the partial molar expansibilities ($\phi_{E,\text{ion}}^0$) of the ions, Hence the partial molar expansibilities of the electrolytes (ϕ_E^0) again be dissociate into ionic contributions:

$$\phi_E^0 = \phi_{E,+}^0 + \phi_{E,-}^0 \quad (49)$$

where $\phi_{E,+}^0$ and $\phi_{E,-}^0$ are the partial molar expansibility of the cation and anion, respectively. Similar to $\phi_{V,\text{ion}}^0$, $\phi_{E,\text{ion}}^0$ can be turned into various contributions as per Frank and Wen model[33] for the hydration of ions:

$$\phi_{E,\text{ion}}^0 = \phi_{E,\text{int}}^0 + \phi_{E,\text{elect}}^0 + \phi_{E,\text{disord}}^0 + \phi_{E,\text{caged}}^0 \quad (50)$$

Here the intrinsic expansibility ($\phi_{E,\text{int}}^0$) is represents volume change due to expansion of the ion and it negligible for monovalent ions. This term in Eq. (50) incorporates the expansibility of covalent bonds in the ions with hydrocarbon part. The electrostriction expansibility ($\phi_{E,\text{elect}}^0$) is accompanied with the alter in volume due to electrostriction. This value is negative and proportional to z^2/r; where z = charge of the ion and r = crystal radius of the ion. The untidy expansibility ($\phi_{E,\text{disord}}^0$) is due to alter in a disarranged region and it is found to dissimilar for cations and anions of same size but dissimilar in orientation of water molecules around them in the vicinity of first electrostricted zone. This factor depends on the T and magnitude of z^2/r. Hence for the ions with a high electrostricted zone (*i.e.*, large z^2/r), the disordered zone is very small or even not exist. Even so but for ions with a little electrostricted region (*i.e.*, small z^2/r), the disordered zone has an impactful contribution. The caged expansion

($\phi^0_{E,\text{caged}}$) is due to the alter in highly structured water surround the hydrocarbon part of an ion. The value of it is positive and it's magnitude rises with the size of the hydrocarbon part of the ion.

2.1.8. Apparent specific volumes and taste quality

Taste sensor bud present in our tongue have a relationship with solute in presence of a cosolute in a solution and can be expressed from the apparent specific volumes (ϕ_{ASV}). It can be used to understand the difference between the four basic tastes: salty, sour, sweet and bitter. It shows the extent of bonding compatibility of a solute present in the water structure and can be obtained from apparent molar volumes (ϕ_V) at the experimental temperatures using the relation:

$$\phi_{Vsp} = \frac{\phi_V}{M} \qquad (51).$$

Apparent specific volume provide an knowledge about its relation with taste quality which in the order of salty < sour < sweet < bitter.[48-50] The human taste bud have range lies with apparent specific volumes (ϕ_{Vsp}) between 0.1 and 0.95 $cm^3.g^{-1}$; for salty the range is ϕ_{Vsp} < 0.33 $cm^3.g^{-1}$, for sour the range is ϕ_{Vsp} = 0.33-0.52 $cm^3.g^{-1}$, for sweet the range is ϕ_{Vsp} =0.52-0.71 $cm^3.g^{-1}$ and for bitter the range is ϕ_{Vsp} = 0.71-0.93 $cm^3.g^{-1}$).[51] When the degree of solute-solvent interaction is found to be large, the solute molecules reach easily the taste receptors present much deeper in the lingual epithelium. Thus solvation or hydration of solutes can be useful to understand the particular solute tastes phenomena characteristically bitter or salty, sour, *etc*.

2.2. Viscosity

Viscosity is another important non-thermodynamic transport property of liquid that shows the force needed to produce unit shear rate between two layers of the molecules separated by unit distance. It important tool for the measuring the solute-solvent or ion-solvent interactions. Viscosities of an electrolytic solution will give us noticeable information about the solute-solvent or ion-solvent interactions and also the structural behaviour of the electrolytic solutions.

2.2.1. Viscosity of Electrolyte Solution

The viscosity equations for electrolytic solutions are much complicated, since numerous type of interactions like ion-ion and ion-solvent interactions are found in

the solution and differentiate between these two forces is really a hard task. Since viscosity is attached with the friction between adjacent, relatively moving parallel planes of the liquid, anything which influence the interaction between these planes will shows collateral effect on the viscosity. In general large spheres when placed in the liquid, the planes will be pile up together and viscosity will rises. In the same way if the hydrogen bonding takes place in between the planes, it will rises the friction between two planes and this will impact overall rise in viscosity. An ion having large rigid co-sphere will also behave like a rigid sphere and it can rises the inter-planar friction. In the same way, ion can rises the extent of hydrogen bonding between the nearest solvent molecules and that will rises the viscosity. On the other hand, ions that try to destroy above-mentioned effect will lower down the viscosity value. Jones and Dole propound an empirical equation to relate between the relative viscosities of the electrolytes present in the solution with molar concentrations[52] (c):

$$\eta/\eta_1 = \eta_r = 1 + A\sqrt{c} + Bc \qquad (52)$$

By rearranging the equation can be written as:

$$(\eta_r - 1)/\sqrt{c} = A + B\sqrt{c} \qquad (53)$$

Here the coefficients A and B denotes the ion-ion and ion-solvent interactions. Eq. (53) is universally applicable for aqueous and non-aqueous solutions mixture with minimum ionic association. The term $A\sqrt{c}$ in Eq. (52) denote Grüneisen effect (*i.e*, the long-range coulombic forces between the ions) can be expressed as Debye-Hückel theory[53] of inter-ionic attractions. The ion-ion interaction coefficient A can be measured from interionic attraction theory[54, 55] by the Falkenhagen Vernon[55] equation:

$$A_{\text{Theo}} = \frac{0.2577\Lambda_0}{\eta_1(\varepsilon_r T)^{0.5}\lambda_+^0\lambda_-^0}[1 - 0.6863(\frac{\lambda_+^0 - \lambda_-^0}{\Lambda_0})^2] \qquad (54)$$

where Λ_0, λ_+^0 and λ_-^0 are the limiting molar conductances of the electrolyte as a whole and its cation and anion, respectively; other symbols have their usual significance. When the A-coefficients obtained by fitting η_r values to Eq. (53) for aqueous solutions[56] were compared with the values derived from Eq. (54), are found to good agreement with each other. But the accuracy was fond to be very poor with partially aqueous solutions.[57] Crudden *et al.*[58] Suggested that if association of the ions happened to produce an ion pair, the viscosity must be measured by the equation:

$$\frac{\eta_r - 1 - A\sqrt{\alpha_{IP} c}}{\alpha_{IP} c} = B_i + B_P(\frac{1-\alpha_{IP}}{\alpha_{IP}}) \quad (55)$$

where A, B_i and B_P are the constants and α_{IP} is the extent of dissociation of ion pair of the electrolyte. Thus an extrapolation of the $(\eta_r - 1 - A\sqrt{\alpha_{IP} c})/\alpha_{IP} c$ *versus* $(1-\alpha_{IP})/\alpha_{IP}$ plot to $(1-\alpha_{IP})/\alpha_{IP} = 0$ results the intercept B_i. However for the most of the electrolytic solutions both in aqueous and non-aqueous media, the Eq. (53) is valid up to 0.1 (M)[4, 59, 60] within experimental errors. However, for higher concentrations the modified Jones-Dole equation, with an additional coefficient *D* was originally used by Kaminsky, is used[61]:

$$\eta/\eta_1 = 1 + A\sqrt{c} + Bc + Dc^2 \quad (56)$$

The significance of the coefficient *D* is not always meaningful and therefore, Eq. (53) is the most popular. The A-coefficients, obtained from the $(\eta/\eta_1 - 1)/\sqrt{c}$ *versus* $\sqrt{c}$ plots for the electrolytes, are found to be somewhile negative, scattered and distracted from linearity.[4, 62, 63] In this cases the coefficients A determined by Eq. (54). In accordance with the inter-ionic attraction theory of the electrolytes the ions try to construct and regulate a space lattice structure in solution and that hindered any influence or force that tend to disturb this space lattice structure; hence the inter-ionic forces try to congeal or rises the viscosity of the solution mixture. Thus the A-coefficient expected to might have a negative value for all type of strong electrolytes and a value of zero for non-electrolytes.[52] The value of B-coefficient may have any of positive or negative value. The influence of solute size on the B-coefficient is realize from hydrodynamic theories applied to particles in a fluid persistence. While probing between the solute and solvent happened, the steric effect may lead to the B-coefficient and thus B-coefficient is very much sensitive towards the "rigidity" or "flexibility" of the solute. So the B-coefficient is measured from the solute or ion size and the behavior of the solvent. The viscosity coefficient B are calculated from the slopes of the straight lines by using the least square method and intercepts represents the magnitude of *A*. The factors that govern the viscosity coeffecient B- are as follows: [64, 65](i) salvation of ions and the exertion of the field of the ion create long-range order in solvent molecules and thereby increases η or B-values, (ii) By destroying the three dimensional bulk structure of the solvent molecules that lowers η

values,(iii) high molar volume and low dielectric constant results into high B-values for the same type of solvents and (iv) high molar volume solvents or weak solvation of any of the ion of the binary electrolyte system results into steric hindrance of the primary solvation of ions causing lowers the B-values.

Water is a structured solvent and like it others solvent having a solute with or without a primary solvation shell can impart recognizable influence on the extent of 'structure' of the solvent molecules at relatively longer distances. A 'structure-making' solute can minimize the mean effective temperature of the solvent molecules. So it increases the viscosity of the solution mixture and which results into a high B-coefficient values. Due to the exponential relationship between temperature and viscosity, a increase in temperature of the solution may results into fall of B-coefficients. This fall is found to be more at lower temparature than at high temperatures.[59] This behavior can be utilise to detect the 'structure-making' solutes.[66] However, 'structure-breaking' solutes possesses low B-coefficients that may rises with increase in temperatures.[54] If it is obtained that solvation minimizes with rising in temperature, the B-coefficient of a solvated species also minimize and hence both structure making and primary salvation should have more B-coefficient at low temperature and the derivative with respect to temperature i.e $\partial B/\partial T$ give negative values.

2.2.2. Ionic Viscosity *B* -Coefficients

The viscosity B-coefficients of ionic compound is somewhat different from the nonionic compound, so it can measured based on some additional thermodynamic theory. The methods that can use for differentiating the viscosity B- coefficients in the ionic contributions:

(1) Cox and Wolfenden consider that B_{ion} values of Li^+ and IO_3^- in $LiIO_3$ are proportional to their respective ionic volumes[67], that are again proportional to the third power of the individual ionic motilities. Gurney[41] and Kaminsky[61] are propsed that:

$$B_{K^+} = B_{Cl^-} \text{ (in water)} \qquad (57)$$

This can explained on the regards that the B-coefficients for KCl is lower and that the mobilities of K^+ and Cl^- are same type though out the temperature range 15-45 ºC. This theory is supported by other thermodynamic parameters.

(2) The Desnoyers and Perron method[68] another type of method that consider the Et_4N^+ ion in water is nearest to be neither structure breaker nor a structure maker. They proposed that the application of the Einstein's equation[69] with a higher extent of accuracy:

$$B = 0.0025\phi^0_{V,\text{ion}} \tag{58}$$

and with an precise value of the partial molar volume ($\phi^0_{V,\text{ion}}$) of the ion, it is very much easier to measure a value of 0.359 for $B_{Et_4N^+}$ in water at 25 ºC. Sacco *et al.*[70] put forward that the "reference electrolytic" method for the differentiation of the B-values, *e.g.*, for tetraphenyl phosphonium tetraphenyl borate (Ph_4PBPh_4) in water:

$$B_{Ph_4B^-} = B_{Ph_4P^+} = B_{Ph_4PBPh_4}/2 \tag{59}$$

Since As Ph_4PBPh_4 is sparingly soluble in water, $B_{Ph_4PBPh_4}$ represents as:

$$B_{Ph_4PBPh_4} = B_{NaBPh_4} + B_{Ph_4PBr} - B_{NaBr} \tag{60}$$

The benchmark to adopt for the differentiating of the viscosity B-coefficients in non-aqueous solvents separated from those used for aqueous solutions, Although these methods[63, 64, 71, 72] are based on the similarity of the equivalent conductance of the counter ions at zero dilution.

According to Krumgalz[73, 74] the method useful for the separation of the B-coefficients into ionic components is based on the fact that the large. Hence the ionic viscosity B-values for large tetraalkylammonium ions, R_4N^+ (where R > Bu) in organic solvents, are proportional to their ionic dimensions, *i. e.*,

$$B_{R_4NX} = a + br^3_{R_4N^+} \tag{61}$$

where $a = B_{X^-}$ and b is a constant dependent on temperature and solvent nature. The extrapolation of the plot of B_{R_4NX} (R > Pr or Bu) *versus* $r^3_{R_4N^+}$ to zero cation dimension results directly B_{X^-} in the precise solvent and thus B-ion values can be had. The B-ion values measured from the relations:

$$B_{R_4N^+} - B_{R'_4N^+} = B_{R_4NX} - B_{R'_4NX} \tag{62}$$

$$B_{R_4N^+}/B_{R'_4N^+} = r^3_{R_4N^+}/r^3_{R'_4N^+} \tag{63}$$

using the radii of the tetraalkylammonium ions ($r^3_{R_4N^+}$ and $r^3_{R_4^{'}N^+}$) obtained from the conductance measuremnt.[77]

Gill and Sharma[78] used Bu_4NBPh_4 as a reference electrolyte. The method of resolution is based on the consideration that Bu_4N^+ and Ph_4B^- ions with big size R-groups are not solvated in non-aqueous solvents and their dimensions in such solvents are remain fixed. The ionic radii of Bu_4N^+ (5.00Å) and Ph_4B (5.35 Å) were remain fixed in different non-aqueous and mixed non-aqueous solvents used by Gill and co-workers. They given the following equations:

$$B_{Ph_4B^-} \big/ B_{Bu_4N^+} = r^3_{Ph_4B^-} \big/ r^3_{Bu_4N^+} = (5.35/5.00)^3 \qquad (64)$$

$$\text{and,} \qquad B_{Bu_4NBPh_4} = B_{Bu_4N^+} + B_{Ph_4B^-} \qquad (65)$$

The method need only the B-values of Bu_4NBPh_4 and is applicable in the same way to non-aqueous solvents. The B-ion values measured from this method quite agree with those shown by Lawrence *et al.*[70] in various organic solvents using the consideration as given below:

$$B_{[(i-Am)_3\,BuN^+]} = B_{Ph_4B^-} = 1/2 B_{[(i-Am)_3\,BuNPh_4B]} \qquad (66)$$

Lawrence *et al.*[70] utilise tetrabutylammonium tetrabutylborate (Bu_4NBBu_4) as 'reference electrolyte' since the cation and anion are similar in shape and have nearly same van der Waals volumes. Thus,

$$B_{Bu_4N^+} \big/ B_{Bu_4B^-} = V_{W(Bu_4N^+)} \big/ V_{W(Bu_4B^-)} \qquad (67)$$

$$\text{or,} \; B_{Bu_4N^+} = B_{Bu_4NBBu_4} / [1 + V_{W(Bu_4B^-)} \big/ V_{W(Bu_4N^+)}] \qquad (68)$$

A same type differentiation can be created for Ph_4PBPh_4 system and Lawrence *et al.*[70] done the viscosity measurements of tetraalkylammonium bromides (from Pr to Hept.) in DMSO and HMPT. The B-coefficients, $B_{R_4NBr} = B_{Br^-} + a[f(r_{R_4N^+})]$, were plotted against van der Waals volumes. The B_{Br^-} values thus calculated and were compared with the precisely measured B_{Br^-} value by using Bu_4NBBu_4 and Ph_4PBPh_4 as 'reference electrolyte'. They stated that the 'reference electrolyte' method is one of the best obtainable method for division into ionic contributions. However, all these methods are based on certain approximations and anomalous results may arise except the proper mathematical theory is developed to calculate B-values.

2.2.3. Viscosity *B* – Coefficients and it relations with temperature

A fixed nature of $B_{\pm}$ and $\partial B_{\pm}/\partial T$ has been found in both aqueous and non-aqueous solvents. This is depicted by Kaminsky.[79] He found that (i) In periodic table within a group the B-ion values decrease with the increase in the radius of the ion, and (ii) the temperature co-efficient of B_{ion} values while rises with the increase the ionic radius along down the group. In summary of result, it shows:

For structure breaking ions-

$$\text{(i) } A \text{ and } \partial A/\partial T > 0 \tag{69}$$

$$\text{(ii) } B_{\text{ion}} < 0 \text{ and } \partial B_{\text{ion}}/\partial T > 0 \tag{70}$$

For structure making ions-

$$\text{(iii) } B_{\text{ion}} > 0 \text{ and } \partial B_{\text{ion}}/\partial T < 0 \tag{71}$$

When water molecules around an ion forming a solvent shell, the behavior of the solvent in the solvation layer may be deviate from those found in the bulk structure. Gurney,[41]in his 'Co-sphere' model of A, B, C zones of Frank and Wen[32] and hydrated radius of Nightingle clearly explain this property.[80]The viscosity of a dilute electrolyte solution measured from the summative value of viscosity of the solvent (η_1) with the the viscosity alteration obtaining from the contesting between numerous effects happening in the ionic background. So the Jones-Dole equation becomes redefined as,

$$\eta = \eta_1 + \eta^* + \eta^E + \eta^A + \eta^D = \eta_1 + \eta(A\sqrt{c} + Bc) \tag{72}$$

Where η^*, the positive rise in viscosity is results from a columbic interaction. The viscosity B-coefficient then can be elucidate in terms of the competitive viscosity effects. According to the following Stokes, Mills and Krumgalz[73] the B_{ion} is represented by:

$$B_{\text{ion}} = B_{\text{ion}}^{\text{Einst}} + B_{\text{ion}}^{\text{Orient}} + B_{\text{ion}}^{\text{Str}} + B_{\text{ion}}^{\text{Reinf}} \tag{73}$$

whereas Lawrence and Sacco suugested the following:[70]

$$B_{\text{ion}} = B_{\text{w}} + B_{\text{solv}} + B_{\text{shape}} + B_{\text{ord}} + B_{\text{disord}} \tag{74}$$

$B_{\text{ion}}^{\text{Einst}}$ is the positive enhancement arising due to the hindrance in the viscous flow of the solvent which cauased by the shape and size of the ions (the term corresponds to η^E or B_{shape}). $B_{\text{ion}}^{\text{Orient}}$ is the positive enhancement evolving from the alignment or the structure making action of the electrostatic region of the ion on the dipoles of the solvent molecules (the term corresponds to η^A or B_{ord}). $B_{\text{ion}}^{\text{Str}}$ is the negative

enhancement which shows the disrupter of the solvent structure in the vicinity of the ionic co-sphere evolving from the opposing inclination of the ion to orientate the molecules around itself centro symetrically and solvent to retain its self structure (this are correlate with η^D or B_{disord}). B_{disord} is showing positive enhancement govern by the effect of 'reinforcement of the water structure' by large tetraalkylammonium ions (R_4N^+) which due to hydrophobic hydration. The event is built-in the intrinsic water structure but it is not found in organic solvents. B_{w} and B_{solv} represents for viscosity rising and contributing towards the van der Waals volume and the solvated ion`s volume. Hence, a tiny and highly charged cations such as Li^+ and Mg^{2+} produce a strongly adjoin primary solvation shell surrounding these ions ($B_{\text{ion}}^{\text{Einst}}$ or η^E positive). At the normal temperature, the arrangement of the solvent molecules surrounding the inner layer also results into increase in $B_{\text{ion}}^{\text{Orient}}(\eta^A)$, $B_{\text{ion}}^{\text{Str}}(\eta^D)$ is found to be lower for these ions. Hence, B_{ion} will found to be higher and positive as $B_{\text{ion}}^{\text{Einst}} + B_{\text{ion}}^{\text{Orient}} > B_{\text{ion}}^{\text{Str}}$. But for the, $B_{\text{ion}}^{\text{Einst}}$ and $B_{\text{ion}}^{\text{Orient}}$ will be lower for the ions of highest ionic radii (present in a group) such as Cs^+ or I^- cause of lower surface charge densities yielding in poor orienting and structure forming effect. It is expected that $B_{\text{ion}}^{\text{Str}}$ will have a higher value due to structural disarray in the next neighbor zone of the ion due to competition between the ionic field and the bulk structure. So $B_{\text{ion}}^{\text{Einst}} + B_{\text{ion}}^{\text{Orient}} < B_{\text{ion}}^{\text{Str}}$ and B_{ion} is found to be negative. The Ions with the moderate size (*like* K^+ and Cl^-) have maintain a close balance of viscous forces in their vicinity, *i.e.*, $B_{\text{ion}}^{\text{Einst}} + B_{\text{ion}}^{\text{Orient}} = B_{\text{ion}}^{\text{Str}}$, hence value of B_{ion} is approaches to zero. Large molecular ions like tetra alkyl ammonium ions (R_4N^+) have a large $B_{\text{ion}}^{\text{Einst}}$ because of big size but $B_{\text{ion}}^{\text{Orient}}$ and $B_{\text{ion}}^{\text{Str}}$ found to be lower, *i.e.*, $B_{\text{ion}}^{\text{Einst}} + B_{\text{ion}}^{\text{Orient}} >> B_{\text{ion}}^{\text{Str}}$ and B_{ion} must be positive and higher in values. The value will be further strenghtened in water evolving from $B_{\text{ion}}^{\text{Reinf}}$ because of hydrophobic hydrations. Rising in temperature do not impact on $B_{\text{ion}}^{\text{Einst}}$. But the solvent molecules that present in the second layer have somewhat restricted its orientation due to rise in the thermal motion that results into lower the $B_{\text{ion}}^{\text{Str}}$. $B_{\text{ion}}^{\text{Orient}}$ will lowered slowly with the rise in the temperature. Since there will be a fewer confliction between reduced solvent structure and the ionic field. The relative

magnitudes of B_{ion}^{Orient} and B_{ion}^{Str} will impart a net effect on positive or negative temperature co-efficient. In addition to this the change in viscosity of ions due to temperature (or entropy of solvation or mobility of ions) would be more effective in case of smaller ions than the larger ions of electrolyte. So there exist a relation among the viscosity, entropy of solvation and mobility of ions (a factor of temperature). Hence the ionic B-coefficient and the entropy of solvation of ions can be utilize as exploring of ion-solvent interactions and can provide valuable information about the structure making and structure breaking character of ions.

2.2.4. Viscosity of Non-Electrolyte Solutions

Falkenhagen suggested that,[54, 55] for a neutral solutes are havin the *A*-coefficients is zero and solution viscosities (η) of non-electrolytes examined with the rectified Jones-Dole equation:[41, 59]

$$\eta_r = 1 + Bc \qquad (75)$$

where $\eta_r = \eta/\eta_1$; η_1, η and c represent solvent viscosity, solution viscosity and molar concentration of the solute in the solution, respectively. The experimental results of viscosities can be fitted to the following linear relation with equal weights to all the viscosities:[81]

$$\eta = C' + B'c \qquad (76)$$

where B' and C' are fixed; C' values are fairly agree with the perceived η_1 values within the experimental error and B' is related to the *B*- coefficients as follows:[81]

$$B = B'/C' \qquad (77)$$

2.2.5. Viscosity *B*-Coefficient of Transfer

As like $\Delta_t\phi_V^0$, viscosity *B*-coefficient of transfer ($\Delta_t B$) is independent from solute-solute or ion-ion interactions and gives us valuable information about solute-cosolute interactions taking place in soltion. $\Delta_t B$ values measured from the following equation:

$$\Delta_t B = B(\text{solute} + \text{cosolute} + \text{solvent}) - B(\text{solute} + \text{solvent}) \qquad (78)$$

Gurney's 'Co-sphere' model.[41] explore different types of interaction by the obtained value from the above equation. Normally negative $\Delta_t B$ values supposed that the

solute must be in less structured environment in the solution than that in the solvent whereas positive $\Delta_t B$ values suggest that the solute must be present in the more structured environment in the solution than in the solvent. Such results disclosed the governance of 'solvent structure modification' with the help of solute and cosolute molecules.

2.2.6. Viscous flow causing the change in the shape and size

The ions in solution are supposed to be rigid spheres that are suspended in continuum. The hydrodynamic treatment represented by Einstein leads to the equation:[69]

$$\eta/\eta_1 = 1 + 2.5\phi \qquad (79)$$

where ϕ is the fraction of volume that captured by the particles. New alternate of the above relation have been proposed by: (i) Simha[82] based on the departures from spherical shape and (ii) on the basis of dependence of the flow patterns surrounding the closest particles at a larger concentrations.[83]But considering the various aspects of the problem, spherical shapes have been considered for electrolytes to be hydrated ions of higher effective size. Thus from Eq. (79):

$$2.5\phi = A\sqrt{c} + Bc \qquad (80)$$

Since $A\sqrt{c}$ term can be nullified compared with Bc and $\phi = c\phi^0_{v,\text{ion}}$, where $\phi^0_{v,\text{ion}}$ is known as partial molar volume of the ion, so the above equation turn into:

$$2.5\,\phi^0_{v,\text{ion}} = B \qquad (81)$$

The ionic $B_{\pm}$-coefficient varied linearly of partial molar volume of the ion, $\phi^0_{v,\text{ion}}$ with slope to 2.5 in an ideal cases.

Thus, $B_{\pm}$ represented by :

$$B_{\pm} = 2.5\phi^0_{v,\text{ion}} = 2.5 \times 4/3(\pi R^3_{\pm} N_A/1000) \qquad (82)$$

In such cases, the ions are supposed to as rigid spheres with an effective radii ($R_{\pm}$) which proceed in a continuum and 2.5 is the shape factor for a sphere. $R_{\pm}$, calculated by using Eq. (82), should be nearest to crystallographic radii or corrected Stoke's radii[84] if the ions are barely solvated and act as spherical entities. However, normally, $R_{\pm}$ values are found to be higher than those of the crystallographic radii of the ions

supporting the appreciable solvation of the ions. The number n_s of the solvent molecules held to the ion in the primary solvation shell can be had from the relation:[69]

$$B_{\pm} = 2.5/1000(V_i + n_s V_S) \qquad (83)$$

Where V_i is the molar volume of the stripped ion and V_S, the molar volume of the solvent.

2.2.7. Viscosity and its thermodynamic character:

Viscosity supposed to by means of the theory of absolute reaction rates.[85] As a gas is supposed to made up of molecules mobile about in vacant space, aslike that liquid may also be considered as made up of "holes" moving about the matter. So the "holes" act similar role in a liquid as molecules do in the gas phase. The energy needed to produce a hole of molecular dimension in a liquid system is same as that of the energy of vaporization per molecule of the liquid.[85] If the two layers of molecules present in a liquid are detached by a distance λ_1 and one layer slips over the other under the influence of a force f per square centimeter and Δu denotes the difference in the velocity of the two layers, then the coefficient of viscosity (η) is represent by the relation: $\eta = f\lambda_1 / \Delta u$. A molecule from one equilibrium position to another position through a passage, in the same layer needs a appropriate hole to be available and energy is utilize to produce that type of a hole in the liquid. The overall process is represent in following Figure 2.3 below.

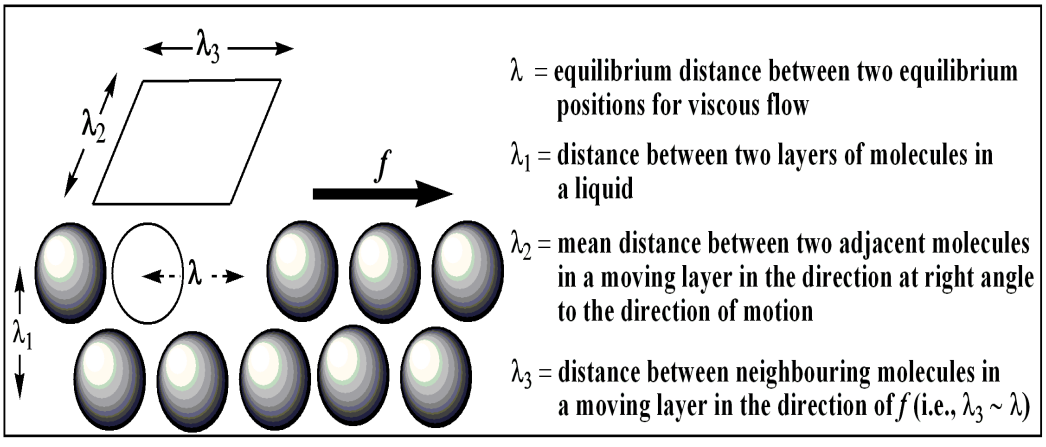

Fig 2.3. A molecule travel from one equilibrium position to another in the similar layer of a liquid with the availability of a appropriate hole.

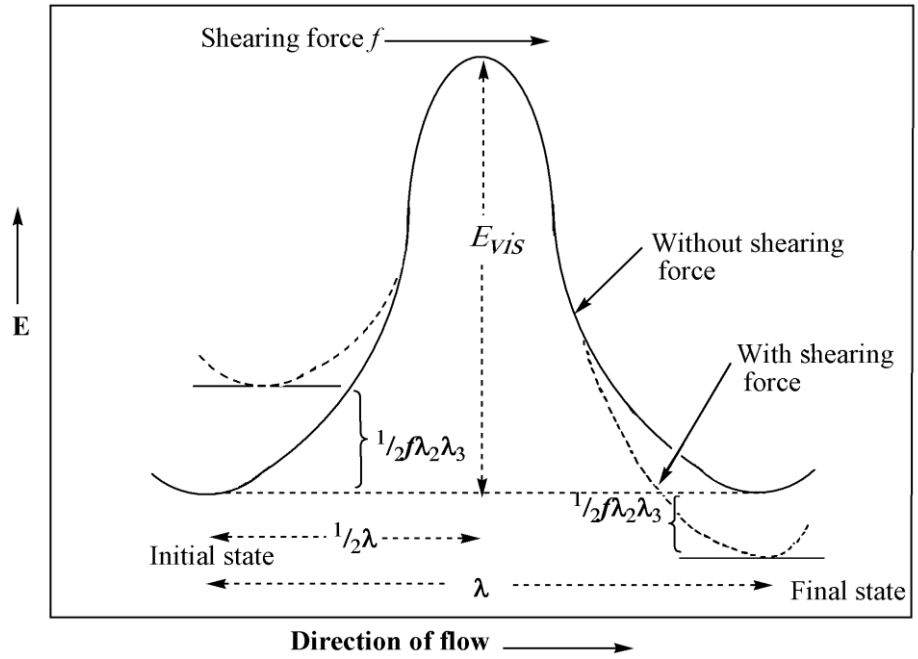

Fig 2.4. Potential energy barrier of viscous flow.

This phenomena can be expressed with the help of the symmetrical potential energy barrier represented in the Figure 2.4. consider that the potential energy barrier is found to be symmetrical, and the distance between the initial equilibrium position and the activated state is given by $\lambda/2$.The applied force on a molecule in the way of motion is thus given as $f\lambda_2\lambda_3$, Since $\lambda_2\lambda_3$ is representing effective area per molecule. So the energy possessed by the molecule in motion that has reached to the top of the potential energy barrier is $f\lambda_2\lambda_3\lambda/2$. Such energy is minimize the height of the energy barrier in the forward direction by the amount of $f\lambda_2\lambda_3\lambda/2$ and rises the height of the energy barrier in the backward direction by the same amount. With some consideration and statistical thermodynamic operation, described in the literature,[85] the viscosity (η) of a solution can be shown by the Eyring's relation:[85]

$$\eta = Ae^{E_{vis}/RT} = (hN/V)e^{\Delta G^*/RT} = (hN/V)e^{(\Delta H^*/RT - \Delta S^*/R)} \qquad (84)$$

Here, E_{vis} = experimental energy of activation calculated from a plot of $\ln\eta$ against $1/T$; $\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are the free energy, enthalpy and entropy for the activation of viscous flow, respectively. The net activation energy for viscous flow may be considered as consisting of two parts: (i) the energy needed to create the hole, (ii) that needed to the molecule to go towards the hole and maximum of the energy is needed

for the creation of the holes rather than that needed to move the molecules into the holes. According to Eq. (84), the free energy of activation for viscous flow per mole of the solvent/solvent mixture ($\Delta\mu_1^{0\neq}$) as:

$$\Delta\mu_1^{0\neq} = \Delta G_1^{0\neq} = RT\ln(\eta_1\phi_{V,1}^0/hN_A) \tag{85}$$

Where N_A , $\phi_{V,1}^0$ are the Avogadro's number and the molar volume of the solvent, respectively. The other symbols have their usual significances. For a binary system utilize as solvents, $\phi_{V,1}^0$ is considered as the mole fraction average of molecular weights of components normalized by densities at the study temperature. Another form of the above equation is like that[57, 86]

$$\ln(\eta_1\phi_{V,1}^0/hN_A) \quad = -\frac{\Delta S_1^{0\neq}}{R} + \left(\frac{\Delta H_1^{0\neq}}{R}\right)\frac{1}{T} \tag{86}$$

Therefore linear regression of the ($\ln(\eta_1\phi_{V,1}^0/hN_A)$ data Vs $1/T$ provides the $\Delta H_1^{0\neq}$ and $\Delta S_1^{0\neq}$ values. A relation between the viscosity *B*- coefficients and the separation between the contribution per mole of a solute towards the free energy of activation for viscous flow of the solution ($\Delta\mu_2^{0\neq}$) and the free energy of activation of viscous flow per mole of the pure solvent or solvent mixture ($\Delta\mu_1^{0\neq}$) was given by Feakins *et al.*[86]:

$$B = (\nu\phi_{V,1}^0 - \phi_{V,2}^0) + \phi_{V,1}^0\left(\frac{\Delta\mu_2^{0\neq} - \nu\Delta\mu_1^{0\neq}}{RT}\right) \tag{87}$$

Where the coefficient ν is 1 for non-electrolytes, 2 for 1:1 electrolytes and so on. Thus $(\Delta\mu_2^{0\neq} - \Delta\mu_1^{0\neq})$ values can be obtained from Eq. (87) using the *B*- coefficients. $(\Delta\mu_2^{0\neq} - \Delta\mu_1^{0\neq})$ values can also be expressed as:

$$\frac{\Delta\mu_2^{0\neq} - \Delta\mu_1^{0\neq}}{RT} = -\frac{\Delta S_2^{0\neq} - \Delta S_1^{0\neq}}{R} + \left\{\frac{\Delta H_2^{0\neq} - \Delta H_1^{0\neq}}{R}\right\}\frac{1}{T} \tag{88}$$

where $\Delta S_i^{0\neq}$ and $\Delta H_i^{0\neq}$ are the standard partial molar entropy and enthalpy of activation for viscous flow per mole of i^{th} component in the solution. Therefore a linear regression of Eq. (88) provides the values of $(\Delta S_2^{0\neq} - \Delta S_1^{0\neq})$ and $(\Delta H_2^{0\neq} - \Delta H_1^{0\neq})$ from the slopes and intercepts. According to Eq. (87), $\Delta\mu_2^{0\neq}$ is depends on the viscosity *B*-coefficients and $(\phi_{V,2}^0 - \phi_{V,1}^0)$ terms. In various cases $\Delta\mu_1^{0\neq}$

are almost unchanging of the solvent compositions and temperatures, shows that $\Delta\mu_2^{0\neq}$ is dependent on the viscosity *B*-coefficients and $(\phi_{V,2}^0 - \phi_{V,1}^0)$ terms. The $\Delta\mu_2^{0\neq}$ values show the free energy of activation of solute molecules and the contribution from the motion of the solute molecules. If $\Delta\mu_2^{0\neq}$ values are found to be positive and higher than $\Delta\mu_1^{0\neq}$ values at the study temperatures, the solute (ion)-solvent interactions is found to be higher in the ground state than in the transition state. In the transition state the solvation of the solute (ions) becomes poorly favored energetically. However, a popular method uses the following relations,

$$d(\Delta\mu_2^{0\neq})/dT = -\Delta S_2^{0\neq} \qquad (89)$$

$$\Delta H_2^{0\neq} = \Delta\mu_2^{0\neq} + T\Delta S_2^{0\neq} \qquad (90)$$

in order to calculate of the entropy and enthalpy of activation of viscous flow for the respective solute.

2.2.8. Solvation Number

The term 'primary solvate ion'[87] for a electrolyte denotes the compacted fitting of solvent molecules towards the ion so that the ions and the solvent molecules move as a single entity in the vicinity of electrolyte transport process, mean the solvent molecules loose their individual translation degree of freedom. While the term 'secondary solvation' designate all of the other solvent molecules. It's solvation number of a considered ion, depends on this union of solvent molecules. The first solvation shell composed of the set of next nearest solvent molecules surround the ion. Primary solvation layer created by the interaction of solvent strongly or coordinately with the ion. The second solvation shell is represents the set of next nearest solvent molecules of the ion. Solvent molecules present in the primary and secondary solvation sheath of the ion are arranged in such a way by its field that it is separate from the normal orientation of the solvent molecules present in the bulk solvent. There will be a zone present around the ion by the solvent molecules with neither the central orientation nor the bulk orientation. This untidy region is familiar as the "thawed zone".[88] The volume of the solvation layer(V_S) can be calculated from the relation:

$$V_S = (4\pi/3)(r_S^3 - r_C^3) \qquad (91)$$

where r_C = crystal radius of the ion; (S_n) = the solvation number then be hydration no. calculated as:

$$S_n = V_S / V_0 \tag{92}$$

Considering Stokes' relation to hold, the ionic solvated volume should be calculated, due to packing effects[87] from:

$$V_S^0 = 4.35 r_S^3 \tag{93}$$

where V_S^0 is expressed in mol.L^{-1} and r_S in angstroms. In another way, solvation numbers (S_n) can easily derived from the following relation:[89]

$$S_n = B / \phi_V^0 \tag{94}$$

S_n is signifies that the formation of a primary solvation sphere surrounding a solute molecule and the range 0-2.5 for S_n which shows that the unsolvated solutes present in the solution.[89] If the magnitudes of ionic viscosity *B*-coefficients ($B_\pm$) are known, then the ionic solvation numbers ($S_{n,\pm}$) can be derived from Eq. (94) by utilizing ionic partial molar volumes ($\phi_{V,\pm}^0$) of the ions.

2.3. Ultrasonic Speed measurement for acoustic property

The acoustic property- 'ultrasonic speed' is a very much important factor to reveal the molecular interactions and can give valuable information about these event, Mostly when partial molar volumes alone fail to gives an unambiguous explanation of the interactions. Ultrasonic speed ismeasured of the interactions between the components of liquid mixtures and alter with the structures and binding forces in the solutions.

2.3.1. Apparent Molal Adiabatic Compressibility

The apparent molal adiabatic compressibility calculated for the electrolytes are more familiar techniques used for a long time to investigate the interaction between the solute, solvent other compounds in aqueous solutions[90]. But the experiment done in non-aqueous[7] solvents are still limited. It is propose by many pioneers that the apparent molal adiabatic compressibility is a valuable parameter to reveal the interactions taking place between solute-solvent and solute-solute. The easiest procedure to measure the compressibility of a solvent or solution is from the

ultrasonic speed of sound in it. The isentropic compressibility (β_S) of a solvent or solution measured from the following relation:[91]

$$\beta_S = 1/(u^2\rho) \qquad (95)$$

Where ρ = solution density and u = ultrasonic speed in the solvent or solution. The isentropic compressibility (β_S) calculated by Eq. (95) is adiabatic in nature,[25] not an isothermal one, since when the ultrasound passes through the solvent or solution neighborhood compressions occurred were too much rapid to allow an get away of the heat formed. The apparent molal isentropic compressibility (ϕ_K) of the solutions was measure from the following relation:

$$\phi_K = M\beta_S/\rho_1 + 1000(\beta_S\rho_1 - \beta_{S,1}\rho)/m\rho\rho_1 \qquad (96)$$

$\beta_{S,1}$ = isentropic compressibility of the solvent mixture, M = molar mass of the solute, m = molality of the solution. The limiting apparent molal isentropic compressibility (ϕ_K^0) can be obtained by extrapolating the plots of ϕ_K *Vs* the square root of molal concentration of the solute ($\sqrt{m}$) to zero concentration with the help of least-squares method:[92, 93]

$$\phi_K = \phi_K^0 + S_K^*\sqrt{m} \qquad (97)$$

Where, S_K^* = experimental slope showing solute-solute or solute-cosolute interaction. The apparent molal isentropic compressibility (ϕ_K^0) at infinite depicted about the solute-solvent and solute-solute interactions, respectively. It is already proven that due to the electrostriction of the solute, the compressibility will tends to decrease in the solution.[94] Negative values of ϕ_K^0 of electrolytic solutions is reflected by the hydrophobic solutes due to the ordering bring about by them in the water structure. [94] The compressibility of structure having hydrogen-bonding within it, however, variation depending on the behavior of the hydrogen bonding get engaged.[94] However, the weak fit of the solute molecules[95, 96] and the probabilities of flexible hydrogen bond creation found to be answerable for a more compressible neighborhood and so positive ϕ_K^0 values are often for aqueous non-electrolyte[97] and non-aqueous non-electrolyte[98] solutions.

2.4. Refractive Index

Theoretical background

Refractive index (n_D) is another important parameter which obtained from optical property of the solution and it varies with the change of molecular arrangement of solutions, pure liquids and mixtures. Refractive index (n_D) of the substance supposed to the ratio between the speed of light in vacuum to another substance, *i.e.*,

$$n_D = \frac{speed\ of\ light\ in\ vaccum}{speed\ of\ the\ light\ in\ substance} \tag{98}$$

Lorentz and Lorenz[99] suggested a theoretical relation between refractive index (n_D) and density (ρ) of a respective solution as follows:

$$R_S = \frac{n_D^2 - 1}{n_D^2 + 2} \cdot \frac{1}{\rho} \tag{99}$$

where R_S is the specific refraction. The molar refraction or refractivity (R_M) can be calculated from the relation:

$$R_M = \frac{n_D^2 - 1}{n_D^2 + 2} \cdot \frac{M}{\rho} \tag{100}$$

M denote the molar mass of the solute. Molar refractivity (R_M) for a solution mixture can calculated from the following equation:

$$R_M = \frac{n_D^2 - 1}{n_D^2 + 2} \cdot \sum_{i=1}^{n} \frac{x_i M_i}{\rho} \tag{101}$$

where M_i = molecular weight and x_i = mole fraction for the i^{th} component of the solution mixture. Molar refraction is found to be independent on the phase and behave as a fundamental property of a compound.[100] The atomic refractions as well as refraction of the bonds results in the molar refraction for most organic compounds. However, some exception is found in case of many inorganic or organometallic solid materials or substances such as metal complexes. Marcus *et al.*[101] give following equation for the apparent molar refractivity (R_D) for a solute:

$$R_D = \frac{1000}{c}\left[\frac{n_D^2 - 1}{n_D^2 + 2} - \frac{1}{\rho_1}\left(\rho - \frac{cM}{1000}\right)\frac{n_{D,1}^2 - 1}{n_{D,1}^2 + 2}\right] \tag{102}$$

Where n_D and $n_{D,1}$ representing the refractive indices of the solution and solvent or solvent mixture, and other symbols have their own usual meanings. The molecular polarizability (α_M)[102] denotes the ability of deformation of the molecular orbital's under the influence of electrical field. In addition to this, it is observed that if the structure of a molecule is more complex, then its electron cloud is supposed to be decentralized at a greater extent. So the molecular polarizability rises cause molecular polarizability (α_M) is directly proportional to the R_D, So the trend of rising in R_D magnitude indicate net increase in molecular polarizabilities. [103] This is shown by the following relation:[101]

$$\alpha_M = \frac{3R_D}{4\pi N_A} \qquad (103)$$

2.5. Study of UV-Visible Spectra for solvent effect in solution:

The absorptions spectra of organic solutes are often shifted due to the solvation, mainly in solvents of variable polarity. As a result of these the solvents can alter the intensities, positions and shapes of the absorption bands.[102-105] The reason behind of shifts of the absorption band are due to specific solute-solvent and solute-solute interactions through ion-dipole, hydrogen bonding, dipole-dipole, dipole-induced dipole interactions, *etc*. Many other things like acid-base chemistry and charge-transfer interactions do also play a role in spectral shifts in solutions. All these forces causing the change in the energy between the excited and the ground state of the absorbing species through as a physical agitation of appropriate molecular states of the chromophores.[106-108] Therefore, the effect of solvent on the absorption spectra can give important information about any respective solute-solvent interactions[102-105] and it helpful to reveal the primary solvation structure of the solvated ion.[109] The net effects of solvents on the absorption band depend mainly on the chromospheres and the type of the transitions: where $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ are charge-transfer transitions. The extent and behavior of shifting in the band in different solvents of varying polarity depend on the strength of intermolecular hydrogen bonding between the certain groups (contain N, For O atom) of the solute and those of the solvent molecules. If intermolecular hydrogen bonding does not takes place between the solute and the solvent then the spectral shifts depend only on the solvent polarity. In such cases, if

the solvent polarity rises due to hydrogen bonding takes place between the solute and solvent molecules, the $\pi \rightarrow \pi^*$ bathochromic or hypsochromic shift in the band are found. On the other hand, for solutes having intramolecular hydrogen bonding, the spectral shifts are very negligible. The spectral shifts can be well expressed by solvent polarities when the solute-solvent systems are lacking of intermolecular hydrogen bonds. It is familiar that π-electrons containing molecules shows effctive solvatochromism. These electrons are mainly accountable for the change in charge distribution, accordingly in the dipole moment between the electronic excited and ground state of the solute. The Negative solvatochromism is obtained during blue or hypsochromic shift with rising in polarity of solvent and the positive solvatochromism is depicted as the bathochromic (or red) shift. The higher negative solvatochromism is obtained for various solvation of the zwitterionic electronic ground state, highly dipolar, and the relatively lower dipolar first excited state.[110] If it found that the excited state more polar than ground state, mainly a bathochromic shift with increased polarity of solvents for a long-wave length absorption band is found and if the ground state is more polar than the excited state, rising solvent polarity results into the hypsochromic shift. Inverted solvatochromism shown by Polyene dye,[111] Since there is a shifts obtained from positive to negative solvatochromism when solvent polarity become rises. Solvatochromism is also helpful to know the solute-solvent interactions in respect of the polarizability or dipolarity parameter (π^*), hydrogen bond acceptor (β) and hydrogen bond donor (α) abilities of the solvents.

2.6. Theoretical Approach

2.6.1. Molecular Theory for Partial Molar Volume

In Statistical mechanics of liquids proposed two theoretical model for the measurement of the partial molar volumes of the solute. First one model is the scaled particle theory (SPT) and second one is the Kirkwood-Buff (KB) solution theory.[112-113] In the first approach solute-solvent interactions in solution can be expressed as interms of interaction volume ($\bar{\phi}_{\text{int}}$) as follows:

$$\phi_V^0 = \bar{\phi}_{\text{cav}} + \bar{\phi}_{\text{int}} + \kappa_1^0 RT \qquad (104)$$

$\bar{\phi}_{\text{cav}}$ = contributed volume to the partial molar volume of the solute that associated with a cavity produce in the water, κ_1^0 is the isothermal compressibility of water and

other symbols retain their usual significances. $\bar{\phi}_{cav}$ derived from the following relation:[114]

$$\bar{\phi}_{cav} = \kappa_1^0 RT\{y/(1-y) + 3yz(1+z)/(1-y)^2 + 9y^2z^2/(1-y)^3\} + \pi\sigma_2^3 N_A/6 \quad (105)$$

Here $z = \sigma_2/\sigma_1$, σ_1 and σ_2 are hard sphere diameters of water and the solute. The parameter y is equal to the ratio of volume occupied by one mole of hard sphere solvent molecules to its molar volume $\phi_{V,1}^0$. So an imprecise free energy for cavity creation in a fluid can be measured with the help of SPT theory. In spite of broad application of the SPT theory, there is found two major limitations when applied to chemical and biochemical field. First one is it is only applicable for the spherical solute that can be understood by the original SPT and second one is the theory does not incorporate the electrostatic effects on partial molar volumes. Nagayama, Irisa and Hirata[115] expanded this theory for solutes of random shape. They successfully achieved to measure the partial molar volumes of molecular solutes with the help of extended SPT[116] and resolved the previous problem. However, the second limitation was not solved even with the merger of the dielectric continuum models.[117, 118] The other perspective is based on the Kirkwood-Buff (KB) solution theory.[119] This theory, suggest that the partial molar volumes of solutes can be measured from the relation below:

$$\phi_V^0 = k_B T\kappa_T - \int_0^\infty [g(r) - 1]4\pi r^2 \partial r \quad (106)$$

κ_T = isothermal compressibility of the solution, k_B = Boltzman constant and $g(r)$ = radial distribution function (RDF) between the solvent and solute. The radial distribution function (RDF) obtained from molecular simulation. Various attempts were done to adjoin molecular simulation with the KB theory but it still restricted to the small molecules.[120-122] There are many other molecular liquid theories like Reference Hypernetted Chain (RHNC)[123] and Reference Interaction Site Model (RISM)[124] were proposed.The KB theory adjoint with RHNC theory was used to measure the partial molar volume of the ions or solute in aqueous media.[125, 126] Where as the RISM theory combined with the KB theory has successfully measured and interprete the partial molar volumes for wide range of molecular systems such as hydrocarbons,[139, 130] ions,[127,128] and biomolecules[131, 132] in non-aqueous and aqueous and solutions.[133,134] The RISM theory has been transformed to include the three-

dimensional spatial correlation functions of solvent molecules surrounding a solute molecule.[135, 136] The 3D-RISM theory adjoin with the KB theory was able to interpret the partial molar volumes of the bimolecular systems.[137-144] Hence the RISM theory is considered as most beneficial method to interpret the partial molar volumes and other thermodynamic parameters of solutions mixture.

2.6.2. Solvation Models

Two methods are applied here to short out the interaction[144]: the semi-empirical CNDO-type theory and the *ab initio* calculation theory. The *ab initio* calculation depicts the energy gap between a solvate and the different constituents is analyzed as a function of the geometry, *i.e.*, in respect of bond angles and bond length. According to these parameters Solvation energy is turned to maximum. Same as in the Free State, the solvent molecules may be regarded as rigid spheres having similar geometry. By omitting the electron correlation, the self-consistent field version of molecular orbital theory has been employed to solve Schrödinger equation for the all component and the solvate ion individually. The main problem arising is due to the genuine selection of basis set of orbitals. Although the separation in energy between the different component and a solvate is measured with less error while given basis of set (Slater or Gaussian type) of full molecular Hamiltonian is introduce for the measurement . Pople *et al.*[145] proposed an theory for semi-empirical calculations. Differential overlap (CNDO) of basis set of orbitals was entirely omitted in this theory. The total number of integrals have to measured is reduced with a set of orbitals. So this version introduce some empirical parameters which based on electron affinities, ionization potential in the Hamiltonian is known as CNDO/2. The energy of the system represented as a addition of total of two-atom and one-atom terms.

In terms of molecular dynamic (MD) , a fewer number of molecules, ions and Newtonian mechanics of movement for all type of solution particles are measured. This theory is dependent on the intermolecular energy of interactions between a pair of particles. A Computer programming simulation model found to be more helpful in this regards and in previous year some pioneer showing their interest to develop a computer soft wares and solvation models and in this event pronounced role played by. A. Galindo *et al.*[146, 147] They are create a Statistical Associating Fluid Theory for Variable Range (SAFT-VR) to explore the phase equilibrium and thermodynamic parameter of an electrolyte in aqueous solutions. The water molecules with the hard

sphered are again related to the four short-range interactive sites to examine the hydrogen-bond interactions. The electrolyte is considered as two hard spheres of dissimilar diameter were employed in expressing the cation and anion. The interactions are again expressed in terms of Debye-Hückel and the mean spherical approximations model. There are many aqueous electrolyte solutions found which shows good agreement with the experimental data.

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CHAPTER III

3.1. Details of the Chemicals Used

3.1.1. Solvents

In this research work numerous aqueous solutions were employed as solvents. For preparing those various aqueous solutions de-ionized water was employed which is collected from the de-ionization plant in laborotary of University of North Bengal. Latter on de-ionized water was doubly distilled by an all glass distilling chamber (as shown in Figure 3.1) with little amount of alkaline $KMnO_4$ solution. The conductivity of the doubly distilled water then measured with a Systronic Conductivity meter- 308 was found to be $<10^{-6}$ $S.cm^{-1}$ at 298.15 K.[1] Adequate mass of solid and liquid components were mixed with required adjustments to have an exact mass fraction of the solid component in the aqueous solvent systems.[2] Precautions must be taken while to keep away contamination by CO_2, moisture and other impurities. Hence the comapritive error in solvent composition was try to be managed within 1% of the expected mass fraction. Various physico-chemical properties of these respective aqueous solvent systems were expressed in respective next chapters.

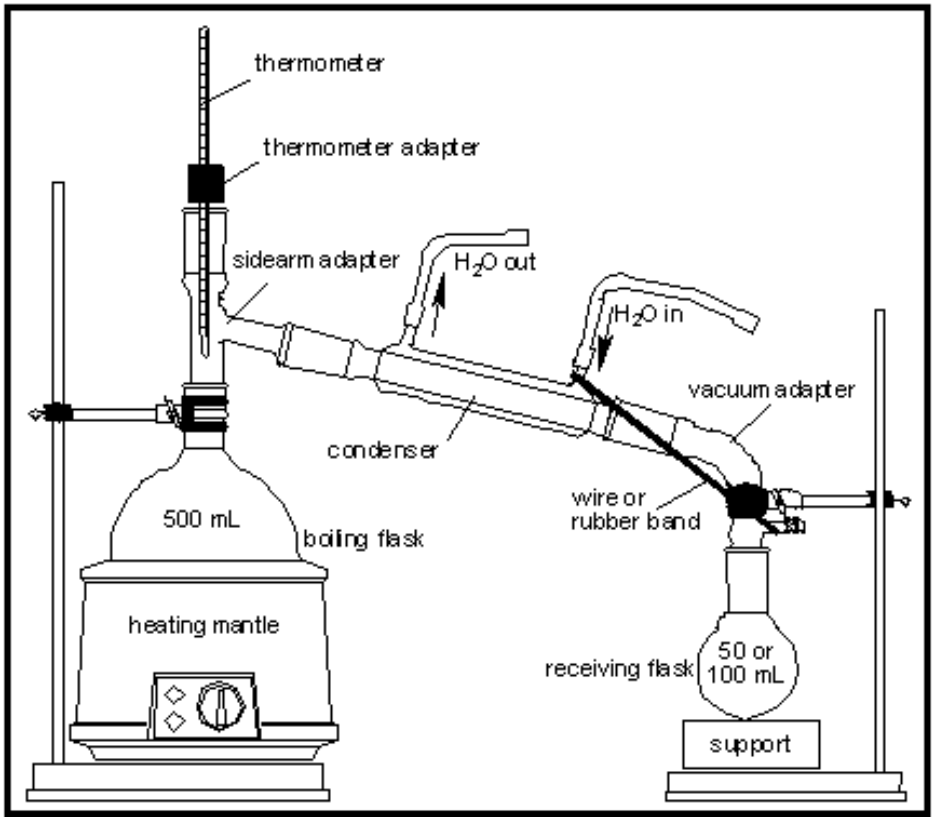

Fig 3.1. Schematic representation of the water distillation set.

Table 3.1. Details (Purity and provenance, *etc*.) of the cosolutes used.

Chemical	**Source**	**Purification**	**Mass Fraction purity**	**CAS No**
β cyclodextrin	Sigma-Aldrich, Germany	-	>0.990	7585-39-9
HP cyclodextrin	Sigma-Aldrich, Germany	-	>0.980	128446-35-5
α cyclodextrion	Sigma-Aldrich, Germany	-	≥0.980 (HPLC)	10016-20-3
Uracil	Sigma-Aldrich, Germany	Recrystalization	>0.990	66-22-8
Tetrabutyl Phosphonium p-Toluene Sulphonate(TBPPTS)	Sigma-Aldrich, Germany	-	≥0.950(NT)	116237-97-9
N,N –Dimethyl Formamide	Sd fine Chemicals, India	Non	>0.998	68-12-2
Dimethyl Sulphoxide	Sd fine Chemicals, India	Non	>0.998	67-68-5
Aniline	Sd fine Chemicals, India	Non	>0.995	62-53-3
Salicylaldehyde	Sd fine Chemicals, India	Non	>0.995	90-02-8
Zinc acetate dehydrate	Sd fine Chemicals, India	Non	>0.995	5970-45-6

Numerous chemicals may employed as cosolutes to prepare the the aqueous solvent systems. Details of these cosolutes are given in Table 3.1. Glycine and L-alanine were purified by recrystalised from warm distilled water at 90-95 ^{o}C. After filtration, the

residues were placed in a *vacuo* for dehydration for several hours. The melting points of glycine and L-alanine were measured by open capillary method and found to be 233 and 258 ^{o}C,[3,4] respectively. Although, uracil was used as found from the commercial sources but before use it was thoroughly dried over anhydrous $CaCl_2$ in *vacuo* for many hours.

3.1.2. Solutes

A number of biologically active compounds were employed here as solutes for the present research works. Stock solutions prepared of these solutes in different aqueous solvent systems were made by mass and the other various working solutions for the ensuing physico-chemical studies were prepared by mass dilution. Molalities (*m*) of solutes were changed into corresponding molarities (*c*) by using of the experimental densities. All solutions have to be prepared afresh with required precautions to nullified any type contamination and then degassed with the help of dry nitrogen. The uncertainty of molality (*c*) of the solutes in solutions was found as ±0.001 mol.kg^{-1}. Details of these solutes are given in Table 3.2.

Table 3.2. Details (Purity and provenance, *etc*.) of the solutes used.

Chemical*	**Purification**	**Mass fraction purity**	**CAS No**
Paracetamol	None	>0.990	103-90-2
L-Proline	Recrystalization	>0.990	147-85-3
L-Leucine	Recrystalization	>0.980	61-90-5
Alanine	Recrystalization	≥0.98	56-41-7
L-phenyl alanine	Recrystalization	≥0.98	63-91-2
Glycine	Recrystalization	≥0.985	56-40-6
N-Acetyl Glycine	Recrystalization	≥0.985	543-2-48
Caffeine	None	>0.990	58-08-2
Allopurinol	Recrystalization	>0.980	315-30-0

*__Source:__ Sigma-Aldrich, Germany.

paracetamol, caffeine were not purified further but they were dried over and placed in chamber and *vacuo* through anhydrous $CaCl_2$ for several hours before use.

3.2. Experimental Methods

3.2.1. Mass measurement

All Mass of the solutes and cosolutes were measured in a digital analytical electronic balance (Mettler Toledo, Switzerland, AG 285) depicted in Figure 3.2. In this balance the weighing pan is present inside a clear enclosure with doors to operate to avoid any type of dust particles gathering and misbalanced from any air currents. It determine the masses with very high precision and accuracy (mass measurements are found to be accurate by ± 0.01 mg).

Fig 3.2. Mettler Toledo digital balance, Switzerland, Model-AG 285.

3.2.2. Density measurement

Since the density is the important parameter for calculation of the volemetric and viscometric properties so it measured in digital density meter where different experimental aqueous solvent systems and the solutions of different concentration are measured at the different experimental temperatures with the aid of a digital density meter (Anton Paar, DMA-4500M). Figures 3.3-3.6 shows the density meter, its display, sample filling and cell drying, respectively.

Fig 3.3. Anton Paar density meter (DMA-4500M).

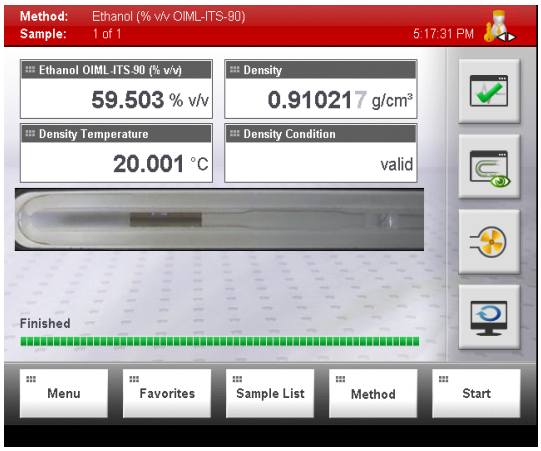

Fig 3.4. Display of Anton Paar density meter.

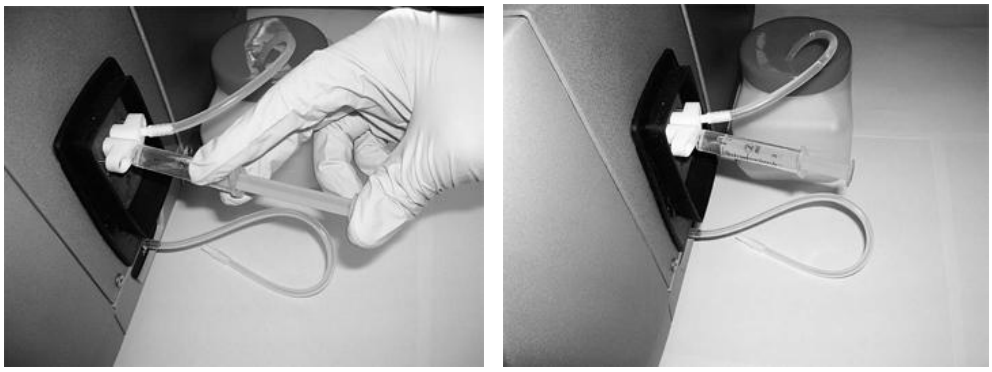

Fig 3.5. Filling of sample with a syringe.

Fig 3.6. Drying the measuring cell.

The mechanical oscillation of the U-tube of this density meter is electromagnetically turn into an alternating voltage having the same frequency. The oscillation period (τ_0) is accurately measured with high resolution and there is a simple relation found between the oscillation period (τ_0) and the density (ρ) of the examined sample is given by the following equation:[6]

$$\rho = \mathrm{A}\tau_0^2 - \mathrm{B} \qquad (1)$$

A and B stand for the instrument constants that can be obtained by calibrated with two liquids of accurately known densities. The densities of these two liquids at least made a difference of $\pm 0.01\,\mathrm{g \cdot cm^{-3}}$ and values of τ_0 of the adjustment media found to change by at least 0.0001 units. Modern tech and modified instruments can measured and store the A and B constants after calibration done, In an average it is so done with water and air. For the numerous experiments, though, the density meter was calibrated before using it by doubly distilled de-ionized degassed water and hot dry air at the various experimental temperatures under atmospheric pressure. In this instrument the temperature is keep at the experimental temperatures with an accuracy of $\pm 1\times10^{-2}\,\mathrm{K}$ with help of an automatic built-in Peltier technique. The stated repeatability and accuracy of the densities are found $\pm 1\times10^{-5}\,\mathrm{g \cdot cm^{-3}}$ and $\pm 5\times10^{-5}\,\mathrm{g \cdot cm^{-3}}$, respectively. But if the instrumental accuracy of the densities of the experimental solutions was compared to the densities of a known molal aqueous NaCl solution by using the given by Pitzer,[7] the calculted uncertainty of the densities for maximum of the solutions was found to be better than $\pm 2\times10^{-5}\,\mathrm{g\,cm^{-3}}$.

3.2.3. Viscosity measurement

The kinematic viscosities were measured from suspended-level Cannon type Ubbelohde viscometer (capillary type). The time of efflux of a constant volume liquid sample through the capillary was measured with the help of digital stopwatch with a time accuracy of ± 0.01s. The viscometer was always placed vertically submersed in the thermostatic bath that maintained at the experimental temperature with accuracy of ± 0.01 K. After a while the thermal equilibrium was established, the flow times of the respective solution were measured thrice and the mean of all these measurements were considered for the calculation of viscosity. During the measurements required precautions were taken to keep away from evaporation loses and any contamination. The efflux time for water at temperature 298.15 K was measured as 428.9 s. The kinematic viscosity (ν) and the absolute viscosity (η) are calculated by using the following equation:[8]

$$\nu = \mathrm{k}t - \frac{\mathrm{L}}{t} \tag{2}$$

$$\eta = \nu\rho \tag{3}$$

k and L are known to be the characteristic viscometer constants; t and ρ stand for the efflux time of flow in seconds and sample density, respectively. The calibration constants (k and L) were determined with purified demonized double distilled water and methanol and they are found to be 4.23×10^{-3} and 4.000, respectively. Considering out of the record, the fact that the correct kinetic energy of the ions were found to be almost negligible and the uncertainty of viscosities was within $\pm 4\times10^{-4}\,\mathrm{mPa\cdot s}$ based on our newest study on different pure liquids. Figure 3.7 depicts the suspended-level Cannon type Ubbelohde viscometer (capillary type) used.

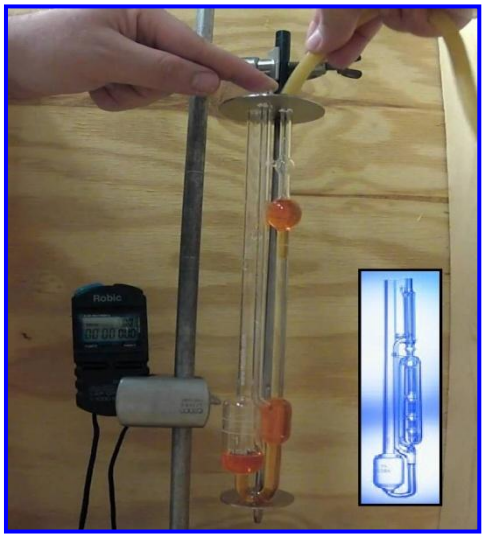

Fig 3.7. A suspended-level Cannon type Ubbelohde viscometer (capillary type).

3.2.4. Refractive index measurement

Refractive indices of the experimental liquid samples were mesured with the help of a Abbe-refractometer (Cyberlab, MA01527, USA) by using sodium D-line light (λ=589.3 nm, an mean of the two emission lines at 589.0 nm and 589.6 nm) at 298.15 K. The Abbe-refractometer is one of the most reliable and widely used refractometer in various laboratory and it has the range within n_D = 1.3 to 1.7. Figure 3.8 schematically represents this optical system. The experiment liquid is directly put in the prism assembly of the instrument using an airtight hypodermic syringe and is sandwiched like a skinny film (~0.1mm) between the two prisms. The upper prism is solidly framed on a bearing that allow its rotation through the side arm presented by dotted lines. The lower prism is hanged to the upper prism to permit the separation for washing and for the introduction of the particular sample. When light reflects into the prism, the lower surface being rough is transformed into origin for the endless number of rays that passage along the sample at all angles.

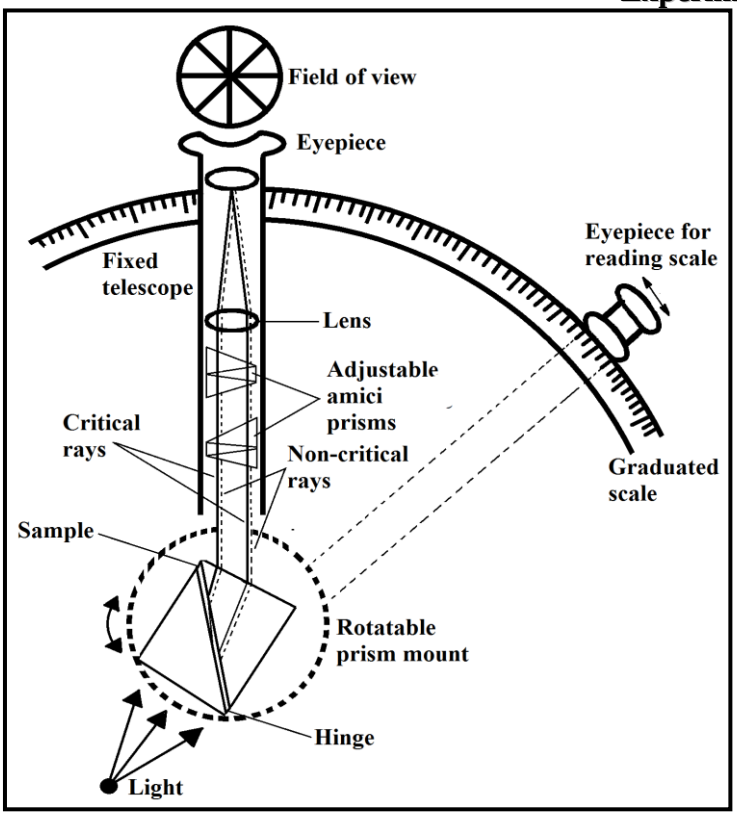

Fig 3.8. Schematic illustration of the Abbe-refractometer optical system.

The light rays are get refracted on the smooth polished-ground face and interface of the upper prism and sample, respectively. Then it travel along a fixed telescope. Divergent rays of various colors are combined into a single white beam by two triangular prisms in contact (Amici prisms). The beam verify almost exactly in the path to that of sodium D-ray. The eyepiece is marked with crosshairs in the telescope shown in the (Figure 3.8). At the time of measurement of the refractive index the angle of the prism is changed until the light-dark interface just coexists with the crosshairs.After that the prism position is read from the locked scale. Mean of three numbers of measurements was taken for each solution mixture. The Abbe-refractometer is represented in Figure 3.9. During the determination, water from a thermostatic bath keep at 298.15 ± 0.01 K was convey along the refractometer and it was calibrated by calculating the refractive indices of doubly distilled de-ionized degassed water at temperature 298.15 K. The uncertainty in refractive indices was found within ± 0.0002.

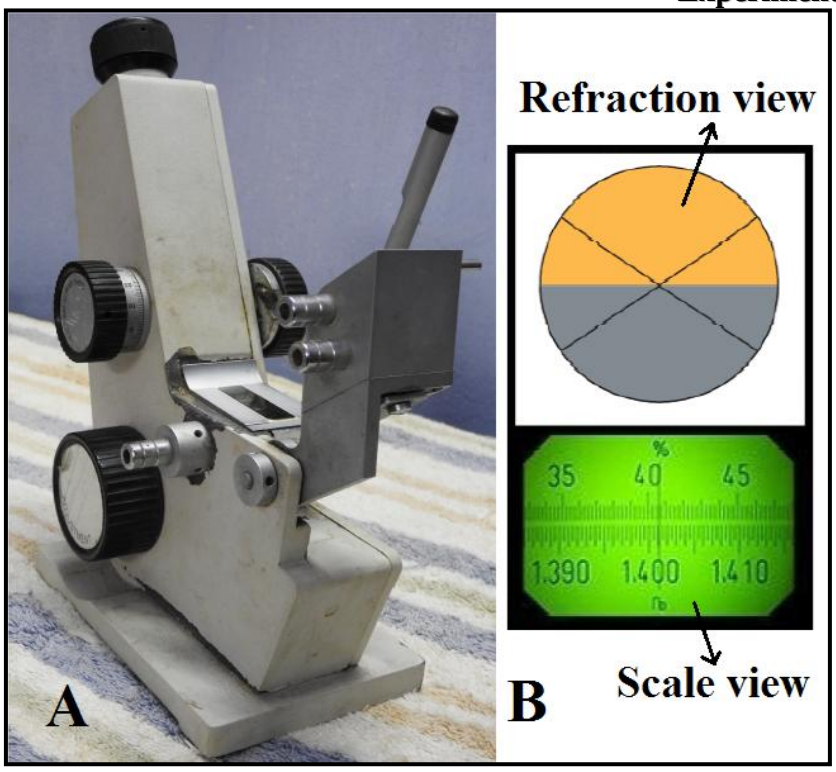

Fig 3.9. A: Abbe-refractometer (Cyberlab, MA01527, USA); B: View of the refractometer through the eyepiece.

3.2.5. Spectrophotometric measurements

Absorption spectra of biologically active compounds or solutes in various aqueous media were measured on a Jasco V-530 double beam UV-VIS spectrophotometer at 298.15 K. Figure 3.10 represents the UV-VIS Spectrophotometer. It was connected with a thermostatic array to controll a temperature of 298.15 ± 0.01 K. Quartz cells of 1 cm path length were employed to keep the samples and the reference solvents at the time of spectral determination. A stock solution of biologically active samples was prepared in the aqueous solvent systems and 2 mL of it was poured into the quartz cell and study of absorption was done against a selected reference solvent system. Then solution of co-solute (of definite concentration) in the reference solvent or in an aqueous solvent was added stepwise by utilizing pre-calibrated Hamilton syringe. After 30 seconds the absorbance of the resulting solution was calculated at each step.

Fig 3.10. Double beam UV-VIS Spectrophotometer (Jasco V-530) and the thermostatic bath.

3.2.6. *Ultrasonic Velocity Measurements*

There are three types of experimental techniques are employed to determine the ultrasonic sound velocities in liquid mixtures and pure liquids. They are: (i) Pulse method, (ii) Continuous wave method and (iii) Interferometer technique. By comparing of the relative merits of the various methods, interferometer method is considered as the most accurate method acceptable for speed measurements. Hunter and Dardy,[9] Dobbs and Fine gold,[10] Fort and Moore[11] measured the speed of sound for liquids and liquid mixtures by using interferometric technique with ± 0.15% uncertainty. In the present study ultrasonic speeds of the experimental liquid samples were measured with an exactness of 0.3% utilizing a multi-frequency ultrasonic interferometer (F-05, Mittal Enterprises; New Delhi, India) operating at 2 MHz. It was calibrated with pure benzene, doubly distilled de-ionized degassed water maintained at 298.15 ± 0.01 K by paasing thermostatic water surrounding the jacketed cell (of 2 MHz) keeping the liquid sample with the help of circulating pump. The uncertainty in ultrasonic speeds was found around ±0.2 m s^{-1}.

The determination of ultrasonic speed (u) by ultrasonic interferometer is dependent on the exact calculation of wavelength (λ) in the medium. In this process ultrasonic waves of frequency (f) are created by a crystal of quartz hanged at the lower part of the cell. These ultrasonic waves are get reflected by a transportable plates of metal (keeping parallel to the quartz crystal). While the interspace between these two plates becomes a whole multiple of the wavelength of ultrasonic sound, the standing waves are created in that medium. In this situation, acoustic resonance is

generated. The acoustic resonance produce an electrical reaction in the generator that shows the quartz crystal and as a result of the current of anode in the generator approached the maximum level. When the distance is enlarged or diminished by exactly one half of the wavelength ($\lambda/2$) or an integer multiple of the wavelength, the current of anode again reached to the maximum level. If *d* represents the separation between consecutive adjoining maxima of current of anode and the full number of oscillation (usually n = 20) counted. Then the total distance moved by the micrometer in n oscillations is given by:

$$d = n \times \frac{\lambda}{2} \tag{4}$$

The speed (u) of the wave and frequency (f) of the cell are found to be related with its wavelength (λ) by the relation,

$$u = \lambda \times f \tag{5}$$

$$\text{Or} \qquad u = \lambda \times f = \frac{2d}{n} \times f \tag{6}$$

So with a known cell, the frequency of the ultrasonic speed (u) can be measured. The ultrasonic interferometer has the three main portions: (i) The high frequency generator (single and multi-frequency) is specially outlined to excite the crystal of quartz hang at the lower part of the measuring cell. Its resonant frequency is provided for the production of the ultrasonic wave in the experimental liquid present in the measuring cell, (ii) shielded cable and (iii) The measuring cell (1, 2, 3 and 4 MHz) is specially drafted with double walled cell which controls the temperature of the sample liquid constant through out the whole process. To increase or minimise the reflector plate in the liquid a good micrometer has been employed. It is organised at the top of the cell and works from a known gap.

The total assembly of the instrument is represented on Figure 3.11 in which the output terminal of that high frequency creator is hanged with the measuring cell by a shielded cable. In the beginning the cell is filled up with the study solution and then keep the switch of the generator is on. Genarally it was found that the ultrasonic waves generally move normal from the crystal of quartz crystal until they are reflected back by the movable plate and the standing waves are created in liquid in between the quartz crystal and the reflector plate. After that the micrometer forwarded very slowly till the anode current exhibits a maximum deflection on the display meter

of the high frequency generator. Different no. of maxima of current of anode are observed and the total number of oscillation (n) is computed. The total space (d) thus moved by the micrometer provides the wavelength (λ) by using the Eq. (4).

Fig 3.11. Ultrasonic interferometer (F-05, Mittal Enterprises, India).

In Fig. 3.12 shows a cross-section view of the measuring cell of ultrasonic interferometer having multi-frequency. The position of reflector *versus* crystal current are also shown in the fig 3.12. The additional peaks [appearing in Figure 3.12 B] in between minima and maxima found due to a various reasons but these are not affecting the $\lambda/2$ values.

3.2.7. pH Measurements

A Systronics digital pH meter employed in the present study to record some the pH's while required for the experimental study solutions. It was calibrated before use at pH = 4.00 using a buffer capsule of pH = 4.00 (purchased from Sigma-Aldrich, Germany). Figure 3.13 shows the Systronics digital pH meter which is utilized during the present study.

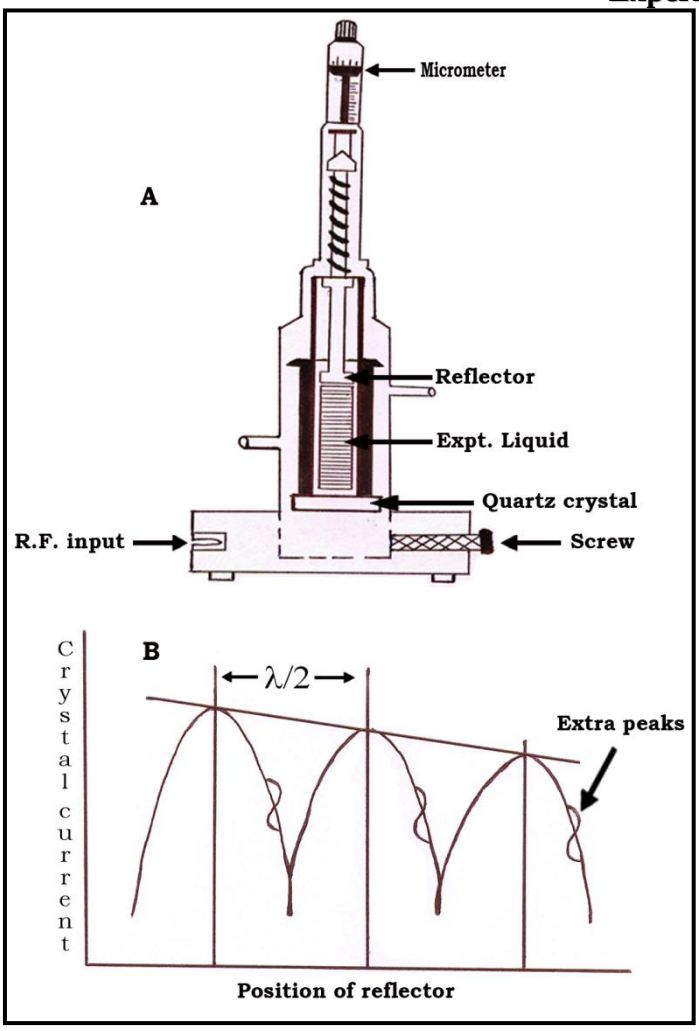

Fig 3.12. (A) A cross-section of the measuring cell of a multi-frequency ultrasonic interferometer; (B) position of reflector *versus* crystal current.

Fig 3.13. Systronics digital pH meter.

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CHAPTER-IV

Physico-chemical studies of L-Proline and L-leucine in aqueous Tetrabutyl Phosphonium *p*-Toluene Sulphonate solutions at 298.15, 303.15 and 308.15K probed by density, viscosity and refractive index measurements.

4.1. Introduction

The exploration of molecular interaction in solution is always an interest to chemists. The study of volumetric and viscometric properties allows investigation into the molecular interaction in solution phase, specifically allows us to understand the nature and strength of the intermolecular forces operating among mixed components.[1-3]

The complexity in the nature of interaction arise in the solution consisting of multiple solutes or solvents and hinders the solution to behave ideally. This deviation from ideality are expressed in terms of thermodynamic parameters such as apparent molar properties in case of solid-liquid mixtures. These thermodynamic properties of solvent mixtures quantifies the difference between the actual property and the ideal property and therefore are useful in the study of molecular interactions and arraangements. In particular, they reflect the interaction that take place between solutes, solute-solvent and solvent-solvent species. At the molecular level, the addition of a solute modifies not only the exisitng solvent structure (the existing interaction) but also rearranges the interaction of the solute molecules. The extent of solute-solvation reorganization stricty depends upon the interactions taking place between solute-solute, solute-solvent, solvent-solvent species. Thus quantification of these interactions becomes important to understand a solution system. For example, the understanding of all the interaction of a drug in solution (blood plasma ,etc) becomes important to formulate its course of dissolution, transport and action in human body. In solution chemistry, elucidation of the nature of interaction are done through experimental studies involving density, viscosity, and refractive index measurements.

The present research work is intimately related to the studies of solute-solute, and solvent-solvent interactions of L-Proline and L-leucine in aqueous Tetrabutyl

Phosphonium *p*-Toluene Sulphonate (TBPPTS) solutions at 298.15, 303.15 and 308.15K probed by density, viscosity and refractive index measurements.

Ionic liquids (ILs) are one of the most interesting and rapidly developing areas of modern physical chemistry, technologies and engineering, their molecular interaction with amino acids would be of utmost importance for pharmaceutical applications.[4-6]

4.2. Experimental Section

4.2.1. Source and purity of samples

Tetrabutyl Phosphonium p-Toluene Sulphonate (TBPPTS) was procured from sigma aldrich (assay >95%), L-Proline and L-Leucine were also purchased from sigma aldrich (assay > 99% and >98%). Triply distilled water with a specific conductance $<10^{-6}$ S cm^{-1} was used for the preparation of different aqueous solutions. The physical properties of 0.001, 0.003 and 0.005 molalities of aqueous TBPPTS solutions are listed in Table 4. 1.

Table 4.1. Densities(ρ) and Viscosities(η) of aqueous tetrabutyl phosphonium *p*-toluene sulphonate solutions at 298.15K, 303.15K and 308.15K and refractive index at 298.15K.

m_{TBPPTS}	T	ρ	η	n_D
0.001	298.15	0.9989	0.902	1.3320
	303.15	0.9974	0.819	
	308.15	0.9959	0.742	
0.003	298.15	1.0004	0.914	1.3332
	303.15	0.9989	0.831	
	308.15	0.9974	0.755	
0.005	298.15	1.0018	0.931	1.3345
	303.15	1.0004	0.855	
	308.15	0.9989	0.772	

Units: m, $\mathrm{mol \cdot kg^{-1}}$; T, K; ρ, $10^{-3}\,\mathrm{kg \cdot m^{-3}}$ and η, $\mathrm{mPa \cdot s}$.

4.2.2. Apparatus and Procedure

The Density (ρ) was measured by means of vibrating-tube Anton Paar Density-Meter (DMA 4500M) with a precision of 0.00005 g.cm^{-3}. It was calibrated by double-distilled water and dry air . The temperature was automatically kept constant within ± 0.01 K.

Viscosities were measured from the well cleaned, thoroughly dried and pre-calibrated Canon-type suspended Ubbelohde viscometer. It was previously-calibrated at study temperatures with triply distilled, degassed water and purified methanol. Mean of triplicate in each case of measurements was assumed and enough precautions were taken to keep evaporation loses minimum during the course of the measurements. The standard uncertainty in viscosities found to be $\pm 4\times10^{-4}$ mPa·s .

Refractive index was measured with the help of a Digital Refractometer Mettler Toledo. The light source was LED with λ=589.3 nm. The refractometer was calibrated twice using distilled water and calibration was checked after every few measurements. The uncertainty of refractive index measurement was ± 0.0002 units. The solutions studied here were prepared by mass and the conversion of molarity into molality was accomplished using experimental density values.[8] The experimental values of densities *(*ρ), viscosities (η) and refractive indices (n_D)of solutions are reported in Table 4.2 and the derived parameters are reported in Table 4.3 and Table 4.4.

m	ρ	η	n_D	m	ρ	η	n_D
L-Proline				L-Leucine			
0.001[a]				0.001[a]			
T = 298.15 K				T = 298.15 K			
0.0100	0.99939	0.921	1.3326	0.0100	0.99943	0.926	1.3335
0.0251	1.00028	0.942	1.3332	0.0251	1.00052	0.955	1.3339
0.0401	1.00126	0.963	1.3337	0.0402	1.00181	0.983	1.3345
0.0552	1.00227	0.982	1.3342	0.0552	1.00322	1.010	1.3350
0.0703	1.00335	1.002	1.3347	0.0703	1.00478	1.039	1.3356
0.0855	1.00445	1.020	1.3353	0.0854	1.00643	1.067	1.3362
T = 303.15 K				T = 303.15 K			
0.0100	0.99784	0.837		0.0100	0.99790	0.841	
0.0251	0.99867	0.859		0.0251	0.99897	0.868	

0.0401	0.99966	0.880		0.0402	1.00038	0.894	
0.0552	1.00079	0.901		0.0553	1.00199	0.920	
0.0703	1.00198	0.920		0.0704	1.00373	0.946	
0.0854	1.00332	0.940		0.0855	1.00567	0.974	
	T = 308.15 K				T = 308.15 K		
0.0100	0.99631	0.764		0.0101	0.99633	0.764	
0.0251	0.99730	0.792		0.0252	0.99747	0.792	
0.0401	0.99854	0.818		0.0403	0.99895	0.819	
0.0552	0.99991	0.846		0.0554	1.00080	0.848	
0.0702	1.00154	0.871		0.0705	1.00284	0.874	
0.0853	1.00324	0.900		0.0855	1.00509	0.902	
	0.003[a]				0.003[a]		
	T = 298.15 K				T = 298.15 K		
0.0100	1.00088	0.933	1.3351	0.0100	1.00087	0.937	1.3360
0.0250	1.00171	0.956	1.3357	0.0250	1.00183	0.967	1.3364
0.0401	1.00264	0.978	1.3362	0.0401	1.00301	0.995	1.3370
0.0551	1.00365	0.999	1.3367	0.0552	1.00437	1.022	1.3375
0.0702	1.00473	1.019	1.3372	0.0702	1.00582	1.051	1.3381
0.0853	1.00586	1.039	1.3378	0.0853	1.00751	1.080	1.3388
	T = 303.15 K				T = 303.15 K		
0.0100	0.99927	0.848		0.0100	0.99932	0.854	
0.0251	1.00009	0.870		0.0251	1.00031	0.884	
0.0401	1.00113	0.891		0.0401	1.00169	0.913	
0.0552	1.00238	0.910		0.0552	1.00331	0.943	
0.0703	1.00372	0.931		0.0703	1.00505	0.970	
0.0854	1.00522	0.952		0.0853	1.00710	1.002	
	T = 308.18 K				T = 308.18 K		
0.0100	0.99751	0.775		0.0100	0.99753	0.778	
0.0251	0.99820	0.804		0.0251	0.99853	0.811	
0.0402	0.99933	0.830		0.0402	1.00008	0.845	
0.0553	1.00074	0.858		0.0553	1.00203	0.876	
0.0704	1.00253	0.886		0.0703	1.00442	0.911	
0.0854	1.00454	0.911		0.0854	1.00693	0.941	

0.005[a]				0.005[a]			
T = 298.15 K				T = 298.15 K			
0.0100	1.00201	0.950	1.3365	0.0100	1.00212	0.954	1.3373
0.0250	1.00252	0.973	1.3369	0.0250	1.00306	0.983	1.3383
0.0401	1.00322	0.995	1.3374	0.0400	1.00436	1.012	1.3393
0.0551	1.00406	1.017	1.3379	0.0551	1.00591	1.041	1.3403
0.0702	1.00508	1.040	1.3385	0.0701	1.00760	1.069	1.3413
0.0853	1.00612	1.061	1.3390	0.0851	1.00955	1.098	1.3423
T = 303.15 K				T = 303.15 K			
0.0100	1.00046	0.866		0.0100	1.00063	0.878	
0.0250	1.00097	0.886		0.0250	1.00159	0.908	
0.0401	1.00173	0.906		0.0401	1.00297	0.939	
0.0552	1.00272	0.927		0.0551	1.00466	0.969	
0.0703	1.00399	0.948		0.0702	1.00667	1.000	
0.0854	1.00531	0.969		0.0852	1.00884	1.028	
T = 308.15 K				T = 308.15 K			
0.0100	0.99897	0.792		0.0100	0.99894	0.796	
0.0251	0.99962	0.821		0.0251	0.99992	0.828	
0.0402	1.00071	0.848		0.0402	1.00139	0.862	
0.0552	1.00207	0.876		0.0552	1.00342	0.897	
0.0703	1.00353	0.905		0.0702	1.00581	0.930	
0.0854	1.00528	0.932		0.0852	1.00846	0.964	

Units: m, $\mathrm{mol \cdot kg^{-1}}$; ρ, $10^{-3}\,\mathrm{kg \cdot m^{-3}}$; η, $\mathrm{mPa \cdot s}$

[a]TBPPTS molalities in various aqueous solutions.

Table 4.2. *Experimental values of densities (ρ) and viscosities (η) of L-Proline and L-Leucine in different molalities (m_1) of aqueous tetrabutyl phosphonium p-toluene sulphonate solutions at 298.15K, 303.15K and 308.15K and refractive Index (n_D) at 298.15K.*

m	$\emptyset_v$	$\frac{(\eta/\eta_1 - 1)}{\sqrt{m}}$	R	m	$\emptyset_v$	$\frac{(\eta/\eta_1 - 1)}{\sqrt{m}}$	R
L-Proline				L-Leucine			
0.001[a]				0.001[a]			
T = 298.15 K				T = 298.15 K			
0.0100	62.2713	0.210	23.6703	0.0100	74.2809	0.266	27.0470
0.0251	58.3966	0.280	23.6867	0.0251	64.8745	0.371	27.0507
0.0401	55.1929	0.338	23.6964	0.0402	57.5194	0.448	27.0540
0.0552	53.1906	0.377	23.7073	0.0552	51.9929	0.509	27.0563
0.0703	51.0453	0.418	23.7145	0.0703	46.6905	0.573	27.0581
0.0855	49.4216	0.448	23.7213	0.0854	42.2000	0.626	27.0598
T = 303.15 K				T = 303.15 K			
0.0100	75.3263	0.220		0.0100	85.4048	0.268	
0.0251	66.0212	0.308		0.0251	70.1711	0.378	
0.0401	59.6951	0.372		0.0402	57.8438	0.457	
0.0552	54.2637	0.426		0.0553	48.5960	0.525	
0.0703	50.2994	0.465		0.0704	41.4503	0.585	
0.0854	45.9623	0.505		0.0855	34.4684	0.647	
T = 308.15 K				T = 308.15 K			
0.0100	75.4286	0.292		0.0101	89.5510	0.296	
0.0251	59.8191	0.426		0.0252	69.0744	0.425	
0.0401	49.3911	0.511		0.0403	55.4233	0.518	
0.0552	42.3505	0.596		0.0554	42.4657	0.608	
0.0702	34.6538	0.656		0.0705	32.3368	0.671	
0.0853	28.7147	0.728		0.0855	23.3029	0.738	
0.003[a]				0.003[a]			
T = 298.15 K				T = 298.15 K			
0.0100	69.1010	0.208	23.7962	0.0100	86.1338	0.252	27.1764
0.0250	63.5033	0.290	23.8138	0.0250	74.7386	0.366	27.1833
0.0401	59.6050	0.350	23.8245	0.0401	66.3921	0.443	27.1894
0.0551	56.3790	0.396	23.8352	0.0552	59.3269	0.503	27.1934
0.0702	53.5361	0.433	23.8423	0.0702	54.0045	0.566	27.1972

0.0853	51.1085	0.468	23.8507	0.0853	47.7382	0.622	27.2003
	T = 303.15 K				T = 303.15 K		
0.0100	80.2166	0.205		0.0100	91.2686	0.277	
0.0251	68.4039	0.297		0.0251	75.6517	0.403	
0.0401	60.0699	0.361		0.0401	62.0620	0.493	
0.0552	52.2774	0.405		0.0552	51.4073	0.574	
0.0703	46.6089	0.454		0.0703	43.6457	0.631	
0.0854	41.0567	0.498		0.0853	34.9725	0.705	
	T = 308.18 K				T = 308.18 K		
0.0100	103.3999	0.265		0.0100	117.4766	0.305	
0.0251	82.9465	0.410		0.0251	85.7939	0.469	
0.0402	66.8044	0.496		0.0402	64.0873	0.595	
0.0553	54.3628	0.581		0.0553	46.9288	0.682	
0.0704	41.8106	0.655		0.0703	30.8219	0.780	
0.0854	31.0935	0.707		0.0854	18.9843	0.843	
	0.005[a]				0.005[a]		
	T = 298.15 K				T = 298.15 K		
0.0100	95.9554	0.204	23.8562	0.0100	100.9862	0.247	27.2391
0.0250	86.9717	0.285	23.8756	0.0250	81.4218	0.353	27.2867
0.0401	79.9844	0.343	23.8910	0.0400	67.5471	0.435	27.3243
0.0551	74.2676	0.393	23.9030	0.0551	56.7032	0.504	27.3550
0.0702	68.4340	0.442	23.9114	0.0701	48.5103	0.560	27.3817
0.0853	64.4245	0.478	23.9199	0.0851	40.1557	0.615	27.4012
	T = 303.15 K				T = 303.15 K		
0.0100	106.0907	0.129		0.0100	105.1311	0.263	
0.0250	91.0963	0.229		0.0250	82.3395	0.392	
0.0401	81.1000	0.298		0.0401	66.2205	0.491	
0.0552	72.3759	0.359		0.0551	53.1503	0.568	
0.0703	63.3923	0.411		0.0702	41.1548	0.641	
0.0854	56.9913	0.456		0.0852	31.5113	0.694	
	T = 308.15 K				T = 308.15 K		
0.0100	106.2490	0.259		0.0100	125.3103	0.311	

0.0251	85.6259	0.401	0.0251	89.6704	0.459
0.0402	69.4578	0.492	0.0402	68.4967	0.583
0.0552	57.1941	0.574	0.0552	48.6791	0.690
0.0703	48.7560	0.650	0.0702	32.2061	0.773
0.0854	39.8805	0.710	0.0852	18.4848	0.853

Units: m, $\mathrm{mol \cdot kg^{-1}}$; and ϕ_V, $10^6\,\mathrm{m^3 \cdot mol^{-1}}$; $\frac{(\eta/\eta_1-1)}{\sqrt{m}}$, $\boldsymbol{kg^{1/2}.mol^{-1/2}}$; R, $\mathrm{cm^3.mol^{-1}}$;

[a]TBPPTS molalities in various aqueous solutions.

Table 4.3. *Molality, apparent molar volume (ϕ_V),$(\eta/\eta_0-1)/m^{1/2}$ of L-Proline and L-Leucine in different molalities (m_1) of aqueous tetrabutyl phosphonium p-toluene sulphonate solutions at 298.15K, 303.15K and 308.15K and molar refraction (R) at 298.15K*

4.3. Results and discussion

4.3.1. Density calculation

Apparent molar volumes (ϕ_V) were determined from the density of the solutions using the following equation[9]

. $$\phi_V = M/\rho - 1000(\rho - \rho_o)/m\rho\rho_o$$

Where, M is the molar mass of the solute (L-Proline or L-Leucine), m is the molality of the solution ρ_0 and ρ are the densities of the mixture (of TBPPTS & water) and the solution respectively. The limiting apparent molar volume ϕ_V^0 was calculated by least-square treatment to the plots of ϕ_V *versus* $\sqrt{m}$ using the Masson equation.[10]

$$\phi_V = \phi_V^0 + S_V^* \sqrt{m} \qquad (3)$$

where ϕ_V^0 is the limiting apparent molar volume at infinite dilution and S_V^* is the volumetric virial coefficient. A plot of ϕ_V against square root of molal concentration ($\sqrt{m}$) is linear with S_V^* as slopes. The values of ϕ_V^0 and S_V^* are reported in Table 4.4.

A perusal of Table 4.4 and Figure 4.1. shows that ϕ_V^0 values for L-Proline and L-Leucine increases with the increase in amount of TBPPTS in solvent mixture and are higher in case of L-leucine than L-proline. This indicates the presence of strong solute-solvent interactions and that these interactions are more in case of L-leucine than L-proline. Furthermore, linear increase with the increase in temperature is also noted, L-Proline < L-Leucine.

T(K)	ϕ_V^0 x 10^6	S_V^* x 10^6	*A*	*B*
L-Proline				
m_1 = 0.001				
298.15	68.94	-67.24	0.085	1.245
303.15	90.27	-151.90	0.072	1.487
308.15	98.78	-241.7	0.067	2.242
m_1 = 0.003				
298.15	78.39	-93.67	0.075	1.355
303.15	100.70	-204.40	0.055	1.510
308.15	141.90	-376.5	0.038	2.308
m_1 = 0.005				
298.15	112.90	-165.90	0.059	1.432
303.15	131.80	-255.80	0.041	1.704
308.15	150.4.	-406.24	0.026	2.341
L-Leucine				
m_1 = 0.001				
298.15	91.16	-167.30	0.075	1.867
303.15	111.90	-266.60	0.068	1.955
308.15	124.10	-345.20	0.062	2.300
m_1 = 0.003				
298.15	106.00	-198.40	0.061	1.905
303.15	121.20	-294.70	0.054	2.203
308.15	168.00	-514.70	0.023	2.827
m_1 = 0.005				
298.15	131.70	-316.40	0.052	1.921
303.15	143.30	-384.50	0.036	2.266
308.15	179.40	-554.70	0.017	2.852

ϕ_V^0 x 10^6,(m^3 mol^{-1}); S_V^* x 10^6(m^3 $mol^{-3/2}$ $kg^{1/2}$); *A*(kg mol^{-1}), *B*($kg^{1/2}$ $mol^{-1/2}$); m_1, *molality of* TBPPTS *in mol/kg*

Table 4.4. *Limiting apparent molar volumes (ϕ_V^0), experimental slopes (S_V^*) and A, B coefficients of L-Proline and L-Leucine in different molalities (m_1) of aqueous tetrabutyl phosphonium p-toluene sulphonate solution at 298.15, 303.15 and 308.15K.*

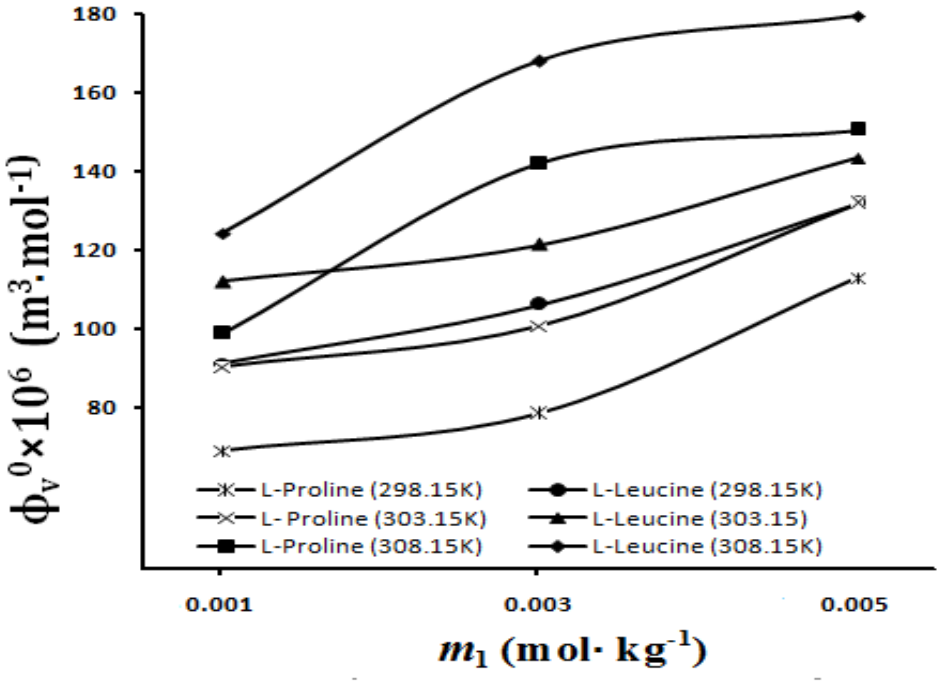

Figure 4.1. *The plots of limiting apparent molar volumes (ϕ_V^0) for L-Proline and L-Leucine in different molalities (m_1) of aqueous tetrabutyl phosphonium p-toluene sulphonate solutions at 298.15K, 303.15K and 308.15K.*

The volumetric virial coefficient S_V^* characterizes the pair wise interaction of solvated species in solution.[11-14] The sign of S_V^* determines the interaction between the solute species. In the present study S_V^* values were found to be negative and decrease further with the increase of temperature and the amount of TBPPTS in solvent mixture. This trend in S_V^* values indicates weak solute-solute interactions in the mixtures. A quantitative comparison of the magnitude of values shows that ϕ_V^0 values are much greater in magnitude than those of S_V^* for all of the solutions. This suggests that solute-solvent interactions dominate over solute-solute interactions in all of the solutions and at all experimental temperatures. Furthermore, S_V^* values are negative at all temperatures, and the values decrease with the increase of all experimental temperatures which may be attributed to more violent thermal agitation at higher temperatures, resulting in diminishing the force of solute-solute interactions. Again, the S_V^* values decrease with the increasing amount of TBPPTS in the solvent mixture which may be attributed to the increase in the solvation of ions.

4.3.2. Viscosity calculation

The viscosity data has been analyzed using Jones-Dole equation.[15]

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$$(\eta / \eta_0 - 1) / \ m^{1/2} = A + Bm^{1/2} \qquad (4)$$

where η_0 and η are the viscosities of the solvent and solution respectively. *A* and *B* are the viscosity co-efficient estimated by a least-squares method and are reported in Table 4.4. The values of the *A* co-efficient were found to decrease with the increase in amount of TBPPTS in the solvent mixture and also with the experimental temperature. The results indicate the presence of very weak solute-solute interactions. These results are in excellent agreement with those obtained from S_V^* values discuss earlier.

The effects of solute-solvent interactions on the solution viscosity can be inferred from the *B*-coefficient.[16,17] The viscosity *B*-coefficient is a valuable tool to provide information concerning the solvation of the solutes and their effects on the structure of the solvent. From Table 4.4 and Figure 4.2 it is evident that the values of the *B*-coefficient are positive, thereby suggesting the presence of strong solute-solvent interactions, and strengthened with the amount of TBPPTS in solvent mixture and with the experimental temperatures and is in excellent agreement with the results obtained from ϕ_V^0 values discussed earlier.

4.3.3. Refractive index calculation

The molar refraction, R can be evaluated from the Lorentz-Lorenz relation.[18]

$$R = \left\{(n_D^2\text{-}1)/(n_D^2 + 2)\right\}(M/\rho) \qquad (5)$$

where R, n_D, M and ρ are the molar refraction, the refractive index, the molar mass and the density of solution respectively. The refractive index of a substance is defined as the ratio c_0/c, where c is the speed of light in the medium and c_0 the speed of light in vacuum. Stated more simply, the refractive index of a compound describes its

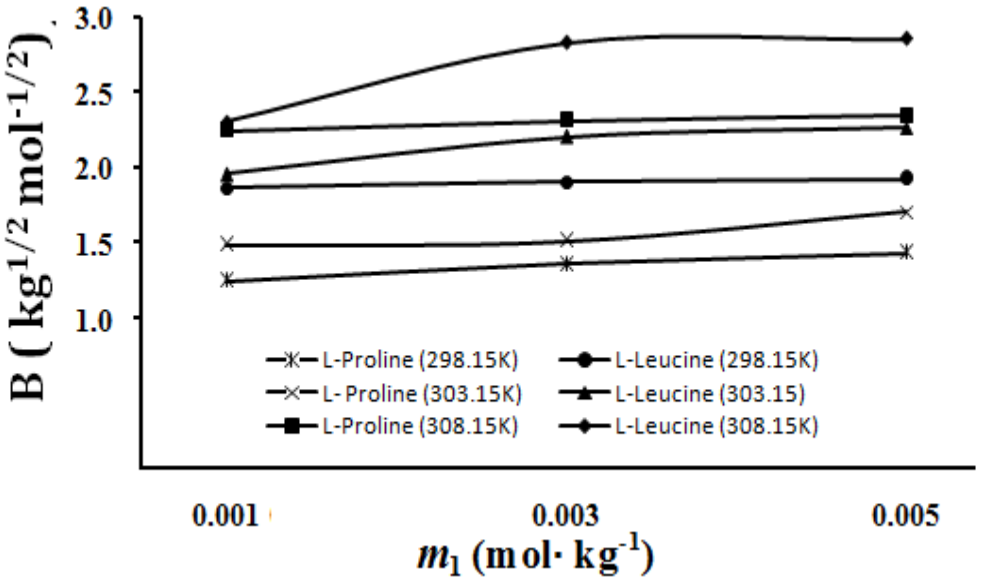

Figure 4.2. *The plots of viscosity B-coefficient for L-Proline and L-Leucine in different molalities (m_1) of aqueous tetrabutyl phosphonium p-toluene sulphonate solutions at 298.15K, 303.15K and 308.15K.*

ability to refract light as it moves from one medium to another and thus, the higher the refractive index of a compound, the more the light is refracted.[19]

As stated by Deetlefs et al. [20], the refractive index of a substance is higher when its molecules are more tightly packed or in general when the compound is denser and with the increase of amount of TBPPTS in solvent mixture refractive index value also increases. Hence a perusal of Table 4.2 and 4.3 it is inferred that the refractive index and the molar refraction values respectively are higher for L-Leucine compare to L-Proline, indicating the fact that the molecules are more tightly packed in the mixture. The interaction in the solution is basically solute-solvent interaction and a small amount of solute-solute interaction. This is also good agreement with the results obtained from density and viscosity parameters discussed above. The trend in the package of the studied amino acid in aqueous TBPPTS is

L-Proline < L-Leucine

4.4. Conclusion

The values of the limiting apparent molar volume (ϕ_V^0) and viscosity *B*-coefficients indicate the presence of strong solute-solvent interactions which increases

with the increase in amount of TBPPTS in solvent mixture and with the increase in the experimental temperature. The refractive index and the molar refraction values suggest that L-Leucine molecules are more tightly packed in the solution leading to higher solute-solvent interaction than L-proline.

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CHAPTER V

Studies on the Solvation Consequences of Aqueous Solutions of Uracil on Paracetamol and Caffeine

5.1. Introduction

Uracil, thymine, cytosine and adenine are called nucleoside bases and they are crucial structural components of the nucleic acids. Their derivatives can often act as drugs, *e.g*., acyclovir is used as anti-viral agent against herpes simplex, chickenpox and singles viruses.[1] Amongst the nucleoside bases, uracil is an important structural part of RNA and it also helps in the synthesises of various enzymes in human body for cell functions.[2] Therefore studies on the solvation consequences of its aqueous solution on bio-active solutes will certainly reveal the nature and extent of various interactions in solution phase particularly with respect to their conformations and functionalities.[3,4] Because the degree of solute-solute, solute-cosolute and solvent-solvent interactions in such aqueous solutions will certainly help to extent our knowledge about their functionalities in various biological processes. Such interactions depend on the structural fragments and temperature, hence studies on the solution thermodynamics of systems with uracil and bio-active solutes such as paracetamol and caffeine would be very informative although there are ample reports on the volumetric properties of the nucleo bases (as solutes) in aqueous solutions the literature.[5-10]

Paracetamol is used worldwide as an antipyretic and analgesic drug[11] and caffeine, found in plants like coffee, tea and cocoa beans, *etc*[12] is odourless, bitter tasting white coloured alkaloid[13] having a methyl substituted purine structure. Caffeine shows varied bio-activities like: it has effects on vasoconstriction,[14,15] DNA repairing, ageing and heart diseases, *etc*.[16-19] Although there are reports[20-25] on the physico-chemical properties of paracetamol and caffeine[26-29] in different aqueous solutions, there are no reports on the solution properties of these solutes in various aqueous uracil solutions. Therefore, herein this chapter an attempt has been made to study the different physico-chemical and thermodynamic properties of the aqueous solutions containing uracil, paracetamol and caffeine as solutes in solution phase. These physico-chemical and thermodynamic properties including some derived properties were discussed in the light of solute-solute, solute-cosolute and solute-solvent interactions.

5.2. Experimental Section

5.2.1. Chemicals used

Analytical grade uracil (CAS: 66-22-8), paracetamol (CAS: 103-90-2) and caffeine (CAS: 58-08-2) were purchased from Sigma-Aldrich, Germany with mass fraction purities > 0.99 for the present study. While caffeine was recrytallized from ethanol, paracetamol and uracil were dried over anhydrous $CaCl_2$ (in *vacuo*) for several hours before use. Doubly distilled and de-ionized water (with a specific conductance < $1 \cdot 10^{-6} S \cdot cm^{-1}$ at 298.15 K) was used for preparing the aqueous uracil solutions by mass with required volume adjustments as required by adding water to have the following molalities of uracil 0.005, 0.010, 0.015 and 0.020 mol.kg^{-1} in aqueous solutions at 298.15 K. Densities (ρ) and viscosities (η) of various aqueous uracil solutions at the experimental temperatures (298.15, 308.15 and 318.15 K) are found to be very much similar to those reported in the literature[30-32] (Table 5.1). Stock solutions of paracetamol and caffeine in aqueous uracil solutions were also prepared by mass, followed by proper dilution with water to obtain the working solutions afresh. An electronic digital analytical balance (AG 285, Mettler, Switzerland, uncertainly: $\pm 1 \cdot 10^{-4}$ g) was used for the mass measurements. Molalities were converted into molarities when determining the concentrations at various experimental temperatures.[33] and the relative uncertainty for the molalities of the solutes in the solutions was evaluated to be 0.01. All the details of chemicals used have already been given in Chapter III. The molecular structures of solutes used in this work are illustrated in Figure 5.1.

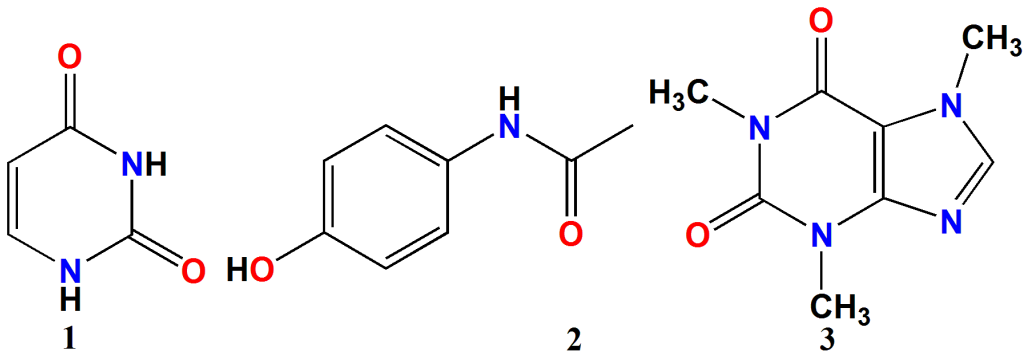

Fig 5.1. Molecular structures of the various solutes: 1, uracil; 2, paracetamol and 3, caffeine.

Table 5.1. Densities (ρ) and viscosities (η) of aqueous solutions of uracil at 298.15, 308.15 and 318.15 K.

m_{uracil}	T	ρ	η
	298.15	0.99722	0.8789
0.005	308.15	0.99424	0.7171
	318.15	0.99041	0.5783
	298.15	0.99743	0.9131
0.010	308.15	0.99443	0.7312
	318.15	0.99058	0.5869
	298.15	0.99762	0.9291
0.015	308.15	0.99462	0.7539
	318.15	0.99078	0.6091
	298.15	0.99782	0.9410
0.020	308.15	0.99482	0.7821
	318.15	0.99098	0.6272

Units: m, $\text{mol} \cdot \text{kg}^{-1}$; T, K; $\rho, 10^{-3}\,\text{kg} \cdot \text{m}^{-3}$ and η, $\text{mPa} \cdot \text{s}$.

5.2.2. Apparatus and procedure

Densities were measured with a vibrating-tube density meter (DMA 4500M, Anton Paar) and the uncertainties for the measured densities for the various experimental solutions were in the range of $\pm 2 \times 10^{-5}\,\text{g cm}^{-3}$. Viscosities were determined with the aid of a well cleaned, thoroughly dried and pre-calibrated Canon-type suspended Ubbelohde viscometer. It was pre-calibrated at experimental temperatures with triply distilled, degassed water and purified methanol.[34,35] An average of triplicate measurements in each case of measurements was considered and enough precautions were taken to keep evaporation loses minimum during the course of the measurements. The standard uncertainty in viscosities was evaluated to be $\pm 4 \times 10^{-4}\,\text{mPa} \cdot \text{s}$. The absorption spectra of various experimental solutions recorded with the aid of a Jasco V-530 double beam UV-VIS spectrophotometer at 298.15 K. Quartz cells of path length 1 cm were used for this purpose and the reference solvent was spectroscopic grade water from commercial source. During the course of

spectrophotometric measurements with paracetamol and uracil, 2 mL of paracetamol or uracil solution ($1\cdot10^{-4}\,\mathrm{mol\cdot L^{-1}}$) was taken in the quartz cell and the respective solution absorbance was measured, followed by stepwise addition of 20 μL of uracil ($1\cdot10^{-4}\,\mathrm{mol\cdot L^{-1}}$) or paracetamol ($1\cdot10^{-3}\,\mathrm{mol\cdot L^{-1}}$) solution alternatively by a micropipette. The solution absorbances were recorded in each step. However in case of the spectrophotometric measurements with caffeine and uracil, same procedure was followed but with caffeine concentration taken was $5\cdot10^{-5}\,\mathrm{mol\cdot L^{-1}}$. Different measurement techniques and apparatus were described in Chapter III.

5.3. Results and discussion

Table 5.2 illustrates the molalities (*m*), densities (ρ), viscosities (η) and apparent molar volumes (ϕ_V) for all the experimental solutions at different temperatures.

5.3.1. Standard partial molar volumes

The apparent molar volumes (ϕ_V) for the solutes (paracetamol and caffeine) in aqueous uracil solutions were determined using Eq. (1):[36]

$$\phi_V = \frac{M}{\rho} - \frac{1000(\rho - \rho_1)}{m\rho\rho_1} \qquad (1)$$

where *M* and *m* denote the molar mass and the solute molalities in the solutions; ρ_1 and ρ denote the densities of the solvent and solutions, respectively. The uncertainty in the determined apparent molar volumes (ϕ_V) was found to be within $\pm(0.14\text{-}0.78)\times10^{-6}\,\mathrm{m^3\cdot mol^{-1}}$. Table 5.2 represents that while the apparent molar volumes (ϕ_V) of the solutions containing paracetamol increase steadily as both the uracil molalities in aqueous solutions and the experimental temperatures increase, those (ϕ_V) for the solutions containing caffeine decrease steadily as the uracil molalities in aqueous solutions increase but such values increase steadily as the experimental temperatures increase, except when uracil was first introduced in the ternary aqueous solution of caffeine and uracil (in 0.005 molal aqueous uracil solution used as the solvent). This fact most probably arised owing to sudden perturbation of the different solute-solvent interactions and H-bond interactions in the solution when

Table 5.2. Molalities (m), densities (ρ), viscosities (η) and apparent molar volumes (ϕ_V) of the solutes in various aqueous uracil solutions at 298.15, 308.15 and 318.15 K.

m	ρ	η	ϕ_V	m	ρ	η	ϕ_V
Paracetamol solutions				Caffeine solutions			
0.000[a]				0.000[a]			
T = 298.15 K				T = 298.15 K			
0.0059	0.99719	0.8927	124.77	0.0281	0.99845	0.8958	143.18
0.0133	0.99739	0.8963	124.53	0.0463	0.99939	0.9027	143.00
0.0267	0.99777	0.9000	123.63	0.0586	1.00002	0.9073	142.87
0.0403	0.99815	0.9060	123.36	0.0770	1.00095	0.9142	142.68
0.0541	0.99854	0.9120	123.07	0.0934	1.00181	0.9203	142.52
0.0678	0.99895	0.9176	122.58	0.1015	1.00231	0.9237	142.45
T = 308.15 K				T = 308.15 K			
0.0059	0.99417	0.7207	125.89	0.0281	0.99535	0.7218	147.14
0.0133	0.99436	0.7242	125.58	0.0463	0.99623	0.7262	146.91
0.0267	0.99472	0.7278	125.06	0.0586	0.99682	0.7313	146.77
0.0403	0.99509	0.7327	124.67	0.0770	0.99771	0.7368	146.55
0.0541	0.99548	0.7377	124.12	0.0934	0.99848	0.7420	146.35
0.0678	0.99588	0.7423	123.62	0.1015	0.99882	0.7442	146.25
T = 318.15 K				T = 318.15 K			
0.0059	0.99038	0.5978	127.12	0.0281	0.99157	0.6029	149.17
0.0133	0.99057	0.6003	126.72	0.0463	0.99227	0.6100	148.45
0.0267	0.99093	0.6052	126.20	0.0586	0.99306	0.6181	147.97
0.0403	0.99128	0.6101	125.55	0.0770	0.99395	0.6271	147.25
0.0541	0.99167	0.6148	125.25	0.0934	0.99475	0.6352	146.58
0.0678	0.99205	0.6196	124.89	0.1015	0.99514	0.6392	146.28
0.005[a]				0.005[a]			
T = 298.15 K				T = 298.15 K			
0.0059	0.99737	0.8938	126.57	0.0281	0.99860	0.8938	145.31
0.0133	0.99756	0.8981	126.01	0.0463	0.99951	0.8981	144.76
0.0266	0.99792	0.9026	125.41	0.0586	1.00014	0.9026	144.28
0.0400	0.99828	0.9111	124.78	0.0770	1.00108	0.9111	143.82
0.0535	0.99868	0.9149	124.30	0.0934	1.00192	0.9150	143.50
0.0670	0.99908	0.9218	123.95	0.1015	1.00235	0.9218	143.20

T = 308.15 K				T = 308.15 K			
0.0059	0.99438	0.7223	127.05	0.0281	0.99553	0.7223	148.84
0.0133	0.99457	0.7261	126.58	0.0463	0.99638	0.7261	148.11
0.0266	0.99492	0.7300	125.97	0.0586	0.99698	0.7300	147.68
0.0400	0.99528	0.7362	125.46	0.0770	0.99787	0.7362	147.01
0.0535	0.99565	0.7423	124.96	0.0934	0.99867	0.7424	146.72
0.0670	0.99603	0.7463	124.51	0.1015	0.99907	0.7463	146.39
T = 318.18 K				T = 318.18 K			
0.0059	0.99056	0.5989	127.45	0.0281	0.99166	0.5990	150.73
0.0133	0.99075	0.6012	126.85	0.0463	0.99251	0.6012	150.00
0.0266	0.99109	0.6062	126.35	0.0586	0.99308	0.6062	149.48
0.0400	0.99147	0.6122	125.78	0.0770	0.99398	0.6122	148.92
0.0535	0.99184	0.6182	125.53	0.0934	0.99478	0.6182	148.40
0.0670	0.99223	0.6218	125.13	0.1015	0.99521	0.6218	148.02
0.010[a]				0.010[a]			
T = 298.15 K				T = 298.15 K			
0.0059	0.99758	0.8951	127.23	0.0281	0.99889	0.8951	142.43
0.0132	0.99776	0.8993	126.74	0.0463	0.99985	0.8993	142.02
0.0265	0.99811	0.9035	125.95	0.0585	1.00048	0.9035	141.76
0.0400	0.99858	0.9122	125.28	0.0768	1.00147	0.9122	141.37
0.0535	0.99886	0.9185	124.84	0.0933	1.00235	0.9185	141.04
0.0670	0.99926	0.9229	124.24	0.1015	1.00279	0.9229	140.88
T = 308.15 K				T = 308.15 K			
0.0059	0.99468	0.7227	127.54	0.0281	0.99576	0.7227	147.38
0.0132	0.99476	0.7263	126.97	0.0463	0.99664	0.7263	146.78
0.0265	0.99511	0.7302	126.28	0.0585	0.99724	0.7302	146.36
0.0400	0.99548	0.7370	125.71	0.0768	0.99816	0.7369	145.73
0.0535	0.99586	0.7428	125.14	0.0933	0.99898	0.7428	145.33
0.0670	0.99626	0.7471	124.58	0.1015	0.99939	0.7471	145.06
T = 318.15 K				T = 318.15 K			
0.0059	0.99076	0.5995	127.94	0.0281	0.99191	0.5995	148.52
0.0132	0.99093	0.6022	127.44	0.0463	0.99278	0.6022	147.82
0.0265	0.99128	0.6074	126.64	0.0585	0.99338	0.6074	147.26
0.0400	0.99165	0.6139	126.09	0.0768	0.99428	0.6139	146.64
0.0535	0.99202	0.6197	125.70	0.0933	0.99509	0.6197	146.25
0.0670	0.99239	0.6226	125.42	0.1015	0.99552	0.6226	145.95

0.015[a]				0.015[a]			
T = 298.15 K				T = 298.15 K			
0.0059	0.99769	0.8981	127.88	0.0281	0.99912	0.8981	141.01
0.0132	0.99795	0.9015	127.09	0.0463	1.00009	0.9015	140.58
0.0265	0.99828	0.9059	126.42	0.0585	1.00076	0.9058	140.36
0.0400	0.99865	0.9134	125.76	0.0769	1.00176	0.9134	140.04
0.0534	0.99903	0.9219	125.19	0.0933	1.00266	0.9219	139.72
0.0669	0.99993	0.9264	124.52	0.1015	1.00311	0.9264	139.58
T = 308.15 K				T = 308.15 K			
0.0059	0.99476	0.7228	128.19	0.0281	0.99601	0.7228	145.09
0.0132	0.99495	0.7268	127.41	0.0463	0.99692	0.7268	144.79
0.0265	0.99529	0.7317	126.68	0.0585	0.99754	0.7317	144.44
0.0400	0.99565	0.7398	126.06	0.0769	0.99848	0.7398	144.06
0.0534	0.99603	0.7437	125.48	0.0933	0.99932	0.7437	143.68
0.0669	0.99642	0.7478	125.01	0.1015	0.99974	0.7478	143.55
T = 318.15 K				T = 318.15 K			
0.0059	0.99092	0.6005	128.58	0.0281	0.99208	0.6005	148.42
0.0132	0.99109	0.6041	127.88	0.0463	0.99295	0.6041	148.01
0.0265	0.99145	0.6084	127.18	0.0585	0.99354	0.6084	147.67
0.0400	0.99180	0.6159	126.66	0.0769	0.99443	0.6159	147.22
0.0534	0.99218	0.6204	126.10	0.0933	0.99522	0.6204	146.88
0.0669	0.99256	0.6245	125.69	0.1015	0.99563	0.6245	146.62
0.020[a]				0.020[a]			
T = 298.15 K				T = 298.15 K			
0.0059	0.99895	0.8989	128.36	0.0281	0.99938	0.8989	138.47
0.0132	0.99813	0.9023	127.58	0.0463	1.00039	0.9023	138.20
0.0265	0.99847	0.9076	126.74	0.0585	1.00108	0.9076	137.93
0.0400	0.99883	0.9173	125.98	0.0769	1.00213	0.9173	137.67
0.0534	0.99919	0.9224	125.55	0.0933	1.00306	0.9224	137.43
0.0669	0.99960	0.9279	124.86	0.1014	1.00353	0.9282	137.22
T = 308.15 K				T = 308.15 K			
0.0059	0.99495	0.7245	128.85	0.0281	0.99623	0.7245	144.11
0.0132	0.99512	0.7281	128.22	0.0463	0.99716	0.7278	144.72
0.0265	0.99546	0.7332	127.35	0.0585	0.99779	0.7332	143.37
0.0400	0.99582	0.7408	126.62	0.0769	0.99874	0.7408	143.05
0.0534	0.99618	0.7456	126.22	0.0933	0.99958	0.7456	142.78

0.0669	0.99657	0.7497	125.68	0.1014	1.00001	0.7497	142.68
	T = 318.15 K				T = 318.15 K		
0.0059	0.99111	0.6021	129.11	0.0281	0.99231	0.6019	147.54
0.0132	0.99129	0.6058	128.55	0.0463	0.99319	0.6058	147.01
0.0265	0.99162	0.6104	127.74	0.0585	0.99378	0.6104	146.79
0.0400	0.99197	0.6174	127.19	0.0769	0.99468	0.6174	146.30
0.0534	0.99235	0.6225	126.49	0.0933	0.99548	0.6225	146.11
0.0669	0.99273	0.6271	126.01	0.1014	0.99587	0.6268	145.97

Units: m, $\mathrm{mol \cdot kg^{-1}}$; ρ, $10^{-3}\,\mathrm{kg \cdot m^{-3}}$; η, $\mathrm{mPa \cdot s}$ and ϕ_V, $10^{6}\,\mathrm{m^3 \cdot mol^{-1}}$.

[a]Uracil molalities in various aqueous solutions.

uracil was first introduced in the ternary solution. However, for both these solutes the apparent molar volumes (ϕ_V) decrease as their molalities in the solutions increase. Such trends of ϕ_V values indicate variations or dependence of the interactions amongst the solute, co-solute and solvent with solvent compositions and experimental temperatures. In this regard more authentic information can be had from the standard partial molar volume (ϕ_V^0) of these solutes. For both these solutes the ϕ_V values correlate linearly with the square root of the solute-molalities ($\sqrt{m}$) at all experimental temperatures (as illustrated in Figure 5.2). Therefore, the standard partial molar volumes (ϕ_V^0) were obtained from the Masson equation:[37]

$$\phi_V = \phi_V^0 + S_v^* \sqrt{m} \qquad (2)$$

Actually a weighted least squares linear regression of the ϕ_V values against $\sqrt{m}$ values was conducted using Eq. (2). The weighing factors have been set equal to the inverse of variances of the ϕ_V values for each data point and the correlation coefficients (R^2) were within the range of 0.913-0.991. While the intercept is the standard partial molar volume (ϕ_V^0) and it signifies the solute-solvent interactions, the corresponding slope S_V^* signifies the solute-solute interactions.

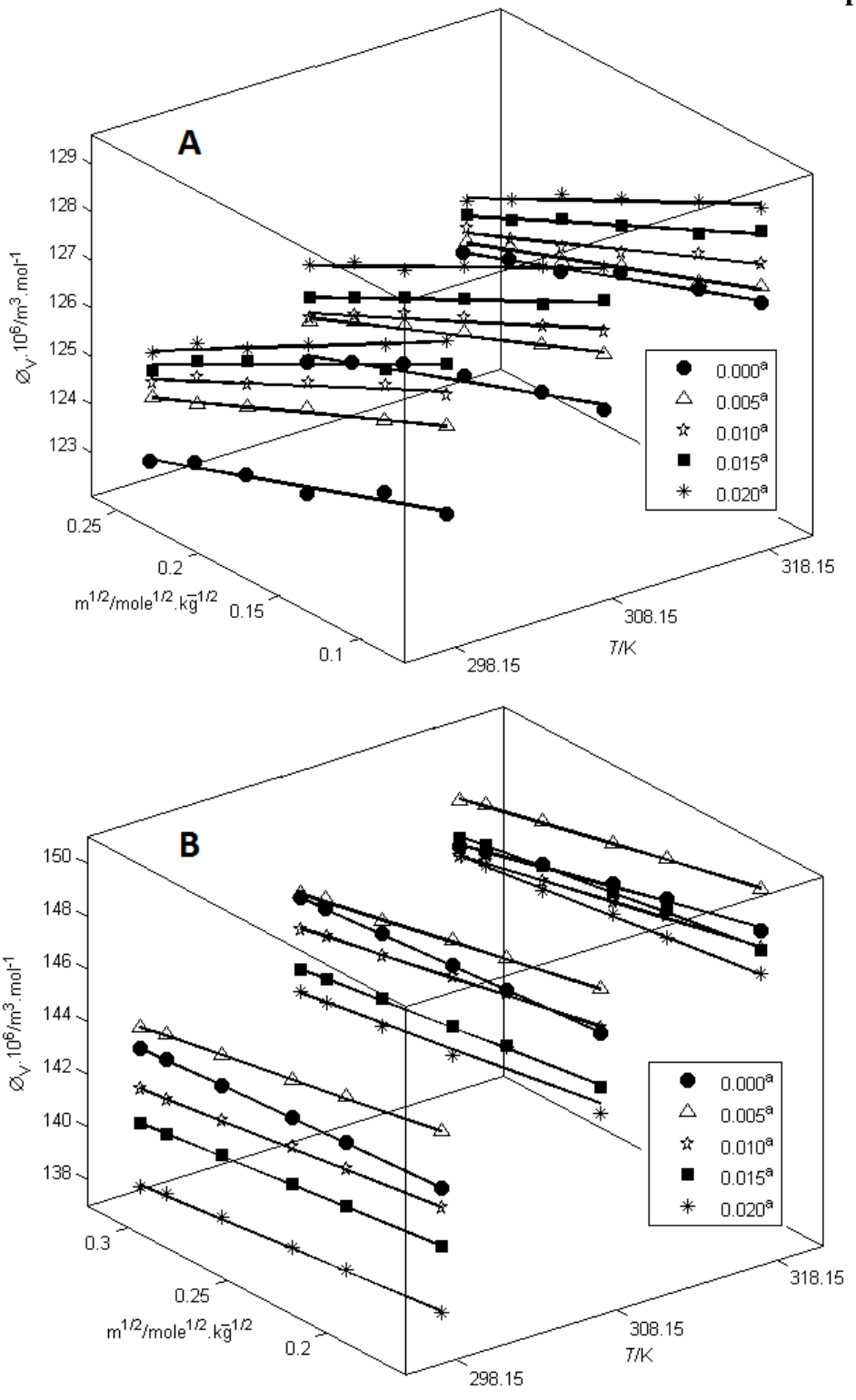

Fig 5.2. Interdependence of apparent molar volumes (ϕ_V), the square root of solute-molalities and the experimental temperatures for the solutes in various aqueous uracil ($^a m_{uracil}$) solutions. Solutes: A, paracetamol; B, caffeine.

Table 5.3. Partial molar volumes (ϕ_V^0), the slopes (S_V^*) and standard deviations (σ) for the solutes in various aqueous uracil solutions.

T	ϕ_V^0	S_V^*	σ	ϕ_V^0	S_V^*	σ
	Paracetamol solutions			Caffeine solutions		
		0.000[a]			0.000[a]	
298.15	125.75 (±0.11)	-12.02 (±0.52)	0.11	144.04 (±0.12)	-4.95 (±0.56)	0.11
308.15	126.96 (±0.12)	-12.31 (±0.65)	0.11	148.16 (±0.13)	-5.91 (±0.71)	0.11
318.15	128.13 (±0.05)	-12.48 (±0.36)	0.05	152.52 (±0.06)	-19.25 (±0.35)	0.05
		0.005[a]			0.005[a]	
298.15	127.71 (±0.16)	-14.43 (±0.88)	0.13	147.66 (±0.15)	-13.79 (±0.87)	0.14
308.15	128.18 (±0.06)	-13.94 (±0.41)	0.05	151.53 (±0.07)	-16.02 (±0.41)	0.05
318.15	128.35 (±0.07)	-12.32 (±0.15)	0.04	153.71 (±0.07)	-17.37 (±0.16)	0.03
		0.010[a]			0.010[a]	
298.15	128.56 (±0.38)	-16.26 (±2.18)	0.29	144.21 (±0.38)	-10.32 (±2.21)	0.36
308.15	128.83 (±0.13)	-15.85 (±0.77)	0.14	150.03 (±0.12)	-15.38 (±0.81)	0.12
318.15	129.02 (±0.11)	-14.13 (±1.13)	0.17	151.42 (±0.14)	-17.05 (±1.12)	0.17
		0.015[a]			0.015[a]	
298.15	129.24 (±0.26)	-17.25 (±1.49)	0.21	142.59 (±0.25)	-9.31 (±1.46)	0.24
308.15	129.46 (±0.25)	-17.06 (±1.14)	0.21	147.15 (±0.22)	-11.27 (±1.12)	0.21
318.15	129.75 (±0.19)	-15.59 (±1.14)	0.18	150.53 (±0.19)	-12.01 (±1.13)	0.20
		0.020[a]			0.020[a]	
298.15	129.78 (±0.42)	-18.68 (±2.48)	0.38	139.88 (±0.37)	-8.15 (±2.49)	0.41
308.15	130.19 (±0.41)	-17.31 (±2.51)	0.35	145.74 (±0.38)	-9.64 (±0.2.51)	0.38
318.15	130.46 (±0.30)	-16.91 (±1.76)	0.32	149.28 (±0.34)	-10.48 (±1.76)	0.31

Units: m, $\mathrm{mol \cdot kg^{-1}}$; ϕ_V, $10^6 \mathrm{m^3 \cdot mol^{-1}}$; S_V^*, $10^6 \mathrm{m^3 \cdot kg^{1/.2} \cdot mol^{-3/2}}$ and σ, $10^6 \mathrm{m^3 \cdot mol^{-1}}$. [a]Uracil molalities in various aqueous solutions. Standard errors are given the parenthesis.

The values of ϕ_V^0 and S_V^* values for the solutes in various aqueous uracil solutions at the experimental temperatures are listed in Table 5.3. It shows that for the solutions containing paracetamol, ϕ_V^0 values are positive and such values increase as the experimental temperature and the uracil molalities in the aqueous solutions increase. These facts indicate presence of strong solute-solvent interactions, which are probably influenced by certain polar interactions and hydrogen bond interactions.[38] For the solutions containing caffeine; however, ϕ_V^0 values are positive for solutions with caffeine and such values increase as the experimental temperature increases but decrease when uracil molalities in the aqueous solutions increase after initial increase at the advent of uracil in the solutions. Therefore, there exists strong solute-solvent interactions that further strengthen at higher temperatures and such interactions become weaker at higher uracil molalities in the ternary solutions with caffeine. It is reported that caffeine aggregates by plane-to-plane staking in aqueous solutions[29] and spectroscopic studies confirmed that aqueous caffeine solutions show more than two molecular species in equilibrium. At low concentration caffeine shows association only within monomers but at higher concentration, it can have trimmers and higher associations, which may be present in the present aqueous solutions. Also it has two H-acceptor groups with no donor groups.[39] In contrust, both H-donor and acceptor groups are present in uracil, thus uracil is exposed to greater H-bond interactions in these aqueous solutions. Therefore, in the aqueous solutions of caffeine and uracil, uracil will experience more H-bonding interactions and this will decrease caffeine-water interactions; thus explaining the observed decrease in ϕ_V values at higher caffeine concentration at experimental temperatures. Figure 5.3 illustrates the variation of ϕ_V^0 values with the solvent composition for these solutes.

The S_V^* values indicate the presence of pair-wise interactions amongst the solvated species (*i.e,* solute-cosolute and solute-solute) in solution state.[40] S_V^* values were negative for both the solute solutions in aqueous and aqueous uracil solutions. While S_V^* values decrease as the uracil molalities increase for the aqueous solutions containing paracetamol, such values increase for the ternary solutions containing caffeine except those for the aqueous caffeine solutions containing no uracil.

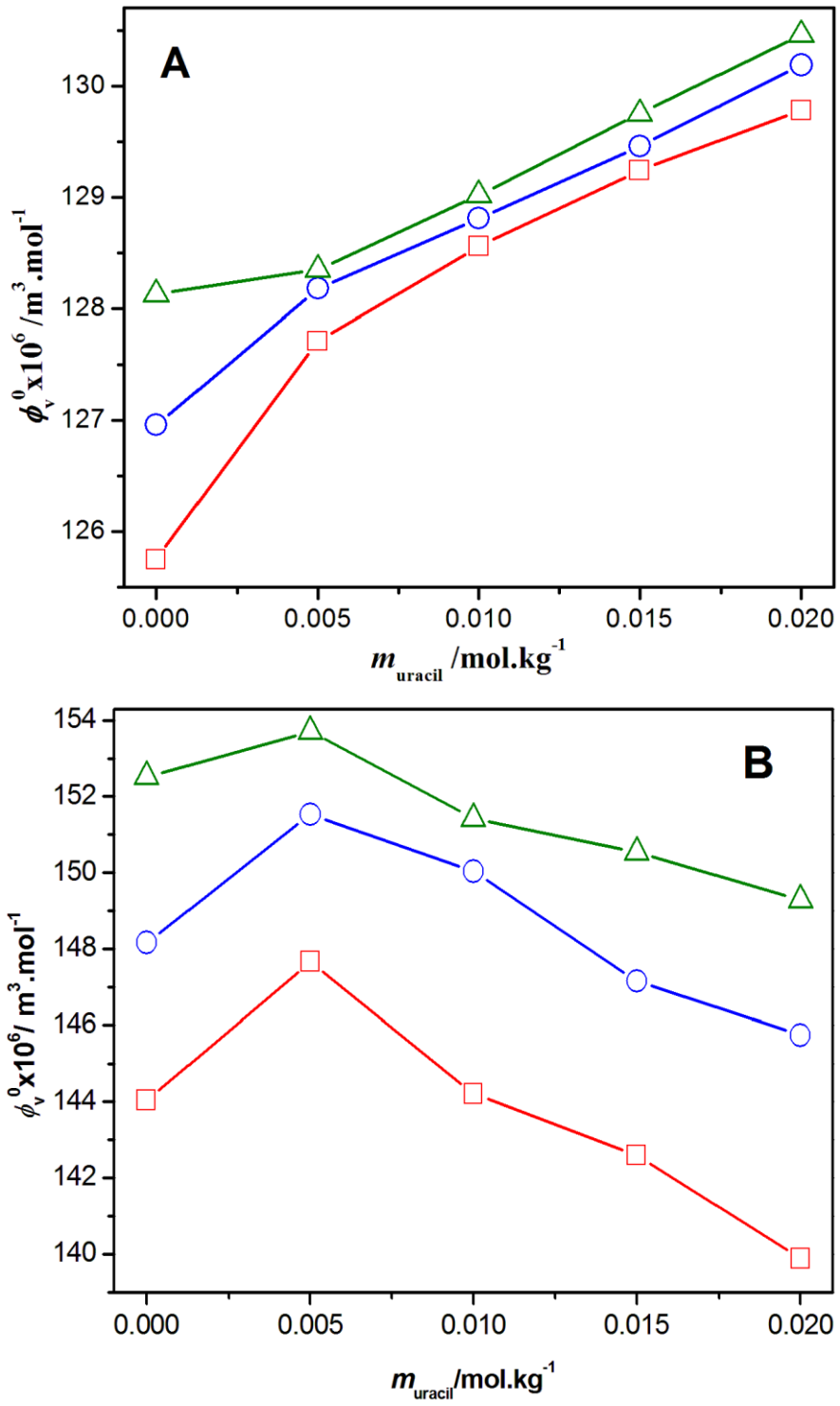

Fig 5.3. Standard partial molar volumes (ϕ_V^0) of the solutes against various uracil molalities (m_{uracil}) in the aqueous solutions at the experimental temperatures. Solutes: A, paracetamol; B, caffeine. Temperatures: □, 298.15 K; ○, 308.15 K and Δ, 318.15 K.

So there exists weak pair-wise interactions between the solute-cosolute or the solute-solute species in the solutions of both the solutes but such interactions decrease at higher uracil molalities for paracetamol due to solute induced hydrophobic hydration and base stacking interactions in water.[41] But for the solutions with caffeine S_V^* values increase as the uracil molalities in the solutions increase. This fact indicates increase in solute-solute or solute-cosolute interactions due to hydrogen bond interactions. Anyway, for these solute solutions such pair-wise interactions further decrease at higher experimental temperatures due to more thermal agitation of the solute or cosolute molecules at higher temperatures.

5.3.2. Apparent molar expansibilities

The apparent molar expansibilities (ϕ_E) of the experimental solute solutions were derived from the expression: [38]

$$\phi_E = \alpha\phi_V + \frac{1000(\alpha - \alpha_1)}{m\rho_1} \qquad (3)$$

where α $[= -\rho^{-1}(\partial\rho/\partial T)_P]$ and α_1 $[= -\rho_1^{-1}(\partial\rho_1/\partial T)_P]$ are the isobaric thermal expansion coefficient of the solution and the solvent, respectively and other symbols carry their usual significance. The uncertainties in the isobaric thermal expansion coefficients and the apparent molar expansibilities (ϕ_E) were within $\pm(2-5)\times10^{-5}\,K^{-1}$ and the uncertainty in ϕ_E values was evaluated to be within $\pm(0.001\text{-}0.022)\times10^{-6}\,m^3\cdot mol^{-1}\cdot K^{-1}$, respectively. The standard partial molar expansibilities (ϕ_E^0) for the solute solutions were determined using the following the expression: [38]

$$\phi_E = \phi_E^0 + S_E\sqrt{m} \qquad (4)$$

The $(\partial\phi_E^0/\partial T)_P$ values were determined from the slope of a linear fit of ϕ_E^0 values against experimental temperature (T) and the corresponding correlation coefficients (R^2) were well within 0.892-0.999. The ϕ_E^0 values of the experimental solutions of the solutes are summarized in Table 5.4. The ϕ_E^0 values provide an idea of the extent of solute-solvent interactions and also interpret the long-range structure making or breaking capacity of solutes in solution phase.[41]

Table 5.4. Partial molar expansibilities (ϕ_E^0), the slopes (S_E) and the $(\partial\phi_E^0/\partial T)_P$ values for the solutes in various aqueous uracil solutions at the experimental temperatures.

Parameters	T	Paracetamol solutions	Caffeine solutions
		0.000 [a]	0.000 [a]
ϕ_E^0	298.15	7.59 (±0.06)	20.01 (±0.06)
	308.15	7.75 (±0.06)	20.21 (±0.07)
	318.15	7.73 (±0.05)	20.43 (±0.05)
S_E	298.15	-2.78 (±0.03)	-2.26 (±0.03)
	308.15	-2.81 (±0.03)	-2.27 (±0.04)
	318.15	-2.83 (±0.04)	-2.31 (±0.04)
$(\partial\phi_E^0/\partial T)_P$		7.85	20.95
		0.005 [a]	0.005 [a]
ϕ_E^0	298.15	-1.19 (±0.06)	27.89 (±0.08)
	308.15	-1.20 (±0.08)	28.30 (±0.06)
	318.15	-1.22 (±0.08)	28.59 (±0.08)
S_E	298.15	1.11 (±0.04)	-4.06 (±0.04)
	308.15	1.14 (±0.04)	-4.11 (±0.06)
	318.15	1.15 (±0.02)	-4.16 (±0.02)
$(\partial\phi_E^0/\partial T)_P$		-1.26	29.12
		0.010 [a]	0.010 [a]
ϕ_E^0	298.15	-2.16 (±0.01)	30.75 (±0.03)
	308.15	-2.18 (±0.02)	31.12 (±0.02)
	318.15	-2.21 (±0.03)	31.38 (±0.03)
S_E	298.15	1.12 (±0.06)	-3.39 (±0.07)
	308.15	1.13 (±0.07)	-3.42 (±0.06)
	318.15	1.15 (±0.06)	-3.47 (±0.05)
$(\partial\phi_E^0/\partial T)_P$		-2.26	31.96

		0.015 [a]	0.015 [a]
ϕ_E^0	298.15	-1.86 (±0.02)	34.55 (±0.02)
	308.15	-1.89 (±0.02)	34.91 (±0.02)
	318.15	-1.91 (±0.01)	35.26 (±0.03)
S_E	298.15	1.08 (±0.05)	-1.48 (±0.06)
	308.15	1.12 (±0.06)	-1.51 (±0.05)
	318.15	1.13 (±0.05)	-1.52 (±0.06)
$(\partial \phi_E^0 / \partial T)_P$		-1.95	35.62
		0.020 [a]	0.020 [a]
ϕ_E^0	298.15	-1.06 (±0.02)	41.88 (±0.02)
	308.15	-1.07 (±0.01)	42.31 (±0.01)
	318.15	-1.11 (±0.02)	42.74 (±0.02)
S_E	298.15	0.95 (±0.06)	-1.37 (±0.02)
	308.15	0.96 (±0.06)	-1.41 (±0.02)
	318.15	0.97 (±0.06)	-1.42 (±0.01)
$(\partial \phi_E^0 / \partial T)_P$		-1.12	42.93

Units: T, K; ϕ_E^0, $10^{-5}\,m^3 \cdot mol^{-1} \cdot K^{-1}$; S_E, $10^{-5}\,m^3 \cdot kg^{1/2} \cdot mol^{-1} \cdot K^{-1}$ and $(\partial \phi_E^0 / \partial T)_P$, $10^{-8}\,m^3 \cdot mol^{-1} \cdot K^{-2}$. [a]Uracil molalities in various aqueous solutions in $mol \cdot kg^{-1}$. Standard errors are given the parenthesis.

Table 5.4 shows that ϕ_E^0 values are positive or slight negative and increase or decrease with the experiment temperatures. Such tendencies of the ϕ_E^0 values may be attributed to the structural perturbations by the gradual appearance or disappearance of caging or packing effects in solution.[42] Hepler[43] proposed that if the term $\left(\partial \phi_E^0 / \partial T\right)_P$ is positive or slight negative, the solute acts as a structure maker, otherwise it is a structure breaker. Therefore, both the solutes seem to act as net structure promoter in aqueous uracil solutions.

5.3.3. Standard transfer volumes

The standard partial molar volumes of transfer ($\Delta_t\phi_V^0$) can be had from the following expression:

$$\Delta_t\phi_V^0 = \phi_V^0[\text{Solute} + \text{water} + \text{uracil}] - \phi_V^0[\text{Solute} + \text{water}] \quad (5)$$

Since at infinite dilution the interactions amongst the individual solute molecules do not exist, so the $\Delta_t\phi_V^0$ values yield valuable information of the solute-cosolute interactions. The $\Delta_t\phi_V^0$ values for both the solute solutions are presented in Figure 5.4 against the various uracil molalities in the aqueous solutions. $\Delta_t\phi_V^0$ values are mostly positive for the solutions with paracetamol at all the experimental temperatures and increase as the uracil molalities in the ternary solutions increase. For the solutions with caffeine the $\Delta_t\phi_V^0$ values are positive when 0.005 and 0.010 molal aqueous uracil solutions were used as solvents but are negative when 0.015 and 0.020 molal aqueous uracil solutions were used as solvents. Anyway, these values decrease as the uracil molalities for all the ternary aqueous solutions with caffeine. According to the cosphere overlap model (Friedman and Krishnan[44]), the overlap of hydration cospheres of two polar species leads to volume expansion but that of hydration cospheres of hydrophobic-hydrophobic and polar-hydrophobic groups lead to volume contraction. Thus the positive $\Delta_t\phi_V^0$ values for the solutions with paracetamol manifests the dominance of the polar-hydrophilic and hydrophilic-hydrophilic group interactions over the polar-hydrophobic, hydrophobic-hydrophobic and hydrophilic-hydrophobic interactions; the net effect is that the electrostriction of water by paracetamol decreases resulting into volume expansion and this effect enhance at higher uracil molalities in the ternary solutions favouring base stacking interactions (for uracil) in water. In case of the solutions with caffeine the observed $\Delta_t\phi_V^0$ values although manifests dominance of the polar-hydrophobic, hydrophobic-hydrophobic and hydrophilic-hydrophobic interactions and the net effect of the overlap of the hydration cospheres of caffeine and uracil increases the electrostriction of water by caffeine and this effect further decreases with uracil molarities in the ternary solutions with caffeine.

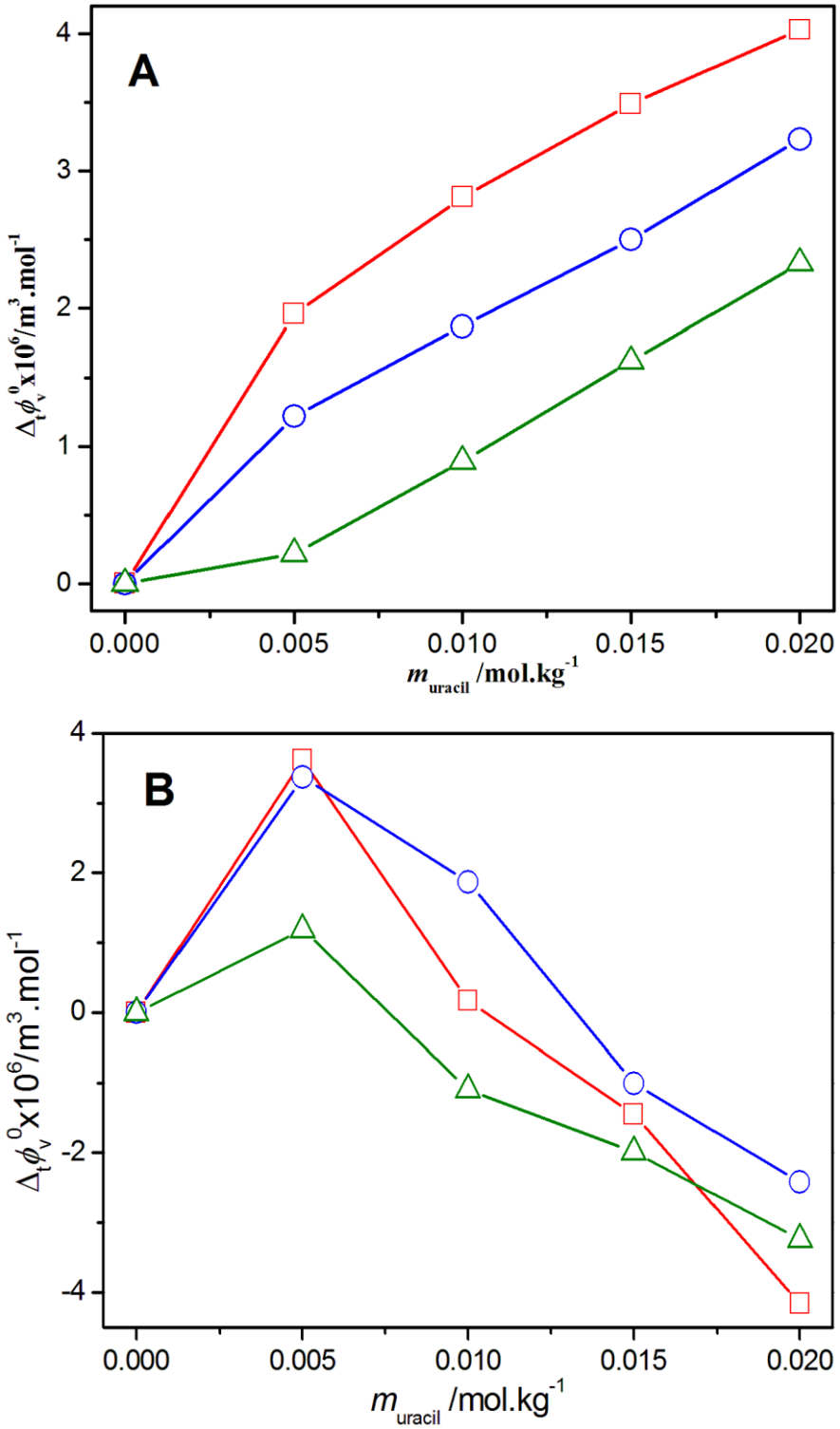

Fig 5.4. Standard partial molar volume of transfer ($\Delta_t\phi_V^0$) for the vsolutes *versus* molality of uracil (m_{uracil}) in the aqueous solutions at the experimental temperatures (□, 298.15 K; ○, 308.15 K and Δ, 318.15 K). Solutes: A, paracetamol; B, caffeine.

The partial molar volumes (ϕ_V^0) of a solute can further be judged in terms of the following model: [45,46]

$$\phi_V^0 = \phi_{VW} + \phi_{Void} - \phi_S \qquad (6)$$

where the terms ϕ_{VW}, ϕ_{Void} and ϕ_S stand for the van der Waals volume, the volume of the void spaces and the shrinkage volume, respectively. The ϕ_{VW} and ϕ_{Void} for a solute can be considered to be of same magnitudes in pure water and aqueous uracil solutions. The increase in ϕ_V^0 values and the resulting positive $\Delta_t\phi_V^0$ values suggest the shrinkage volume (ϕ_S) decrease of water by paracetamol in co-existence of uracil. So it means that uracil probably desolvates paracetamol in water and the interactions between paracetamol and uracil approximates as: (i) the hydrophilic-polar group interactions among the -OH groups of paracetamol and the polar groups of uracil, (ii) hydrophilic-hydrophilic interactions among the -OH groups of paracetamol and –NH part of uracil through H- bonds, (iii) hydrophilic- hydrophilic interactions between -NH part of uracil and O-part (ketonic) of paracetamol through H-bonds, (iv) hydrophilic-hydrophobic interactions among the -OH groups of paracetamol and non-polar groups in uracil and finally (v) hydrophobic-hydrophobic interactions between non-polar groups of paracetamol and uracil. Here interactions of types (i), (ii) can have positive contributions but interactions of types (iii), (iv) and (v) can have negative contribution to the ϕ_V^0 values. So positive ϕ_V^0 values signifies that the polar group interactions spur the polar–hydrophobic interactions and thus decreases the electrostriction of water by paracetamol and yield positive contributions to $\Delta_t\phi_V^0$ values.

In case of the solutions with caffeine the decrease in ϕ_V^0 values and the resulting negative $\Delta_t\phi_V^0$ values suggest the shrinkage volume (ϕ_S) increase of water by caffeine in co-existence of uracil. Here the interactions between caffeine and uracil approximates as: i) H-bond interactions involving -NH group of uracil with N-atom of caffeine through H-bond, (ii) H-bond interactions involving CO groups of caffeine with -NH group of uracil, iii) polar-hydrophobic interaction between polar parts of uracil and non-polar part of caffeine molecules and (iv) hydrophobic-hydrophobic interactions between non-polar parts of caffeine and uracil. Therefore all these effects

ultimately lead to negative $\Delta_t\phi_V^0$ values at higher uracil molalities in the aqueous solutions with caffeine.

5.3.4. UV-Vis spectroscopy

The absorption spectra of the solutes in aqueous uracil ($1\times10^{-4}\,\text{mol}\cdot\text{L}^{-1}$) solutions at 298.15 K are illustrated in Figures 5.5 and 5.6. The absorption spectrum of aqueous uracil ($1\times10^{-4}\,\text{mol}\cdot\text{L}^{-1}$) solution showed a characteristic absorption band at 260 nm. However, on stepwise addition of the solutes solution (concentration $1\times10^{-4}\,\text{mol}\cdot\text{L}^{-1}$ and 20 μL at each step) absorption bands gradually appeared at 243 nm[47] and 273 nm,[48] respectively for the solutions with paracetamol and caffeine. These bands are due to the $n\rightarrow\pi^*$ transitions in paracetamol and caffeine. The absorption spectra of the solutes in various aqueous uracil solutions at 298.15 K are illustrated in Figures 5.5 and 5.6. It is apparent from these figures that while the band at 243 nm for the solutions of paracetamol red shifted to around 250 nm, the band at 273 nm for the solutions of caffeine blue shifted to 263 nm as the uracil molalities (20 μL of $1\times10^{-4}\,\text{mol}\cdot\text{L}^{-1}$ solution in each step) in respective solutions were augmented. All these shifts in peak positions and their intensity changes well corroborate with the earlier results and signifies the presence of strong solute-solvent and other possible interactions as discussed earlier.

5.3.5. Viscometric results

As both the solutes are non-electrolyte, viscosities of their solutions were treated with the modified Jones-Dole equation:[49,50]

$$\eta_r = 1 + Bc \qquad (7)$$

where $\eta_r = \eta/\eta_1$; η_1, η and c stand for the solvent viscosity, the solution viscosity and molarity of the solutes in the studied solutions, respectively. The viscosity *B*-coefficients were determined from the slopes using weighted least squares linear regressions with regression coefficients (R^2) = 0.980-0.999 and such values for both the solutes are listed in Table 5.5. It manifests that the viscosity *B*- coefficients of both the solutes are positive suggesting the presence of strong solute-solvent interactions[51,52] in the studied solutions.

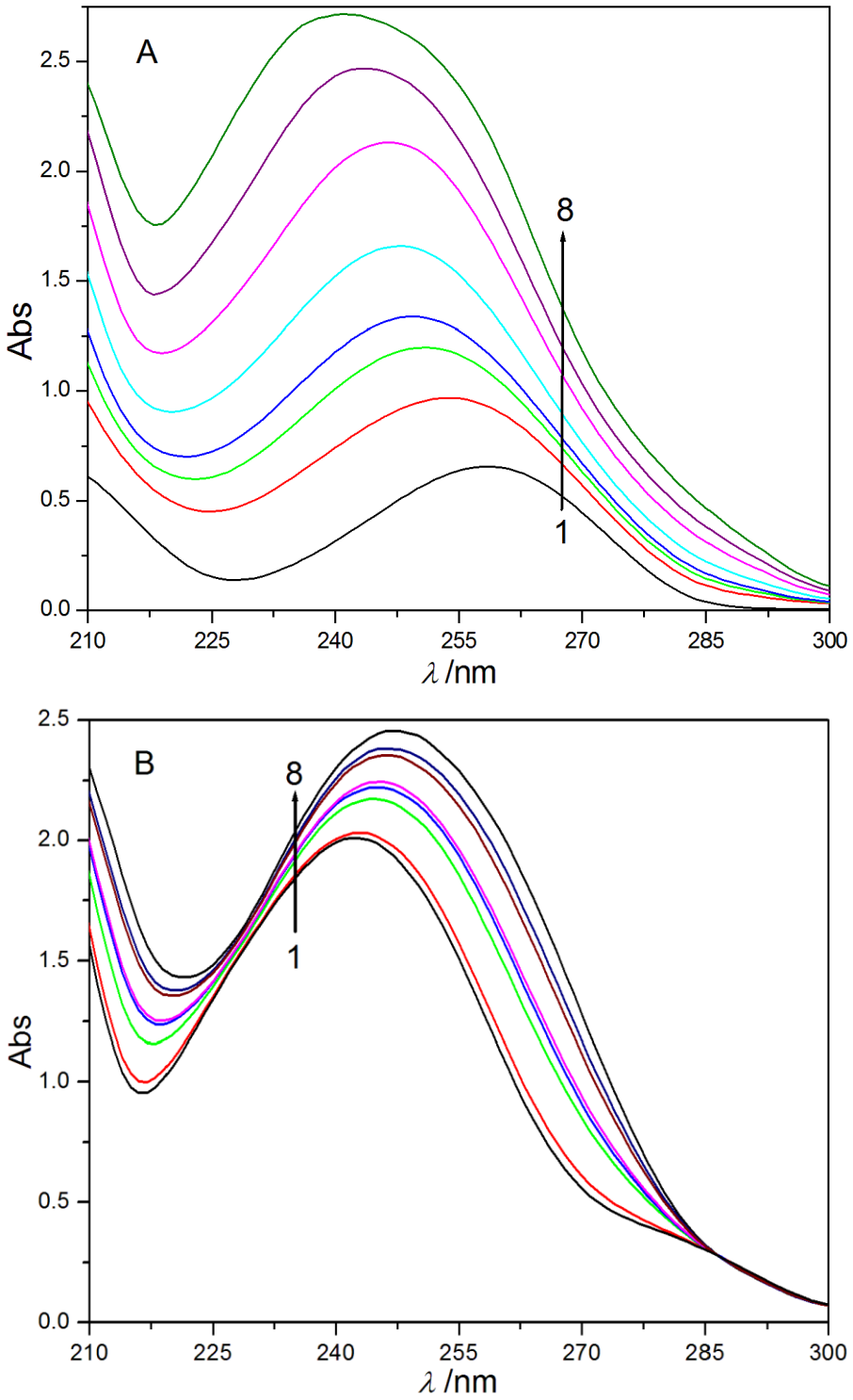

Fig 5.5. Absorption spectra of paracetamol in the aqueous uracil ($1 \cdot 10^{-4}\,\mathrm{mol \cdot L^{-1}}$) solution at 298.15 K. A, various molarities of paracetamol ($10^{-4}\,\mathrm{mol \cdot L^{-1}}$) in solutions: 1, 0.000; 2, 0.0292; 3, 0.0475; 4, 0.0653; 5, 0.091; 6, 0.1303; 7, 0.1524; 8, 0.1795; B, various molarities of uracil ($10^{-4}\,\mathrm{mol \cdot L^{-1}}$) in aqueous solutions: 1, 0.0000; 2, 0.0098; 3, 0.029; 4, 0.0472; 5, 0.0565; 6, 0.0741; 7, 0.0910; 8, 0.1071.

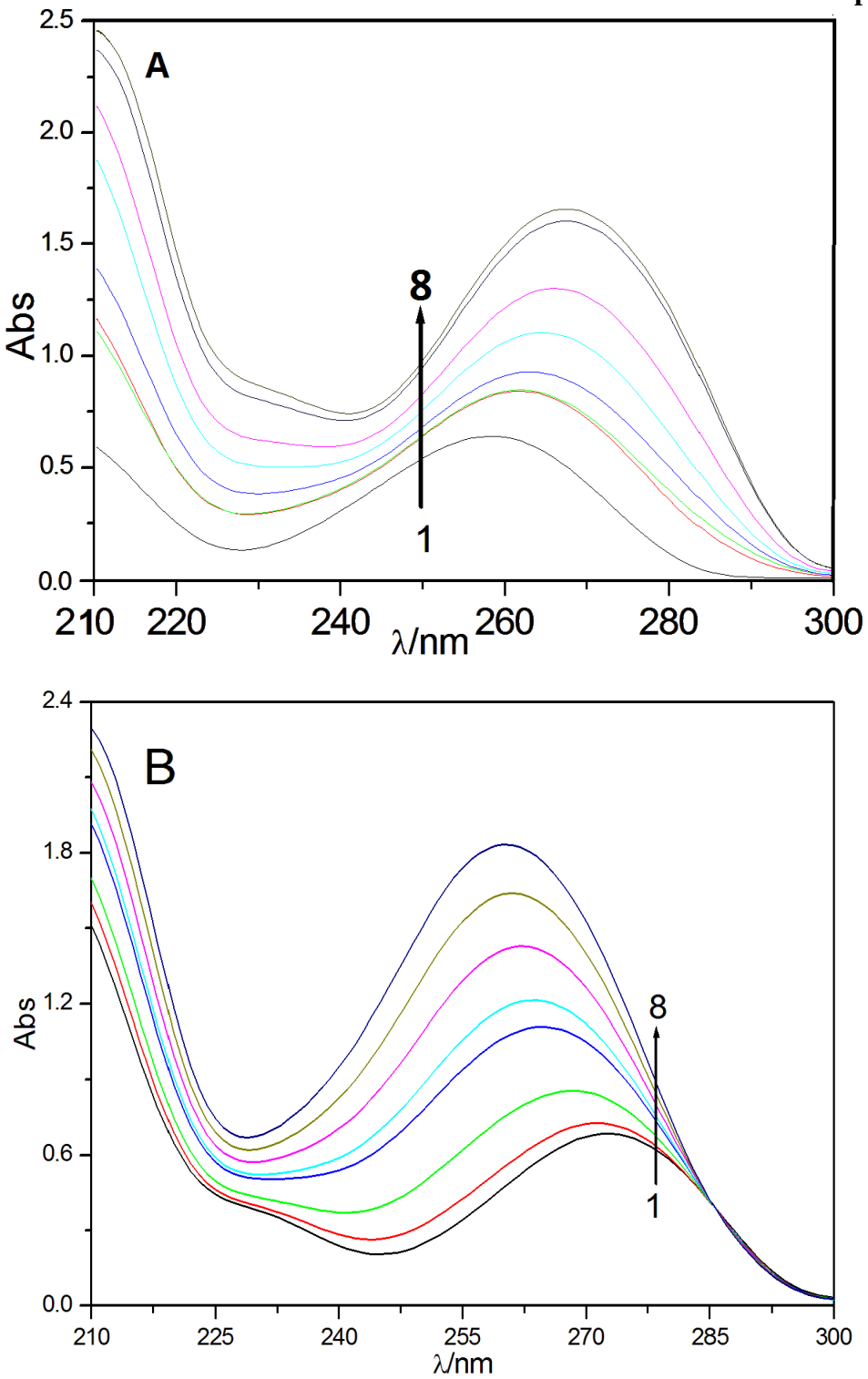

Fig 5.6. Absorption spectra of caffeine in the aqueous uracil ($1\cdot10^{-4}\,mol\cdot L^{-1}$) solution at 298.15 K. A, various molarities of caffeine ($10^{-4}\,mol\cdot L^{-1}$) in solutions: 1, 0.000; 2, 0.0297; 3, 0.0594; 4, 0.0687; 5, 0.0882; 6, 0.0975; 7, 0.1352; 8, 0.1543; B, various molarities of uracil ($10^{-4}\,mol\cdot L^{-1}$) in aqueous solutions: 1, 0.000; 2, 0.009; 3, 0.019; 4, 0.0296; 5, 0.0385; 6, 0.0464; 7, 0.0675; 8, 0.075.

Table 5.5. Viscosity *B*-coefficients of the solutes, the correlation coefficients (R^2), standard deviations (σ) and solvation number (S_n) in various aqueous uracil solutions at 298.15, 308.15 and 318.15 K.

	298.15 K	308.15 K	318.15 K	298.15 K	308.15 K	318.15 K
	Paracetamol solutions			Caffeine solutions		
		0.000 [a]			0.000 [a]	
B	0.452 (±0.025)	0.529 (±0.026)	0.637 (±0.005)	0.540 (±0.025)	0.616 (±0.026	1.106 (±0.006)
R^2	0.9803	0.9838	0.9992	0.9903	0.9838	0.9992
σ	0.003	0.004	0.002	0.003	0.004	0.002
S_n	3.59 (±0.02)	4.17 (±0.03)	4.97 (±0.02)	3.75 (±0.03)	4.16 (±0.02)	7.25 (±0.01)
		0.005 [a]			0.005 [a]	
B	0.503 (±0.017)	0.557 (±0.026)	0.657](±0.022)	0.422 (±0.017)	0.457 (±0.026)	0.549 (±0.022)
R^2	0.9947	0.9891	0.9942	0.9957	0.9837	0.9953
σ	0.003	0.004	0.004	0.003	0.004	0.004
S_n	3.94 (±0.04)	4.34 (±0.03)	5.12 (±0.03)	2.86 (±0.02)	3.01 (±0.02)	3.57 (±0.01)
		0.010 [a]			0.010 [a]	
B	0.521 (±0.018)	0.560 (±0.015)	0.661 (±0.019)	0.409 (±0.018)	0.440 (±0.015)	0.528 (±0.019)
R^2	0.9944	0.9966	0.9957	0.9945	0.9967	0.9956
σ	0.003	0.003	0.003	0.003	0.003	0.003
S_n	4.05 (±0.04)	4.35 (±0.04)	5.12 (±0.02)	2.84 (±0.02)	2.93 (±0.03)	3.49 (±0.01)
		0.015 [a]			0.015 [a]	
B	0.531 (±0.012)	0.572 (±0.013)	0.667 (±0.013)	0.385 (±0.012)	0.415 (±0.013)	0.463 (±0.013)
R^2	0.9978	0.9977	0.9982	0.9976	0.9973	0.9982
σ	0.002	0.002	0.002	0.002	0.002	0.002
S_n	4.11 (±0.036)	4.41 (±0.02)	5.14 (±0.02)	2.70 (±0.01)	2.82 (±0.03)	3.08 (±0.01)
		0.020 [a]			0.020 [a]	
B	0.540 (±0.009)	0.579 (±0.019)	0.679 (±0.019)	0.354 (±0.009)	0.389 (±0.019)	0.453 (±0.019)
R^2	0.9989	0.9955	0.9966	0.9990	0.9994	0.9988
σ	0.002	0.003	0.003	0.002	0.003	0.003
S_n	4.16 (±0.03)	4.45 (±0.02)	5.21 (±0.03)	2.53 (±0.02)	2.67 (±0.01)	3.03 (±0.01)

[a] Uracil molalities in various aqueous solutions in $\mathrm{mol \cdot kg^{-1}}$.

Unit: B, $10^3 \mathrm{m^3 \cdot mol^{-1}}$. Standard errors are given the parenthesis.

These interactions strengthen further as the experimental temperature increases for both the solutes in respective solutions. Interestingly while the viscosity *B*-coefficients increase for solutions with paracetamol, such values decrease for the solutions with caffeine as the uracil molalities in the respective ternary solutions increase. Such changes of viscosity *B*-coefficients indicate that the solutes have orientation effects in their solvation layer[54] and stand in support of solute-solvent interactions discussed earlier in the terms of ϕ_V^0 values. Solvation or hydration numbers (S_n) were also determined using the relation:[55] $S_n = B/\phi_V^0$. S_n values indicate the formation of a primary solvation sphere around a solute. The range $S_n \approx 0-2.5$ indicates unsolvated solutes[55] and $S_n > 2.5$ suggest that the solute remain solvated with the primary solvation sphere in the aqueous solutions. Therefore the S_n values (as given in Table 5.5) suggest that both the solutes exist as solvated with primary solvation spheres in the aqueous solutions studied and higher temperature favors their solvation.

5.3.6. Thermodynamics of viscous flow

In accordance with the Feakin's transition state theory of relative viscosity, the free energy for activation per mole of a solute ($\Delta\mu_2^{0\neq}$) for its viscous flow can be obtained from the following expression:[53]

$$\Delta\mu_2^{0\neq} = \Delta\mu_1^{0\neq} + RT(1000B + \phi_{V,2}^0 - \phi_{V,1}^0)/\phi_{V,1}^0 \qquad (8)$$

where $\phi_{V,1}^0$ and $\phi_{V,2}^0$ stand for the partial molar volumes of the solvent and solute, respectively. The free energy of activation per mole of the solvent ($\Delta\mu_1^{0\neq}$) for viscous flow is given by the expression:[53-55]

$$\Delta\mu_1^{0\neq} = \Delta G_1^{0\neq} = RT\ln(\eta_1\phi_{V,1}^0/hN_A) \qquad (9)$$

where N_A is the Avogadro's number and all other symbols carry their usual significance. The entropy ($\Delta S_2^{0\neq}$) and enthalpy ($\Delta H_2^{0\neq}$) of activation for the ternary solutions were also obtained from the following relations:[53,54]

$$\Delta S_2^{0\#} = -d(\Delta\mu_2^{0\#})/dT \qquad (10)$$

$$\Delta H_2^{0\neq} = \Delta\mu_2^{0\neq} + T\Delta S_2^{0\neq} \qquad (11)$$

The parameters $\Delta\mu_1^{0\neq}$, $\Delta\mu_2^{0\neq}$, $\Delta H_2^{0\neq}$ and $T\Delta S_2^{0\neq}$ are listed in Table 5.6. It shows that $\Delta\mu_1^{0\neq}$ values are almost same irrespective of the experimental temperatures and

solvent compositions. Further, the $\Delta\mu_2^{0\neq}$ values basically depend on the viscosity *B*-coefficients and $(\phi_{V,2}^0 - \phi_{V,1}^0)$ values. The $\Delta\mu_2^{0\neq}$ values signify both the changes in the free energy of activation of solvent molecules at the advent of the solute molecules and the contribution from the movement of the solute molecules for all the aqueous solutions studied. The $\Delta\mu_2^{0\neq}$ values were positive and larger than $\Delta\mu_1^{0\neq}$ values at all the experimental temperatures for all the aqueous solutions studied. This fact suggests that solute-solvent interactions are stronger in the ground state than those in the transition state and the solvation of the solutes is favoured less energetically in the transition state. The greater the value of $\Delta\mu_2^{0\neq}$, the larger is the structure-promoting capacity of a solute and the structure making effect of the solutes is evident from the positive $\Delta\mu_2^{0\neq}$ values in aqueous solutions studied. However, negative $\Delta S_2^{0\neq}$ and $\Delta H_2^{0\neq}$ (Table 5.5) signifies that the transition state formation involves bond formation (between the solute and solvent molecules) resulting into decrease in order and exothermic viscous flow.

5.4. Conclusion

It has been found that the partial molar volumes (ϕ_V^0) and viscosity *B*-coefficients of both the solutes in the aqueous uracil solutions are positive. These results unveil that the solute-solvent interactions are strong and there is structural enhancement at even higher temperatures. Again for the studied aqueous solutions, S_V^* values are found to be negative and always lesser than the ϕ_V^0 values, *i.e*, the solute-solvent interactions spur the solute-solute interactions. Standard transfer volumes ($\Delta_t\phi_V^0$) are all positive for the solutions with paracetamol and such values increase when uracil molalities in the ternary solutions increase at all the experimental temperatures. $\Delta_t\phi_V^0$ values for the solutions with caffeine are positive initially; however, such values decrease as the uracil molalities in the ternary solutions increase and finally they become negative. These values are suggestive of the presence of polar-hydrophobic, hydrophilic-hydrophobic and hydrophobic-hydrophobic interactions and theses interactions result into volume contraction by the increased

Table 5.6. $\Delta\mu_1^{0\#}$, $\Delta\mu_2^{0\#}$, $T\Delta S_2^{0\#}$ and $\Delta H_2^{0\#}$ values for the solutes in various aqueous uracil solutions at 298.15, 308.15 and 318.15 K.

	298.15 K	308.15 K	318.15 K	298.15 K	308.15 K	318.15 K
	Paracetamol solutions			Caffeine solutions		
		0.000 [a]			0.000 [a]	
$\Delta\mu_1^{0\#}$	9.12 (±0.02)	8.89 (±0.01)	8.72 (±0.02)	9.12 (±0.02)	8.89 (±0.02)	8.72 (±0.01)
$\Delta\mu_2^{0\#}$	85.85 (±0.15)	98.85 (±0.14)	116.39 (±0.12)	100.22 (±0.12)	114.04 (±0.16)	187.35 (±0.14)
$T\Delta S_2^{0\#}$	-455.45 (±1.68)	-470.76 (±1.64)	-486.02 (±1.67)	-1298.88 (±1.69)	-1342.45 (±1.75)	-1386.10 (±1.67)
$\Delta H_2^{0\#}$	-369.62 (±2.22)	-371.87 (±2.21)	-369.61 (±2.18)	-1198.56 (±2.25)	-1228.42 (±2.19)	-1198.67 (±2.17)
		0.005 [a]			0.005 [a]	
$\Delta\mu_1^{0\#}$	9.17 (±0.01)	8.94 (±0.02)	8.76 (±0.01)	9.17 (±0.02)	8.94 (±0.01)	8.76 (±0.03)
$\Delta\mu_2^{0\#}$	92.87 (±0.12)	102.81 (±0.14)	119.11 (±0.11)	84.48 (±0.16)	92.01 (±0.18)	107.27 (±0.17)
$T\Delta S_2^{0\#}$	-391.18 (±1.61)	-404.28 (±1.59)	-417.41 (±1.54)	-339.46 (±1.67)	-350.85 (±1.64)	-362.24 (±1.55)
$\Delta H_2^{0\#}$	-298.29 (±2.18)	-301.48 (±1.85)	-298.30 (±1.84)	-254.95 (±1.88)	-258.82 (±1.87)	-254.96 (±1.78)
		0.010 [a]			0.010 [a]	
$\Delta\mu_1^{0\#}$	9.18 (±0.02)	8.95 (±0.01)	8.77 (±0.02)	9.18 (±0.02)	8.95 (±0.01)	8.77 (±0.03)
$\Delta\mu_2^{0\#}$	95.42 (±0.17)	103.36 (±0.18)	119.97 (±0.19)	82.26 (±0.15)	89.46 (±0.17)	103.94 (±0.19)
$T\Delta S_2^{0\#}$	-365.85 (±1.75)	-378.12 (±1.74)	-390.37 (±1.76)	-323.09 (±1.72)	-333.91 (±1.71)	-344.76 (±1.76)
$\Delta H_2^{0\#}$	-270.41 (±2.19)	-274.73 (±2.18)	-270.41 (±2.16)	-240.81 (±2.21)	-244.48 (±2.18)	-240.81 (±2.17)
		0.015 [a]			0.015 [a]	
$\Delta\mu_1^{0\#}$	9.18 (±0.01)	8.95 (±0.02)	8.78 (±0.01)	9.18 (±0.02)	8.96 (±0.01)	8.79 (±0.01)
$\Delta\mu_2^{0\#}$	97.52 (±0.12)	105.27 (±0.13)	120.93 (±0.11)	78.79 (±0.17)	85.53 (±0.12)	94.48 (±0.17)
$T\Delta S_2^{0\#}$	-348.98 (±1.81)	-360.68 (±1.84)	372.39 (±1.87)	-233.87 (±1.78)	-241.71 (±1.79)	-249.56 (±1.78)
$\Delta H_2^{0\#}$	-255.45 (±2.21)	-258.51 (±2.27)	-255.45 (±2.25)	-155.07 (±2.24)	-156.17 (±2.21)	-155.06 (±2.25)
		0.020 [a]			0.020 [a]	
$\Delta\mu_1^{0\#}$	9.19 (±0.01)	8.96 (±0.02)	8.79 (±0.01)	9.19 (±0.02)	8.96 (±0.01)	8.79 (±0.02)
$\Delta\mu_2^{0\#}$	98.31 (±0.13)	106.28 (±0.13)	122.78 (±0.14)	74.20 (±0.16)	81.76 (±0.15)	92.88 (±0.13)
$T\Delta S_2^{0\#}$	-364.68 (±1.85)	-376.91 (±1.84)	-389.15 (±1.87)	-278.48 (±1.84)	-287.81 (±1.85)	-297.13 (±1.82)
$\Delta H_2^{0\#}$	-266.36 (±2.25)	-270.62 (±2.21)	-266.36 (±2.22)	-204.27 (±2.23)	-206.13 (±2.24)	-204.27 (±2.23)

Units: $\Delta\mu_1^{0\#}$, $\mathrm{kJ\cdot mol^{-1}}$; $\Delta\mu_2^{0\#}$, $\mathrm{kJ\cdot mol^{-1}}$; $T\Delta S_2^{0\#}$, $\mathrm{kJ\cdot mol^{-1}}$ and $\Delta H_2^{0\#}$, $\mathrm{kJ\cdot mol^{-1}}$. [a]Uracil molalities in various aqueous solutions in $\mathrm{mol\cdot kg^{-1}}$. Standard errors are given the parenthesis.

electrostriction of water by caffeine. These results are also well reflected by ϕ_E^0 and $\left(\partial\phi_E^0/\partial T\right)_p$ values of these solutes and they act as an overall structure maker in aqueous uracil solutions. Further the fact that $\Delta\mu_2^{0\neq} > \Delta\mu_1^{0\neq}$ and the viscosity *B*-coefficients are all positive for the aqueous solutions investigated support the view that the degree of solute-solvent interactions are greater in the ground state than those in the transition state and the solvation of the solutes is less favoured energetically in the transition state. The absorption spectra for the solutes in various aqueous uracil solutions also well corroborate with the above results.

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CHAPTER VI

Probing Subsistence of Host Guest Inclusion Complexes of Oligosaccharides with Allopurinol for Regulatory Release with the Manifestation of Solvation Consequences

6.1. Introduction

Uric acid is end-product of the purine catabolic path. Enzyme xanthine oxido reductase is concerned in formation of uric acid from hypoxanthine and xanthine. Xanthine oxidoreductase exists in two distinct functional forms including xanthine dehydrogenase and xanthine oxidase. [1-7]. Allopurinol or 1, 5-dihydro-4H-pyrazolo [3, 4-d] pyrimidin-4-one, is a purine inhibitor of the enzyme xanthine oxidase. This material as a significant drug for hyperuricemia can inhibit the synthesis of uric acid. [8-11]. Ever since 50 years ago, it has been administered for treatment of gout. In the year of 1946, allopurinol was developed by Elion and colleagues, at Burroughs-Wellcome Company. Allopurinol (ALP) is quickly oxidized by xanthine oxidase to hypoxanthine and xanthine, respectively. ALP after oral administration is rapidly absorbed and has a short half-life in plasma (about 2-3 hours). Therefore we have used all the supramolecular molecules with various cavity sizes to show its controlled release and increase its longevity in the plasma. Xanthine oxidase is a noteworthy biological source of free radical generation and ALP, as an antioxidant, has direct and indirect antioxidant activity on these free radicals. Furthermore, it can scavenge free radicals such as hydroxyl radical and superoxide anion and numerous studies have shown these effects of ALP. This drug revealed advantageous effects in the treatment of some renal disorders both in experimental and clinical trials. [12-17].

Macrocyclic cyclodextrins (enzymic conversion products of starch) were exposed in 1891, and structures were elucidated in the mid-1930s. Their industrial implication become obvious in the 1970s, by now thousands of tons of the three cyclodextrins (α-, β-, and HP-β-CD) and of their chemical derivatives and inclusion complexes are produced industrially. Outer surface of these doughnut-shaped molecules is hydrophilic, but they have an axial open cavity, which is of hydrophobic character and capable of including other apolar molecules (or their moiety) in case of geometric compatibility. This is the real meaning of molecular encapsulation by

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inclusion complex formation. Taking into account that one, and probably largest, field of practical utilization of CDs is based on their solubilizing capacity (mainly in pharmaceutical industry) due attention must be paid to the above-mentioned, and many other CD-related, apparent anomalies by solution chemistry.[18-25]

The goal of this paper is to give comprehensive information about therapeutic effects and the controlled delivery of allopurinol as an antioxidant agent in some diseases including hyperuricemia, renal IRI, nephrotoxicity, gout, contrast-induced nephropathy etc.

6.2. Experimental section

6.2.1 Source and purity of materials

Allopurinol and CD's purchased from Sigma-Aldrich. Mass fractions purity of both was ≥0.99. The used reagents were placed in the desiccators over P_2O_5 to keep them in dry atmosphere. These chemicals were used as received without extra purification (Figure 6.A). The provenance and purity of the chemical used has been depicted chapter III.

6.2.2 Apparatus and procedure

Prior to start of the experimental work we observed that allopurinol soluble in all proportion of aqueous CD solutions. Therefore mother solutions of Allopurinol were prepared by mass (Mettler Toledo AG-285 with uncertainty 0.0003g) and then the working solutions were prepared by mass dilution. Conversions of molarity into molality had been done using experimental density values of respective solutions and adequate precautions were taken to reduce evaporation losses during mixing in the experiment. ^{1}H NMR and 2D ROESY spectra of the solid inclusion complex prepared were recorded in D_2O using Bruker AVANCE 400 MHz instrument. The signals are presented in ppm using residual protonated solvent signal at 4.79ppm in D_2O as internal standard and all the Data are reported as chemical shift.

UV–visible spectroscopic data was carried out using JASCO V-530 UV/VIS Spectro-photometer with wavelength accuracy of ±0.5nm. Spectra were recorded at (297.15±1) K. FTIR spectra's of solid ICs were recorded by Perkin Elmer FT-IR Spectrometer using KBr desk procedure with scanning range of 200 to 4000 cm^{-1}.

Mass Spectroscopic study was taken by JEOL GC MATE II quadruple double focusing mass analyser using electron impact ionization.

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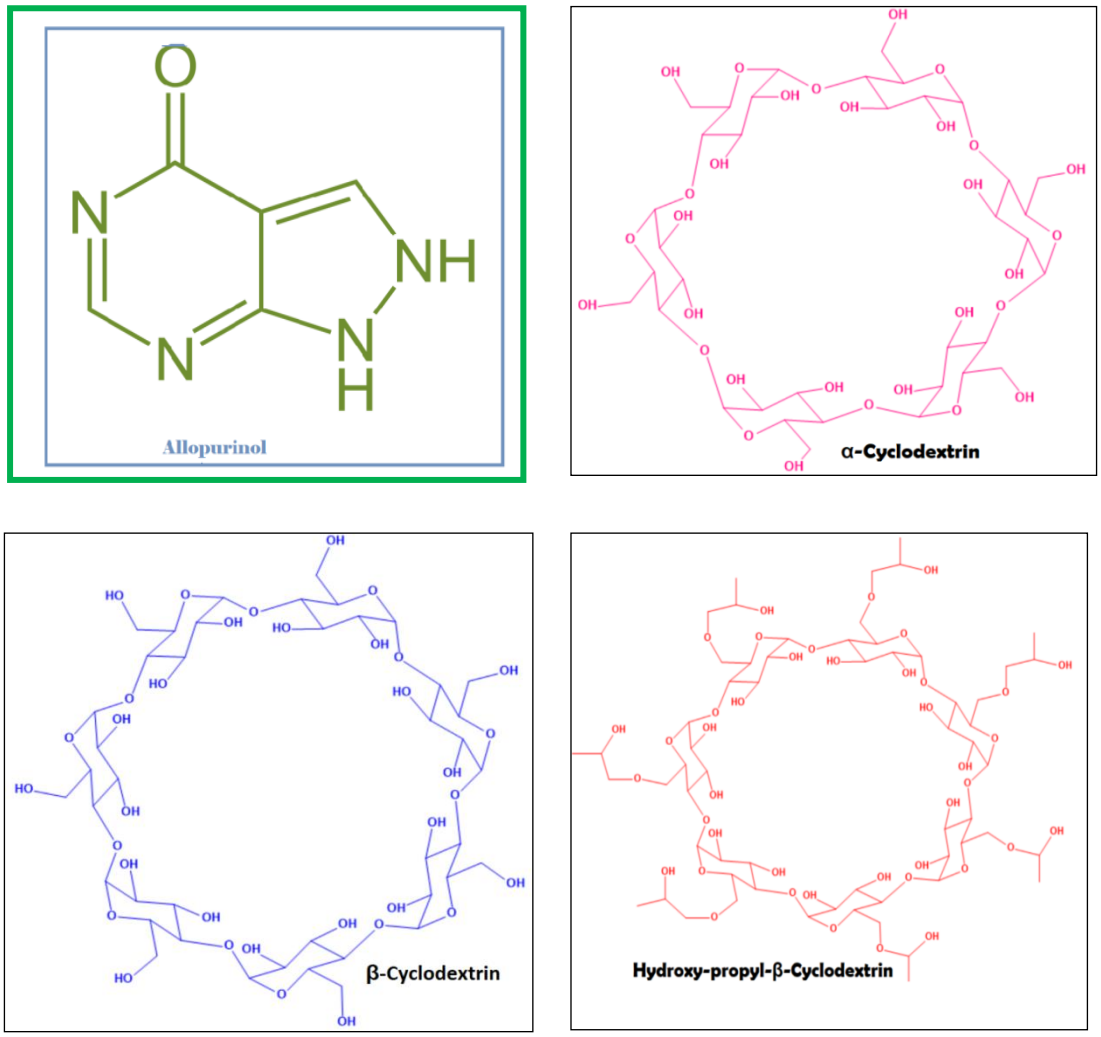

Figure 6.A. Molecular Structures of the hosts and guest.

6.2.3. Preparation of Solid Inclusion Complex:

Preparations of solid inclusion complex 1.34g of CD's were dissolved in 30 ml of triply distilled and degassed water in round bottom flasks. Mixture was stirred to make homogeneous solutions over magnetic stirrer. Alternatively solutions of [ALP] was prepared taking 0.295g of [ALP] in a separate beaker with 15ml water and stirred until homogeneous mixtures were formed. Subsequent to both the homogeneous mixtures are prepared, the ALP solution was then added into CD solution slowly with continuous stirring and after completion of the addition the ALP solution the mixture was stirred for 48 h continuously. Following completion of 48 hours, mixture was allowed to cool at lower temperature when a white solid was

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observed. Then the precipitate was filtered and washed for several times. Lastly, the dry white powder was obtained after drying in oven at 50 °C for 24 h. The solid inclusion complex with all CD's was prepared following the same procedure. The resulting solids of inclusion complex between ALP and CD were found to dissolve in pure distilled water freely. These solids were further analyzed and characterized by means of FTIR, UV-VIS, NMR and ESI-Mass spectroscopic methods.

6.3. Result and discussion:

The experimental physical parameter of mixtures in different mass fractions of ALP solutions at diverse temperatures.

6.3.1 JOB`S Plot:

Job's continuous variation method was applied to determine stoichiometry of the inclusion complexes formed. By the measurement of absorbance of a set of solutions prepared of the ALP and CD in water mixture in the mole fraction range of 0−1 (Tables 6.1, 6.2, and 6.3). Here we calculate (ΔA × R) values against R, where ΔA signifies the difference in absorbance of ALP in the pure form and complexed form and R is [ALP]/ ([ALP] + [CD]). λ_{max} was found at 250 nm at 298.15 K. Ratio of guest and host i.e., stoichiometry is obtained from value of R at maxima on the Job' Plot such as R ≈ 0.33, for 1:2 IC, R≈ 0.5 for 1:1 IC, R≈ 0.66 for 2:1 IC etc. In the experiment of ALP and CD's the maxima in the Job' plots were obtained at R ≈ 0.5 which is the indication of 1:1 stoichiometry of ALP and CD ICs (Figure 6.1a,6.1b and 6.1c).[26-29]

6.3.2 Determination of binding (or association) constant by UV–Vis spectroscopy

The binding constant between α-CD, β-CD, HP-β-CD and ALP has been evaluated via UV–Vis spectroscopy. The Benesi–Hildebrand technique represents one of the most common strategies to determine binding constants based on absorption spectra for inclusion complex. With the help of Benesi−Hildebrand method for 1:1 host−guest ICs, double-reciprocal plots of 1/ΔA against 1/ [CD] were plotted using the following equation (Figure 6.2(a, b, c), 6.3(a, b, c), 6.4(a, b, c)).

$$\frac{1}{\Delta A} = \frac{1}{\Delta\varepsilon[V]K_a} X \frac{1}{[CD]} + \frac{1}{\Delta\varepsilon[V]} \quad (1)$$

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Table 6.1. Data of Job's plot between ALP and α-CD obtained from UV spectroscopy

ALP(ml)	α-CD(ml)	ALP(μM)	α-CD(μM)	[ALP]/([ALP]+[αCD])	ABSORBANCE	ΔA	ΔA*[ALP]/([ALP]+[αCD])
4	0	100	0	1	3.543	0	0
3.6	0.4	90	10	0.9	3.743	0.2	0.18
3.2	0.8	80	20	0.8	3.416	0.327	0.2616
2.8	1.2	70	30	0.7	3.416	0	0
2.4	1.6	60	40	0.6	2.909	0.507	0.3042
2	2	50	50	0.5	2.563	0.346	0.173
1.6	2.4	40	60	0.4	2.133	0.43	0.172
1.2	2.8	30	70	0.3	1.783	0.35	0.105
0.8	3.2	20	80	0.2	1.272	0.511	0.1022
0.4	3.6	10	90	0.1	0.877	0.395	0.0395
0	4	0	100	0	0.299	0.578	0

Table 6.2. Data of Job's plot between ALP and β-CD obtained from UV spectroscopy

ALP(ml)	β-CD(ml)	ALP(μM)	β-CD(μM)	[ALP]/([ALP]+[βCD])	ABSORBANCE	ΔA	ΔA*[ALP]/([ALP]+[β-CD])
4	0	100	0	1	3.997	0.324	1.345
3.6	0.4	90	10	0.9	3.998	0.456	1.461
3.2	0.8	80	20	0.8	3.999	0.567	1.562
2.8	1.2	70	30	0.7	3.999	0.782	1.721
2.4	1.6	60	40	0.6	3.096	0.903	2.503
2	2	50	50	0.5	2.588	0.508	2.508
1.6	2.4	40	60	0.4	2.302	0.286	2.686
1.2	2.8	30	70	0.3	1.73	0.572	3.372
0.8	3.2	20	80	0.2	0.821	0.909	4.109
0.4	3.6	10	90	0.1	0.778	0.043	3.643
0	4	0	100	0	0.417	0.361	3.175

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Table 6.3. Data of Job's plot between ALP and HP-β-CD obtained from UV spectroscopy

ALP (ml)	HP-β-CD (ml)	ALP (μM)	HP-β-CD (μM)	[ALP]/([ALP]+[HP-β-CD])	ABSORBANCE	ΔA	ΔA*[ALP]/([ALP]+[β-CD])
4	0	100	0	1	3.573	0	0
3.6	0.4	90	10	0.9	3.959	0.386	10.386
3.2	0.8	80	20	0.8	3.965	0.006	20.006
2.8	1.2	70	30	0.7	3.999	0.034	30.034
2.4	1.6	60	40	0.6	3.337	0.662	39.338
2	2	50	50	0.5	1.844	1.493	48.507
1.6	2.4	40	60	0.4	1.435	0.409	59.591
1.2	2.8	30	70	0.3	1.225	0.21	69.79
0.8	3.2	20	80	0.2	0.959	0.266	79.734
0.4	3.6	10	90	0.1	0.751	0.208	89.792
0	4	0	100	0	0.58	0.171	0

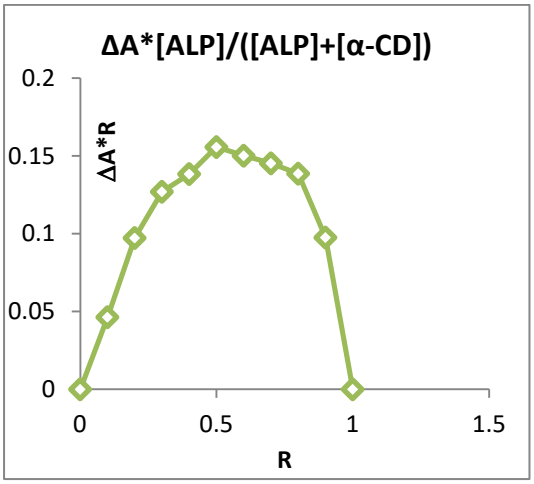

Figure 6.1a. Job's Plot for [ALP] with α-CD

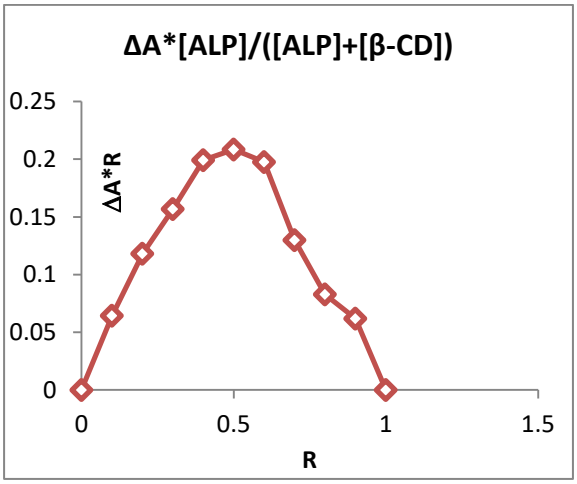

Figure 6.1b. Job's Plot for [ALP] with β-CD

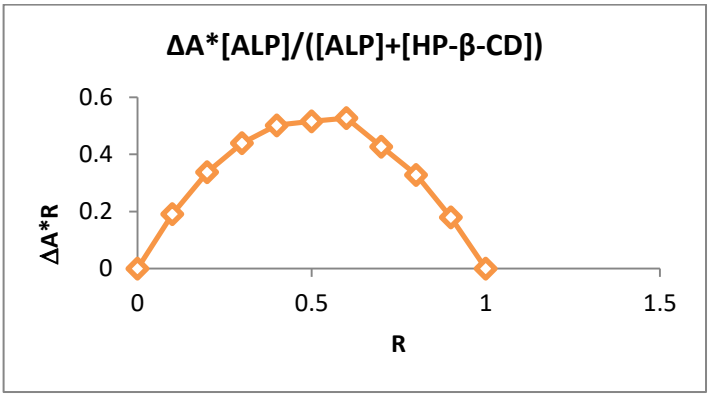

Figure 6.1c. Job's Plot for [ALP] with HP-β-CD

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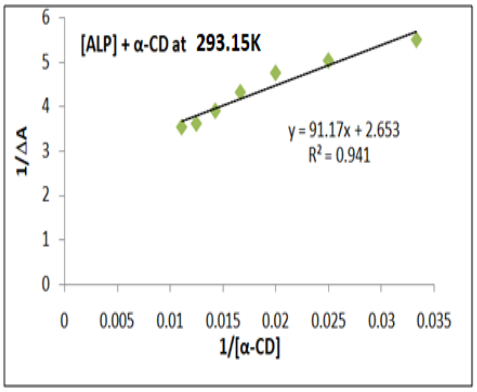

Figure 6.2a. Benesi-Hildebrand double reciprocal plots for the effect of α-CD on the absorbance of [ALP] at 293.15K

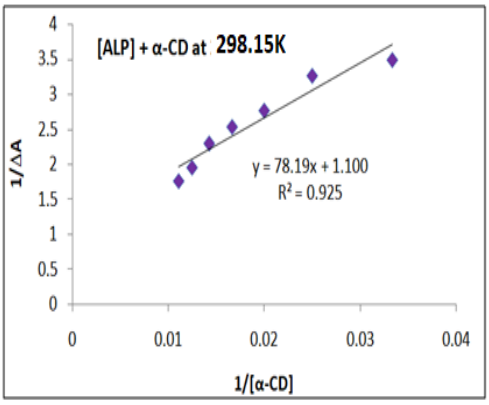

Figure 6.2b. Benesi-Hildebrand double reciprocal plots for the effect of α-CD on the absorbance of [ALP] at 298.15K

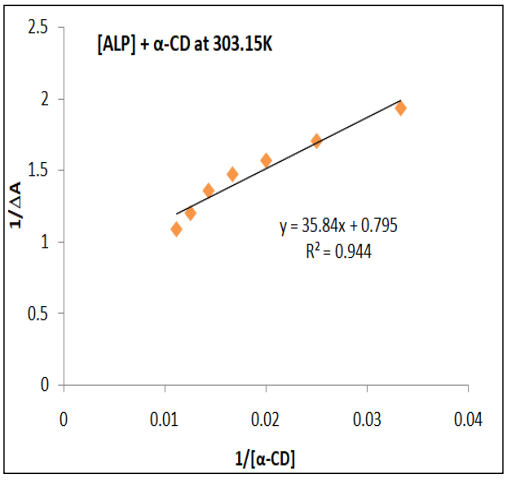

Figure 6.2c. Benesi-Hildebrand double reciprocal plots for the effect of α-CD on the absorbance of [ALP] at 303.15K

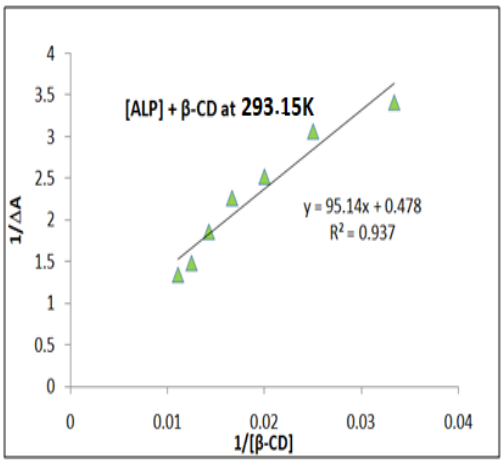

Figure 6.3a. Benesi-Hildebrand double reciprocal plots for the effect of β-CD on the absorbance of [ALP] at 293.15K

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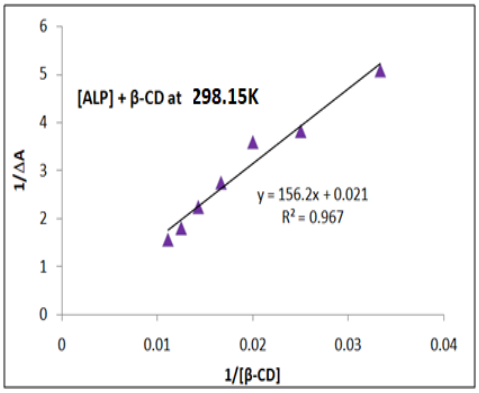

Figure 6.3b. Benesi-Hildebrand double reciprocal plots for the effect of β-CD on the absorbance of [ALP] at 298.15K

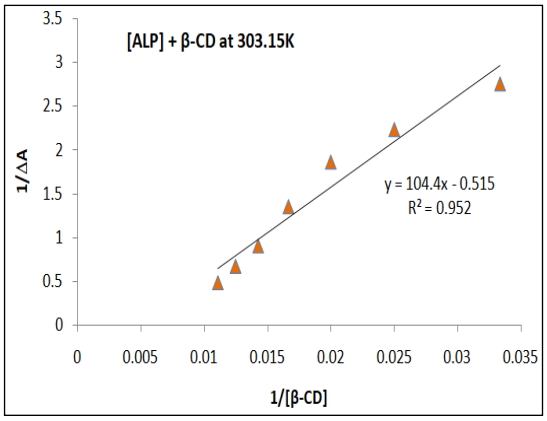

Figure 6.3c. Benesi-Hildebrand double reciprocalplots for the effect of β-CD on the absorbance of [ALP] at 303.15K

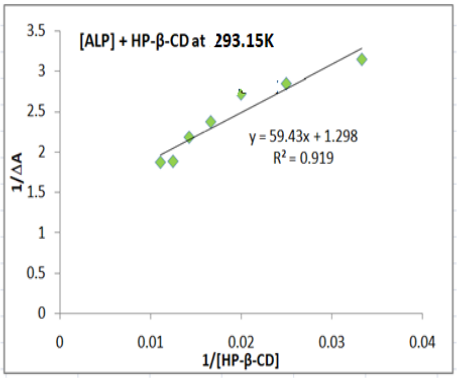

Figure 6.4a. Benesi-Hildebrand double reciprocal plots for the effect of HP-β-CD on the absorbance of [ALP] at 293.15K

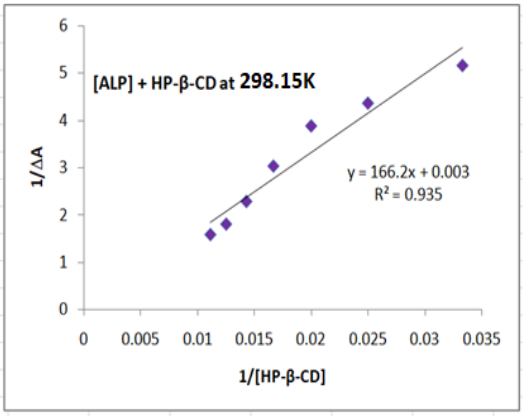

Figure 6.4b. Benesi-Hildebrand double reciprocal plots for the effect of HP-β-CD on the absorbance of [ALP] at 298.15K

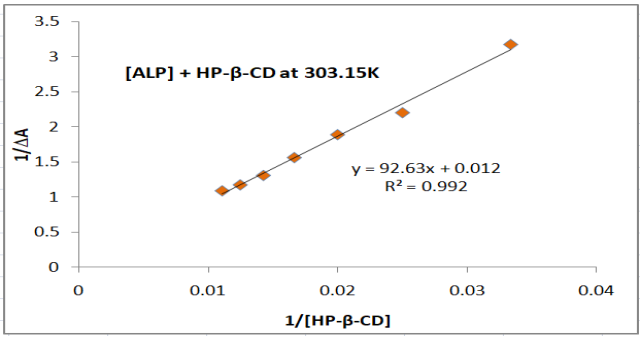

Figure 6.4c. Benesi-Hildebrand double reciprocal plots for the effect of HP-β-CD on the absorbance of [ALP] at 303.15K

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Association constants (K_a^c) were also calculated for the inclusion complexation of ALP and CD by means of conductivity study with the help of a nonlinear program. Basing upon the fact that the insertion of the ALP inside the CD cavity changes the conductivity of the solutions. The equilibrium between ALP and CD can be represented as:

$$\text{ALP} + \text{CD} \xleftrightarrow{K_a} \text{IC} \qquad (2)$$

The equilibrium constant, K_a is represented as,

$$K_a = [IC] / [ALP]\,[CD] * f(IC)/f(ALP)\, f(CD) \qquad (3)$$

Where, [IC], [ALP] and [CD] are molar concentrations of inclusion complex, allopurinol and cyclodextrin's at equilibrium accordingly. (f) is activity coefficients of the respective species (Table 6.4, 6.5, 6.6). The activity coefficient of CD, f (CD), can be assumed as unity as system was dilute. In order to have an accurate estimation of binding constants of the inclusion complexes under investigation, changes in the absorption intensity of the ALP at different wavelength, were monitored as a function of the CD's concentration and non-linear regression estimation of the K_a was chosen.

6.3.3. Fluorescence

Fluorescence was extensively studied for static and dynamic properties of the aggregated system such as the derivatives of the drug. In amphiphile molecules, CD's (quencher) are preferentially solubilized in their core hydrophobic regions. Change in the microenvironment of solution is experienced by (ALP), where the shift in the absorbance is located. Hence is used to aggregate properties in the form of inclusion. Vibronic band spectra endure major perturbation on transferring from non-polar to a polar environment. Fluorescence measurements are used to determine the association and complexation, of studied complex and also in understanding interaction between the host-guest inclusion processes (ICs). Steady-state fluorescence measurements were done at room temperature. Concentration of solutions used in all the system was approximately up to 10^{-6} mol dm^{-3}. The lower the florescence intensity more is the binding with CD's, moreover it is found that in the α-CD inclusion with ALP the controlled release of the drug is more prominent ((Figure 9 (a), (b), (c)).[30, 31]

Table 6.4. *Data for the Benesi-Hildebrand double reciprocal plot performed by UV-VIS spectroscopic study for [ALP]-α-CD systems at (293.15, 298.15, and 303.15) K*

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temp/k	[ALP]/μM	[α-CD]/μM	$A_{\circ}$	A	ΔA	1/[α-CD]/M−1	1/ΔA
	50	30	0.9926	1.1745	0.1819	0.033333333	5.497526
	50	40	0.9926	1.1913	0.1987	0.025	5.032713
293.15K	50	50	0.9926	1.2028	0.2102	0.02	4.757374
	50	60	0.9926	1.2239	0.2313	0.016666667	4.32339
	50	70	0.9926	1.2484	0.2558	0.014285714	3.909304
	50	80	0.9926	1.2684	0.2758	0.0125	3.625816
	50	90	0.9926	1.2747	0.2821	0.011111111	3.544842
	50	30	0.9926	1.2789	0.2863	0.033333333	3.49284
	50	40	0.9926	1.2986	0.306	0.025	3.267974
298.15K	50	50	0.9926	1.3535	0.3609	0.02	2.770851
	50	60	0.9926	1.3867	0.3941	0.016666667	2.537427
	50	70	0.9926	1.4269	0.4343	0.014285714	2.302556
	50	80	0.9926	1.5034	0.5108	0.0125	1.957713
	50	90	0.9926	1.5594	0.5668	0.011111111	1.764291
	50	30	0.9926	1.5096	0.517	0.033333333	1.934236
	50	40	0.9926	1.5791	0.5865	0.025	1.70503
303.15K	50	50	0.9926	1.62991	0.63731	0.02	1.569095
	50	60	0.9926	1.6715	0.6789	0.016666667	1.472971
	50	70	0.9926	1.7286	0.736	0.014285714	1.358696
	50	80	0.9926	1.8247	0.8321	0.0125	1.201779
	50	90	0.9926	1.9105	0.9179	0.011111111	1.089443

Table 6.5. *Data for the Benesi-Hildebrand double reciprocal plot performed by UV-VIS spectroscopic study for [ALP]-β-CD systems at (293.15, 298.15, and 303.15) K*

temp/k	[ALP]/μM	[β-CD]/μM	$A_{\circ}$	A	ΔA	**1/[β-CD]/M−1**	1/ΔA
	50	30	0.9926	1.2854	0.2928	0.033333333	3.415301
	50	40	0.9926	1.3185	0.3259	0.025	3.068426
293.15K	50	50	0.9926	1.3883	0.3957	0.02	2.527167
	50	60	0.9926	1.4331	0.4405	0.016666667	2.270148
	50	70	0.9926	1.5281	0.5355	0.014285714	1.867414
	50	80	0.9926	1.6621	0.6695	0.0125	1.493652
	50	90	0.9926	1.7315	0.7389	0.011111111	1.353363
	50	30	0.9926	1.1892	0.1966	0.033333333	5.08647
	50	40	0.9926	1.2538	0.2612	0.025	3.828484
298.15K	50	50	0.9926	1.2706	0.278	0.02	3.597122
	50	60	0.9926	1.3555	0.3629	0.016666667	2.75558
	50	70	0.9926	1.4366	0.444	0.014285714	2.252252
	50	80	0.9926	1.5434	0.5508	0.0125	1.815541
	50	90	0.9926	1.628	0.6354	0.011111111	1.573812
	50	30	0.9926	1.386	0.3934	0.033333333	2.541942
	50	40	0.9926	1.4405	0.4479	0.025	2.232641
303.15K	50	50	0.9926	1.3297	0.3371	0.02	2.966479
	50	60	0.9926	1.5344	0.5418	0.016666667	1.8457
	50	70	0.9926	2.0923	1.0997	0.014285714	0.909339
	50	80	0.9926	2.1743	1.1817	0.0125	0.846238

	50	90	0.9926	2.3721	1.3795	0.011111111	0.7249

Table 6.6. Data for the Benesi-Hildebrand double reciprocal plot performed by UV-VIS spectroscopic study for [ALP]-HP-β-CD systems at (293.15, 298.15, and 303.15) K

temp/k	[ALP]/μM	[HP-β-CD]/μM	$A_{\circ}$	A	ΔA	1/[HP-β-CD]/M⁻¹	1/ΔA
	50	30	0.9926	1.3111	0.3185	0.033333333	3.139717
	50	40	0.9926	1.3448	0.3522	0.025	2.839296
293.15K	50	50	0.9926	1.3612	0.3686	0.02	2.712968
	50	60	0.9926	1.4141	0.4215	0.016666667	2.372479
	50	70	0.9926	1.4519	0.4593	0.014285714	2.177226
	50	80	0.9926	1.5249	0.5323	0.0125	1.87864
	50	90	0.9926	1.5283	0.5357	0.011111111	1.866716
	50	30	0.9926	1.1863	0.1937	0.033333333	5.162623
	50	40	0.9926	1.2217	0.2291	0.025	4.364906
298.15K	50	50	0.9926	1.2501	0.2575	0.02	3.883495
	50	60	0.9926	1.3222	0.3296	0.016666667	3.033981
	50	70	0.9926	1.4299	0.4373	0.014285714	2.28676
	50	80	0.9926	1.5463	0.5537	0.0125	1.806032
	50	90	0.9926	1.6234	0.6308	0.011111111	1.585289
	50	30	0.9926	1.3078	0.3152	0.033333333	3.172589
	50	40	0.9926	1.4467	0.4541	0.025	2.202158
303.15K	50	50	0.9926	1.5219	0.5293	0.02	1.889288
	50	60	0.9926	1.6324	0.6398	0.016666667	1.562988
	50	70	0.9926	1.7565	0.7639	0.014285714	1.309072
	50	80	0.9926	1.8435	0.8509	0.0125	1.175226
	50	90	0.9926	1.91	0.9174	0.011111111	1.090037

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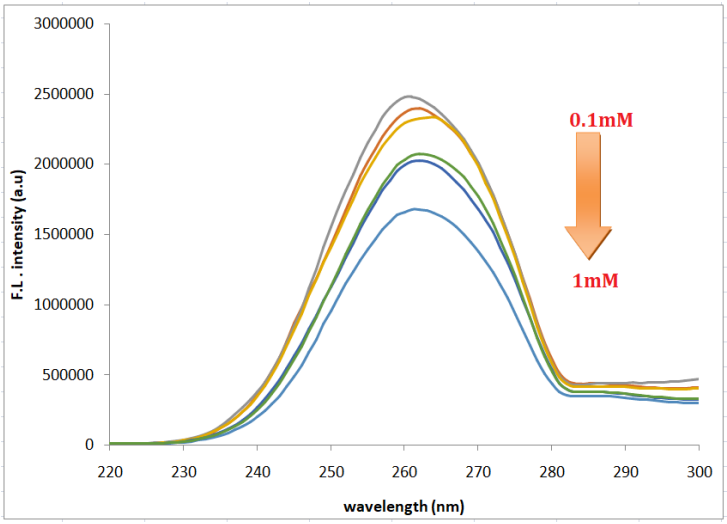

Figure 6.9(a). Fluorescence emission spectrum of aqueous (α-CD) in presence of (0.1mM—1.0 mM) of ALP (λ_{ex} =250 nm, slit width =5/5)

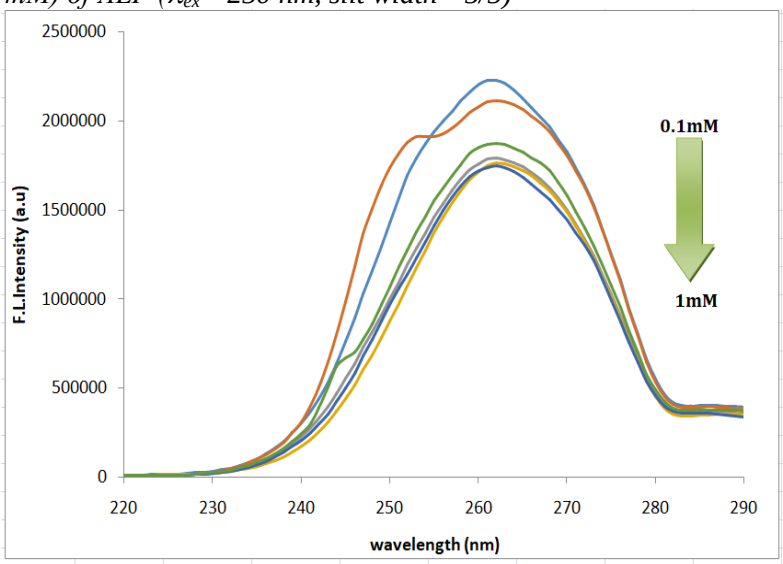

Figure 6.9(b). Fluorescence emission spectrum of aqueous (β-CD) in presence of (0.1mM—1.0 mM) of ALP (λ_{ex} =250 nm, slit width =5/5).

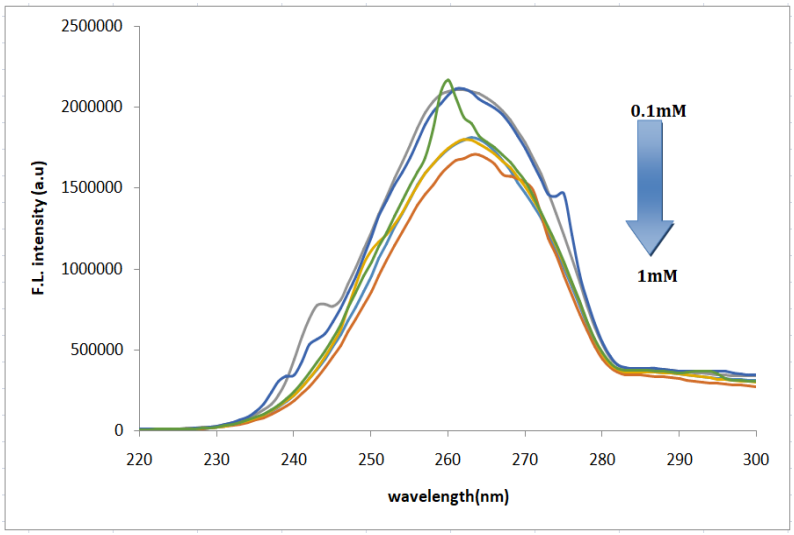

Figure 6.9(c). Fluorescence emission spectrum of aqueous (HP-β-CD) in presence of (0.1mM—1.0 mM) of ALP (λ_{ex} =250 nm, slit width =5/5).

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6.3.4. FTIR:

FT-IR study of the solid ICs formed was performed to investigate the formation of the solid ICs. There are changes in frequencies of bands of the inserted guest molecules as well as some bands are absent in the spectra of complex. This may be due to the formation of the ICs. Data for pure compounds and inclusion complexes are spectroscopic change recorded in wave number before and after inclusion are shown in [Figure 6.5(a), (b), (c), (d)].

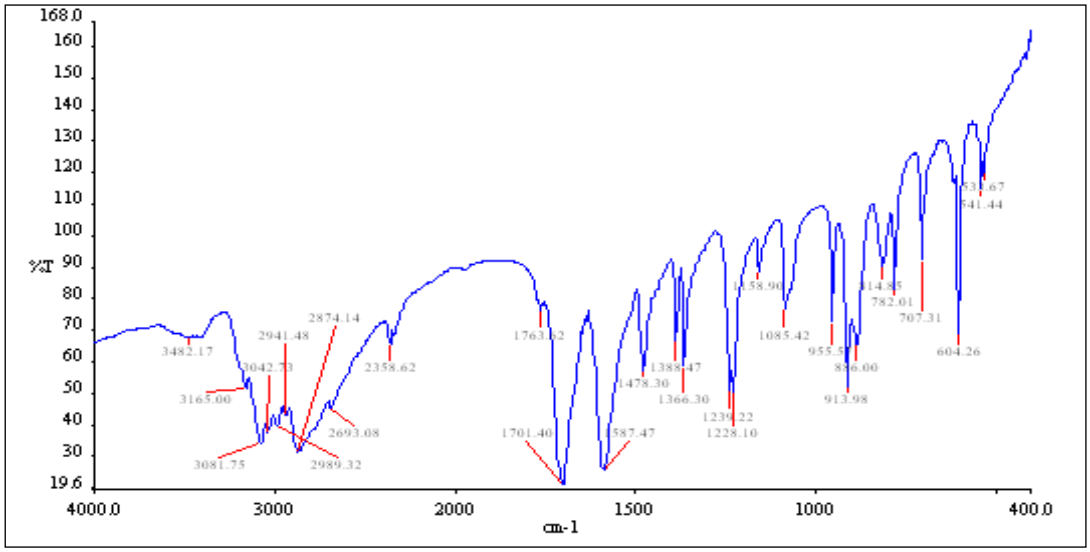

Figure 6.5(a): FT-IR spectra of (pure [ALP]) at 298.15K

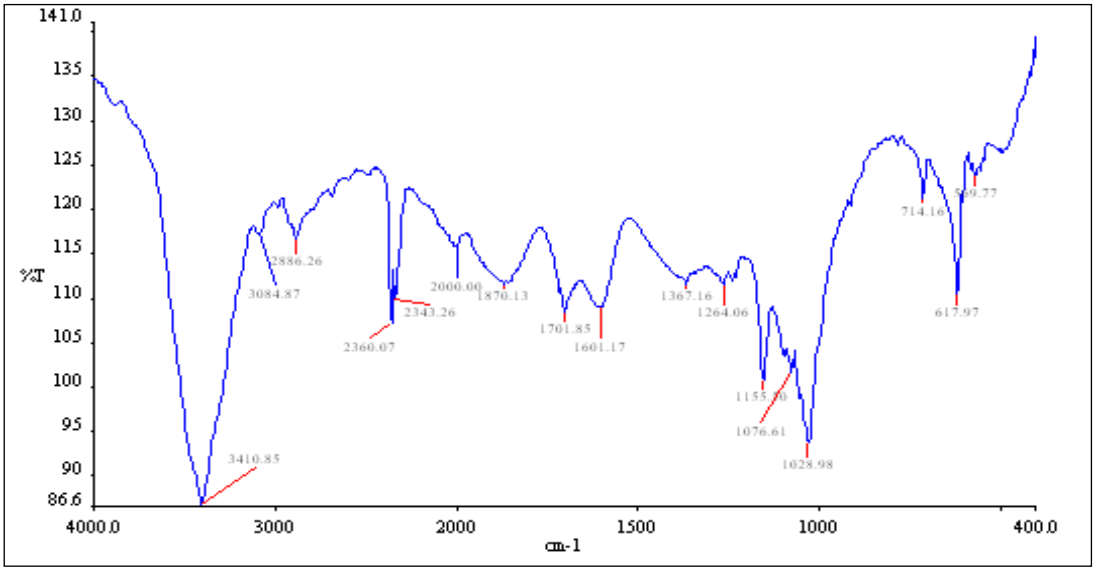

Figure 6.5(b): FT-IR spectra of 1:1 inclusion complexes ([ALP] + α-CD) at 298.15K

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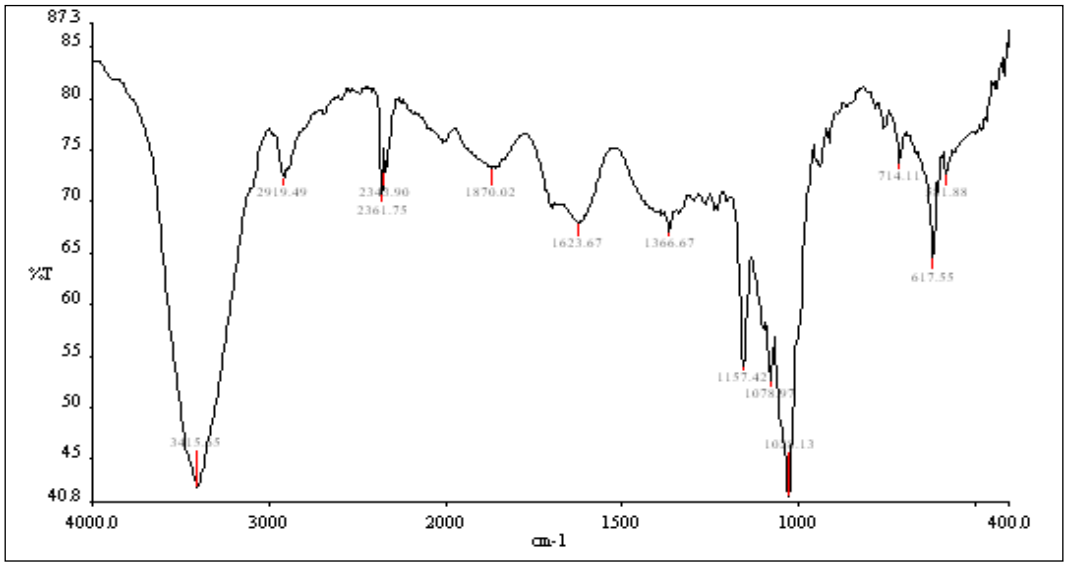

Figure 6.5(c): FT-IR spectra of 1:1 inclusion complexes ([ALP] + β-CD) at 298.15K

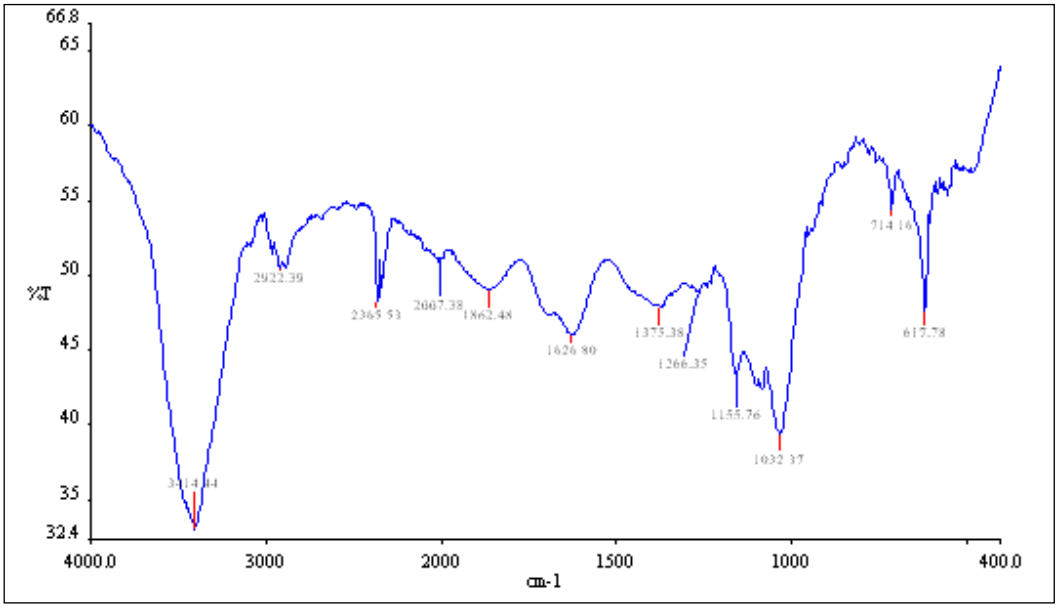

Figure 6.5(d): FT-IR spectra of 1:1 inclusion complexes ([ALP] + HP-β-CD) at 298.15K

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Due to non-covalent interactions the changes of bands are observed. In the spectra of α-CD, β-CD and HP-β-CD the broad band's obtained at 3410 cm^{-1}, 3408 cm^{-1} and 3415.82 cm^{-1} are due to the valence vibrations of -O-H groups linked by H-bond. The O-H stretching for α-CD and β-CD obtained at 3410 cm^{-1} 3408 cm^{-1} and 3415.82 cm^{-1} were obtained in the complexes 3410.85 cm^{-1}, 3415.94 cm^{-1} and 3414.44 cm^{-1} respectively, may be due to the interaction of the positively charged nitrogen atom of the pyrazole ring and the oxygen atom of (C=O) group which is again reflected in the shifted band of C=N stretching for 1701.40 cm^{-1} for the pure ALP to 1601.17 cm^{-1} in IC of α-CD, 1623.67 cm^{-1} in IC of β-CD and 1626.80 cm-1 in IC of HP-β-CD respectively. The C-H stretching and bending are obtained at 2941cm^{-1} and 1404 cm^{-1} for pure β-CD and 2919. 19 cm^{-1} and 1366.67 cm^{-1} and HP-β-CD shift is almost the same. For pure α-CD, which are shifted in the ICs to 2886.26 cm^{-1} from 2927 cm^{-1}, 1367 cm^{-1} for α-CD. The out of plane C-H bending for [ALP] obtained at 814 cm^{-1} and 768 cm^{-1} for α-CD, 761cm^{-1} for β-CD and 762 cm^{-1} for HP-β-CD respectively. This may be due to the closeness of C-H of CD and the aromatic C-H of the ALP. The aromatic stretching bands for pure [ALP] observed at 3165 cm^{-1}, stretching band due to alkyl C-H at 3081cm^{-1} and 3042 cm^{-1}, are absent in the spectra of ICs. The peak due to stretching of C-H from -CH_2- at 2941 cm^{-1} for [ALP] are absent or shifted to 2886 cm^{-1}, 2919 cm^{-1} and 2927cm^{-1}, 2922 cm^{-1} in the spectra of ICs of α-CD, β-CD and HP-β-CD respectively, may be due to interaction inside the cavity of cyclodextrin. In ICs no additional signal is obtained which deny the chance of chemical reaction. Thus the study provides major information about the formation of the ICs in the solid state. [32].

6.3.5. ^{1}H NMR spectroscopy

NMR spectroscopic study in aqueous solution at 298.15K. Figure 6(a), (b), (c) represents 1H NMR spectra of the complex of ALP with α-CD, β-CD and HP-β-CD which describes slight downfield shift of the aliphatic protons of guest molecule.

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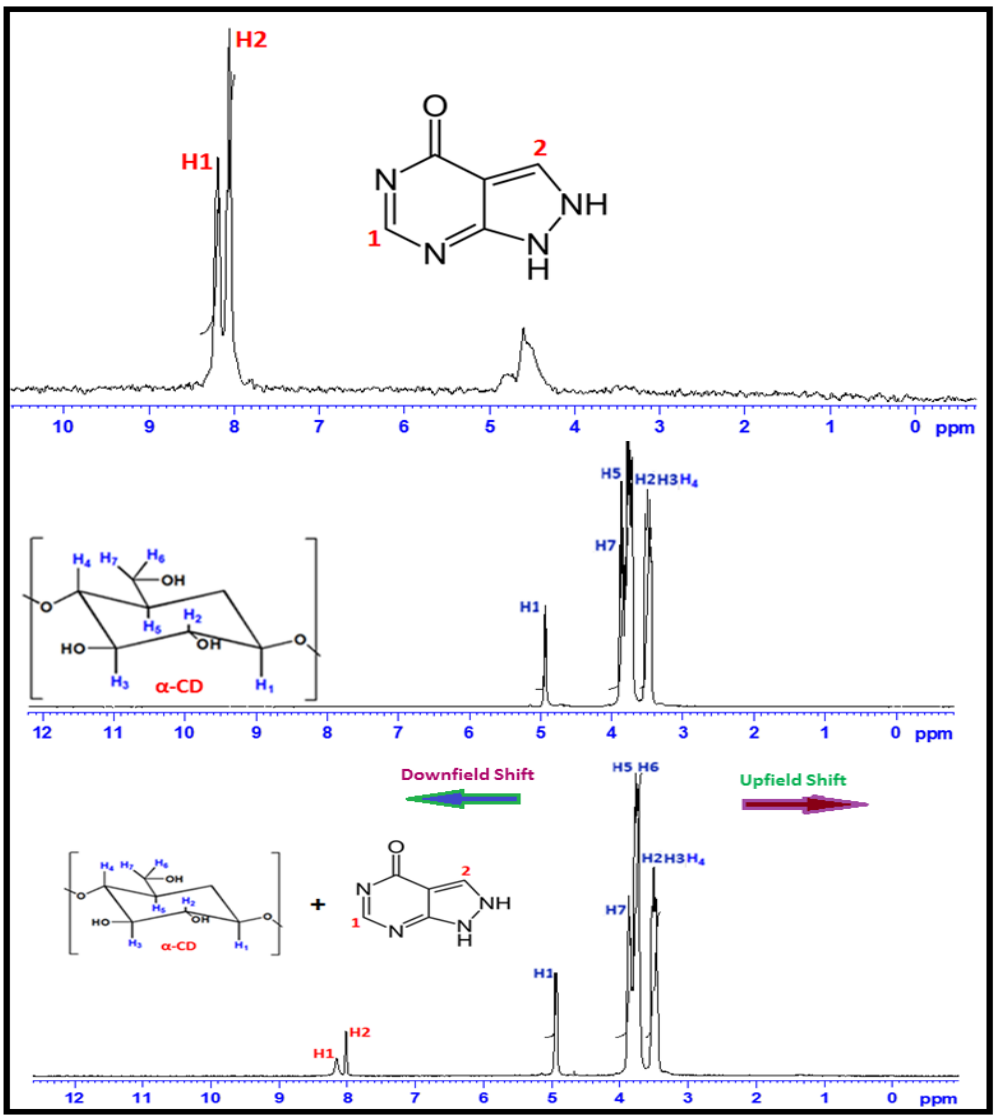

Figure 6.6(a). 1H-NMR spectra of the pure compounds and inclusion complexes with α-CD at 298.15K (400MHz, D_2O)

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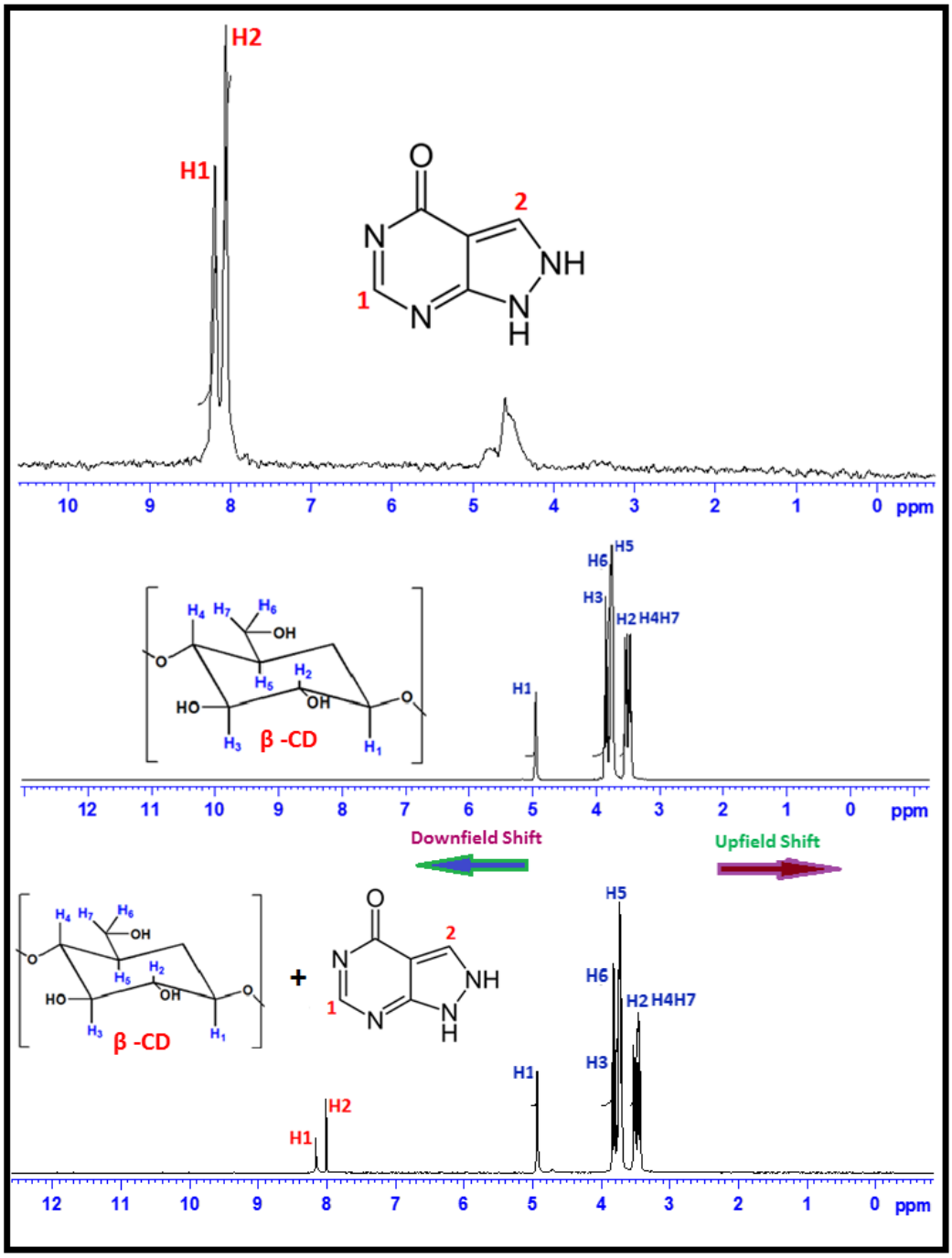

Figure 6.6(b). 1H-NMR spectra of the pure compounds and inclusion complexes with β-CD at 298.15K (400MHz, D_2O)

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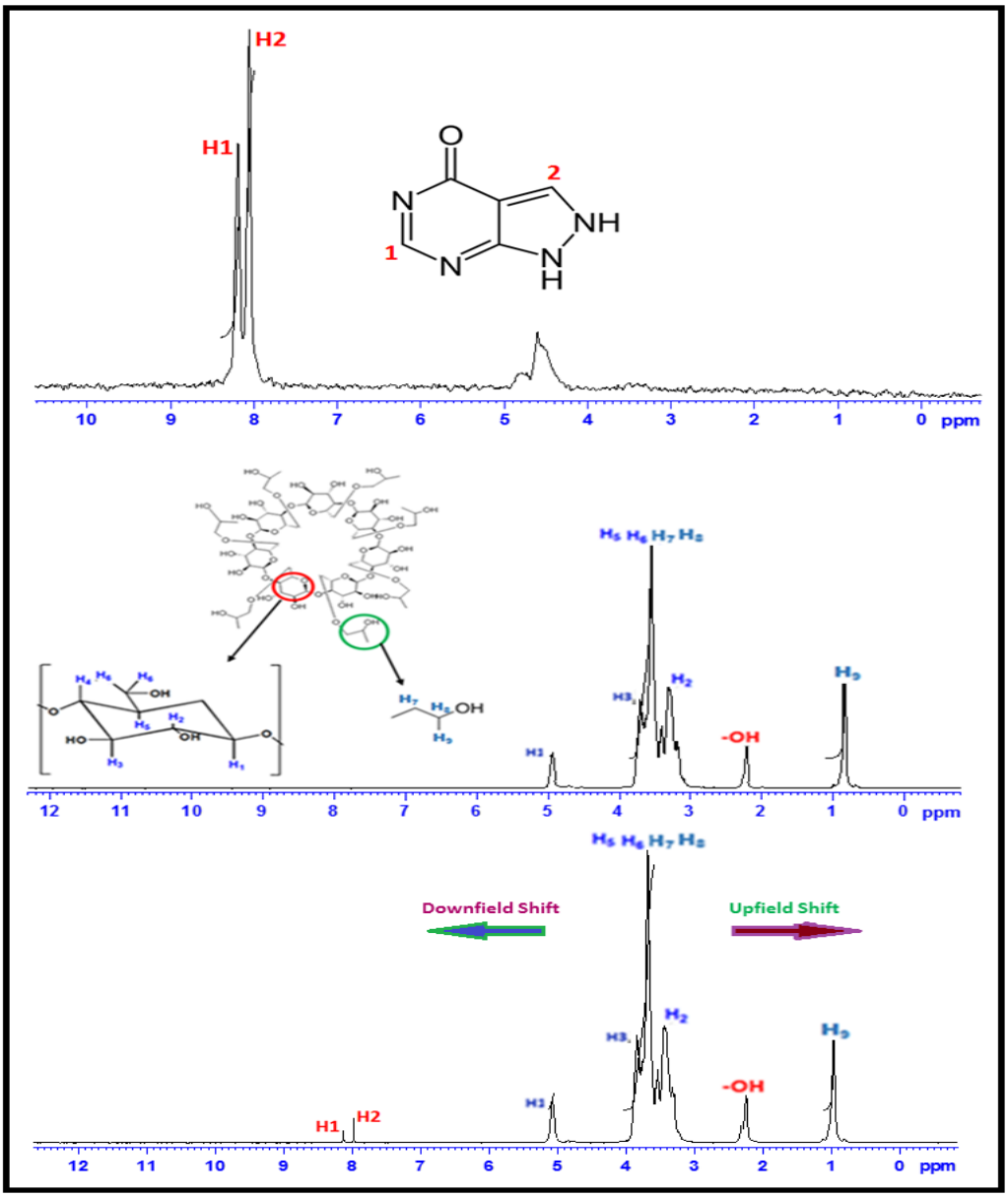

Figure 6.6(c). 1H-NMR spectra of the pure compounds and inclusion complexes with HP-β-CD at 298.15K (400MHz, D_2O)

The signal due to aryl protons are nearly shifted and little broadening. Conversely protons of guest molecules of the aliphatic chain illustrate a slight change in their signals while present in the complex (α, β and γ protons of free ALP appears downfield shift respectively, then complex. This result clearly reveals the existence of some sort of association between the electron rich oxygen atoms of the CD's and the nitrogen atom (scheme 6.2). The aromatic part of the ALP shows no change of their signals indicating their free state in the solvent medium.

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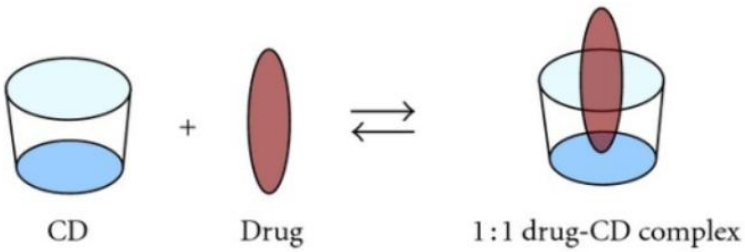

Scheme 6.2. Diagrammatic representation of the probable complexes obtained

Upon inclusion, upfield chemical shift values (Δδ) of the H3 and H5 protons of **α** and β-Cyclodextrins and H3 protons for HP-β-CD have been shown in Figure, which confirm that the interaction of the guest ALP with H3 is greater than that with H5, signifying that the inclusion has taken place through the wider rim of the α, β and HP-β-Cyclodextrins.

It is to be mentioned that upon inclusion some non aromatic peak of the ALP was completely disappeared in the proton NMR spectra of ALP, leave strong evidence of inclusion complexation. [33]

6.3.6. 2D-ROESY spectroscopy

The principle of '2D ROESY' is the interaction of protons which are present in close proximity of 0.4 nm range to each other to produce NMR cross peak. In our study, we investigated the inclusion of ALP inside the α-CD, β-CD, and HP-β-CD hydrophobic cavity. NMR study was carried out in D_2O. It is clear H-3 and H-5 protons of CDs are present inside the cavity and hence if inclusion happens, there should be presence of such close proximity of 0.4 nm of the ALP protons with H-3 and H-5 protons of CD which can produce rotating-frame nuclear overhauser effect spectroscopy (ROESY) to give cross peaks.In the Figure 6.7 (a), (b) and (c) there is the presence of cross peaks of H3 and H5 protons of β-CD with H-3 and H-5 protons of the aromatic ring and H-4' protons of [ALP] ; with the H3 and H5 protons of α-CD and H-1', H-1"and H-4'of [ALP] and negligible cross peaks in HP-β-CD.

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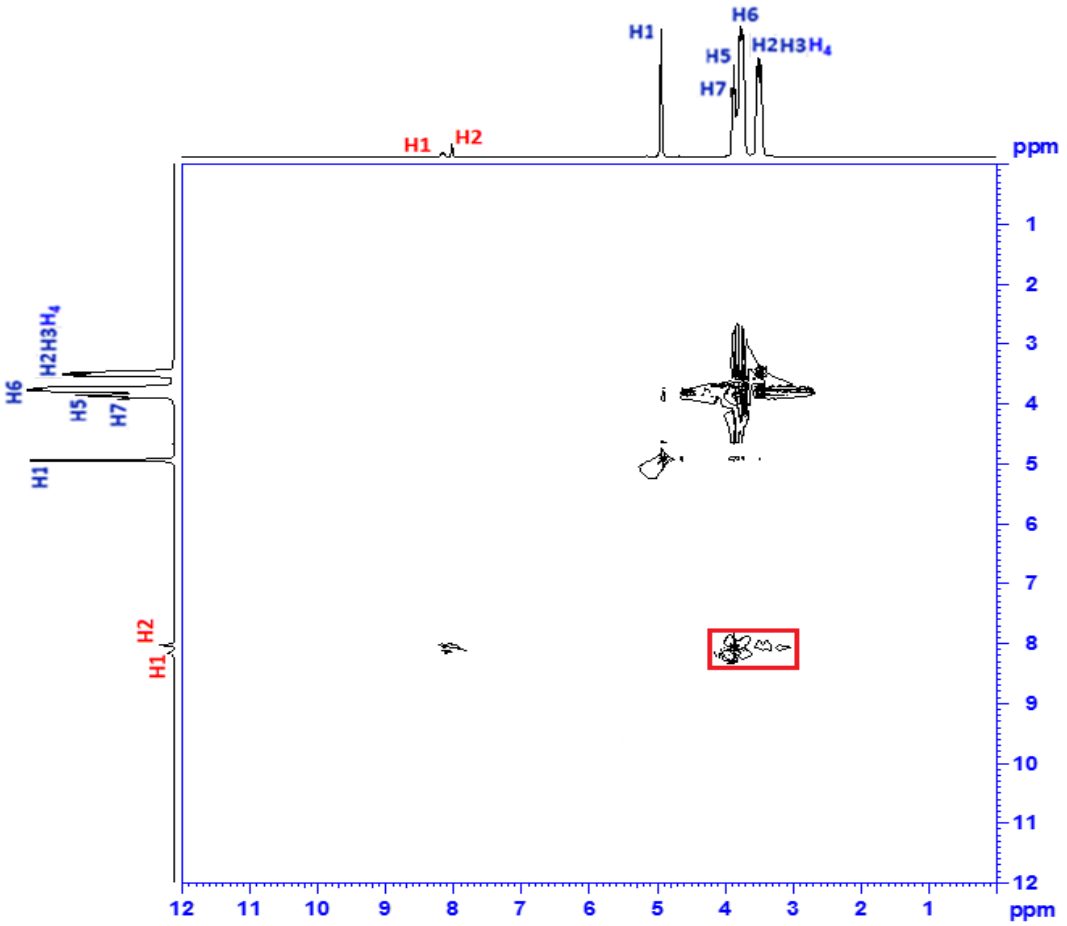

Figure 6.7(a). 2D ROESY spectra of the solid ICs of [ALP].α-CD in D2O. (Cross correlations are indicated by red circles)

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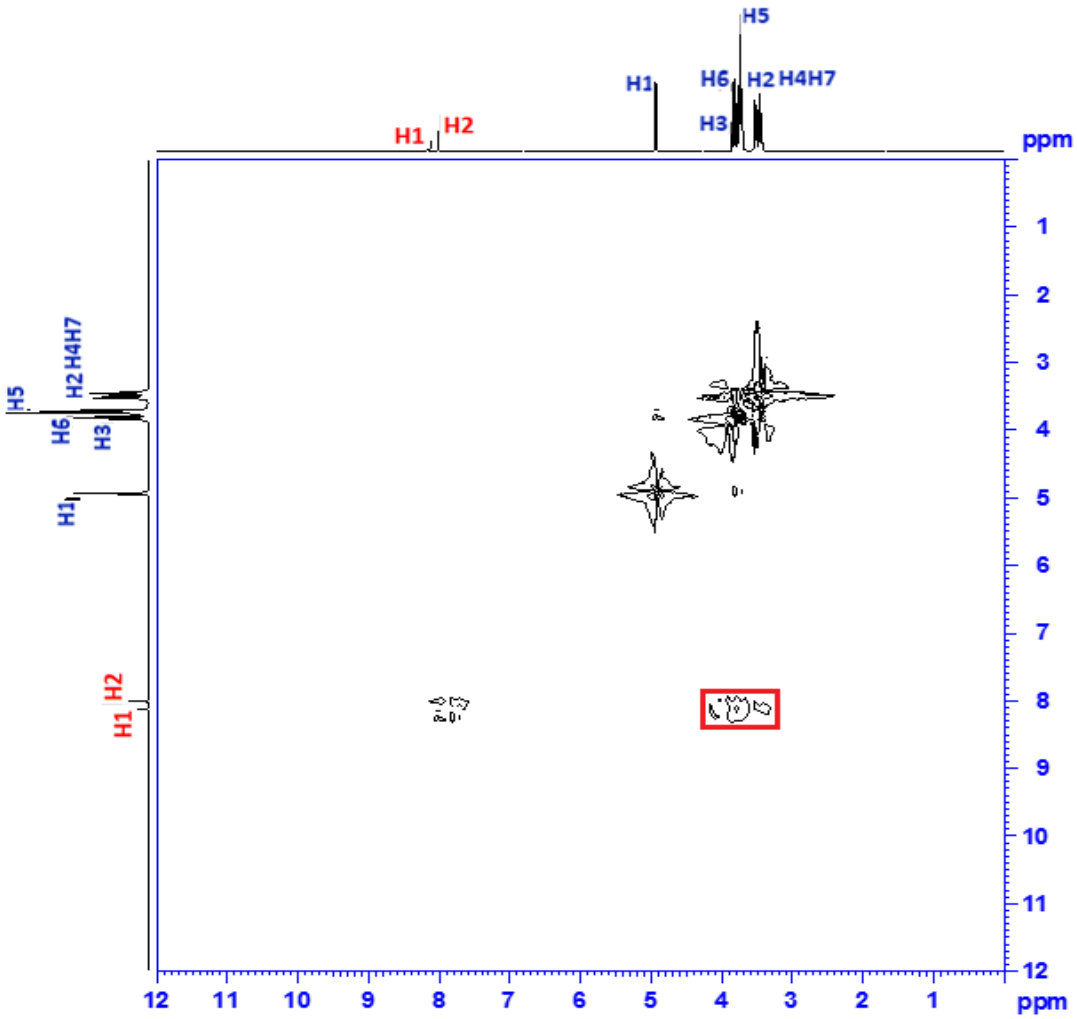

Figure 6.7(b). 2D ROESY spectra of the solid ICs of [ALP].β-CD in D2O. (Cross correlations are indicated by red circles)

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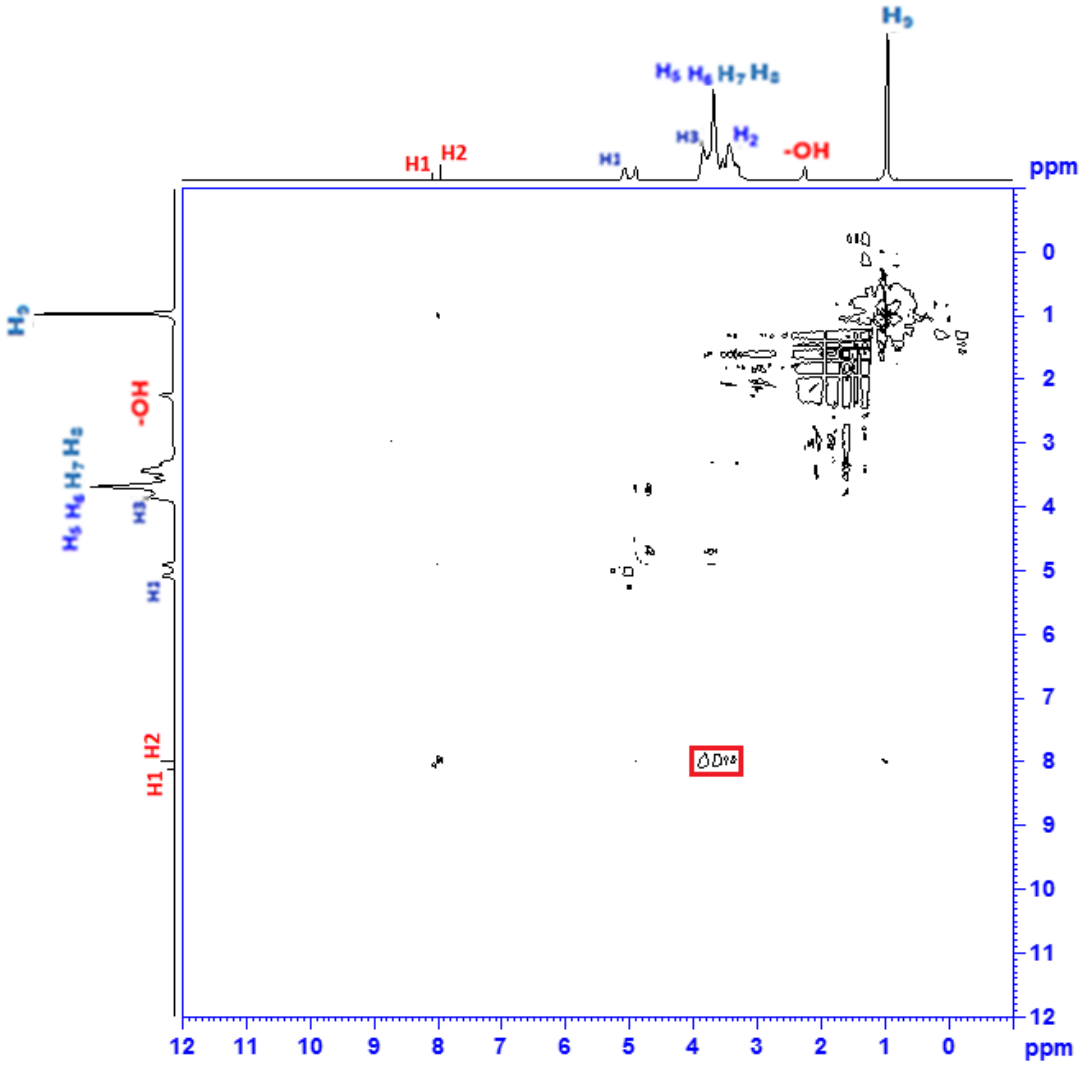

Figure 6.7(c). 2D ROESY spectra of the solid ICs of [ALP]_HP-β-CD in D2O. (Cross correlations are indicated by red circles)

6.3.7. SEM

A very illustrious technique for analyzing the surface texture and particle size of solid materials. The exterior surface morphological structures of (α- , β-, HP-β-) CD and solid IC (ALP: α-CD, ALP: β-CD, ALP: HP-β-CD) are shown in respectively. From (Figure 8 (a), (b), (c)) it is obvious that morphological structures of each are totally different from each other. Moreover as the complexation by α-, β- and HP-β-CD can be viewed distinctly. This provides clear evidence that [ALP] fits adequately into the hydrophobic cavity of CD's to figure solid IC with different morphology. [35]

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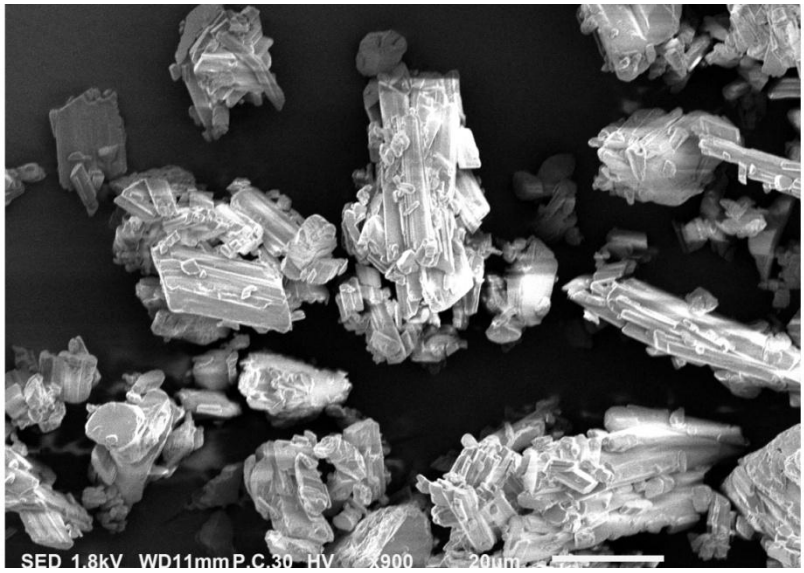

Figure 6.8(a). (SEM) showing morphologic study of [ALP: (α-CD)] in (1:1 M ratio) of inclusion complex

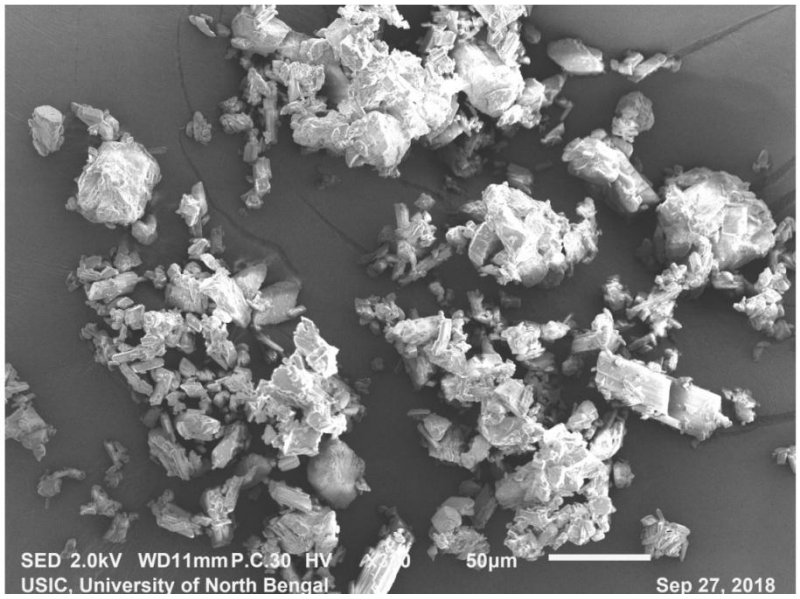

Figure 6.8(b). (SEM) showing morphologic study of [ALP: (β-CD)] in (1:1 M ratio) of inclusion complex

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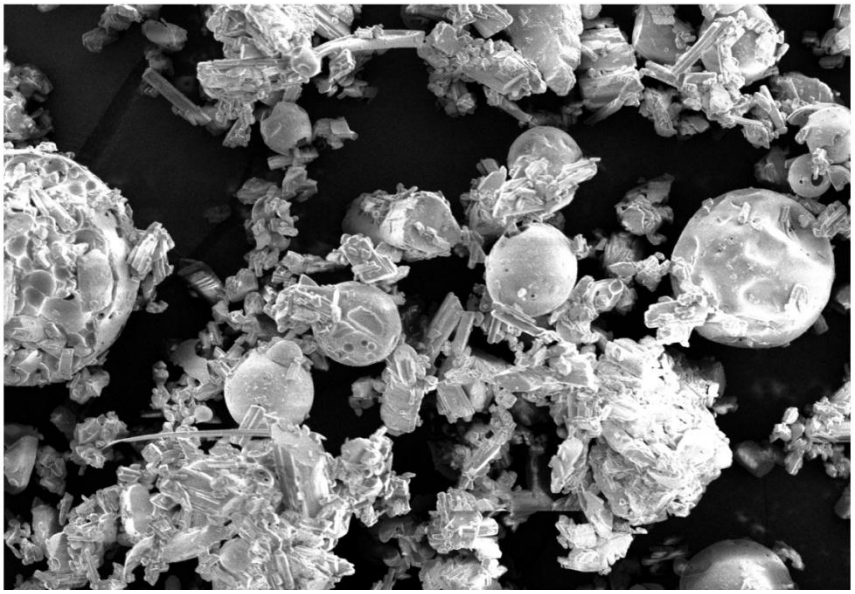

Figure 6.8(c). (SEM) showing morphologic study of [ALP: (HP-β-CD)] in (1:1 M ratio) of inclusion complex

6.3.8 XRD (or PXRD – powdered x-ray diffraction spectroscopy)

X-ray diffraction (XRD analysis or XRPD analysis) is an exclusive method in determination of crystallinity of a compound. It is primarily used for crystalline material of different polymorphic forms. Distinguishing among amorphous and crystalline material, quantification of the percent crystallinity of a sample is the mandatory criteria. We find (Figures.(10a, 10b, 10c,10d) the crystallinity changes in the complexes by definite angles.[36]

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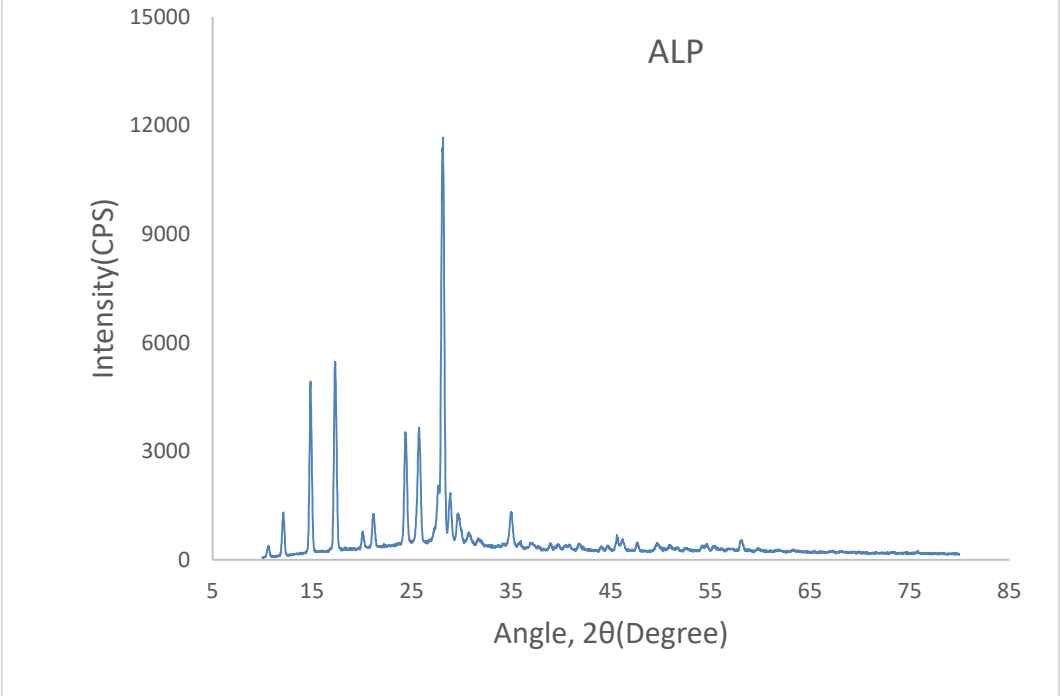

Figure 6.10 (a). Powder X-ray diffraction pattern of ALP

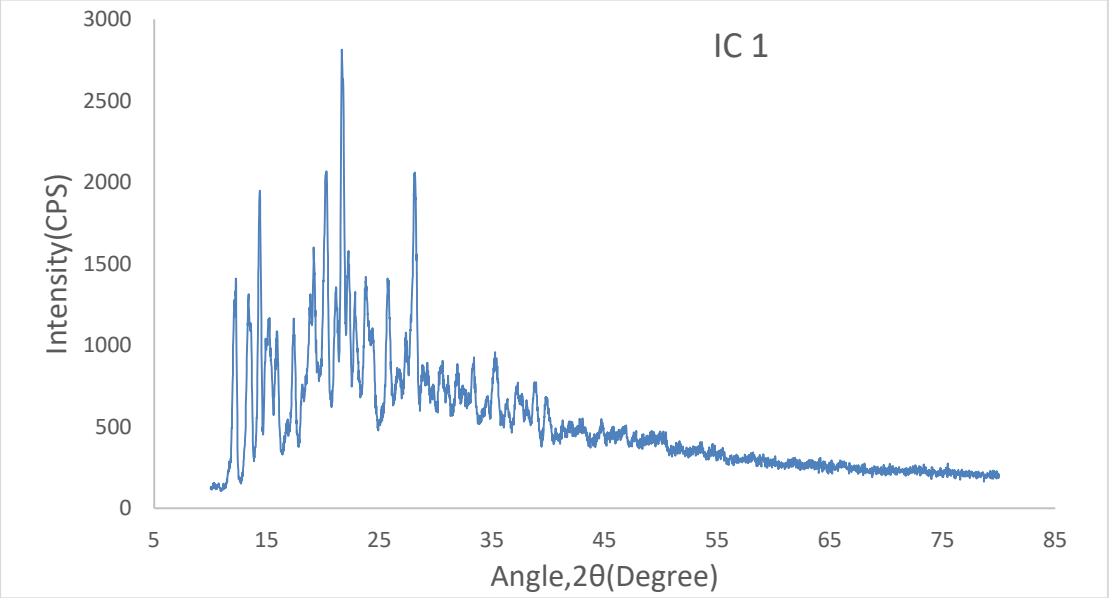

Figure 6.10(b). Powder X-ray diffraction pattern of ALP+ α-CD

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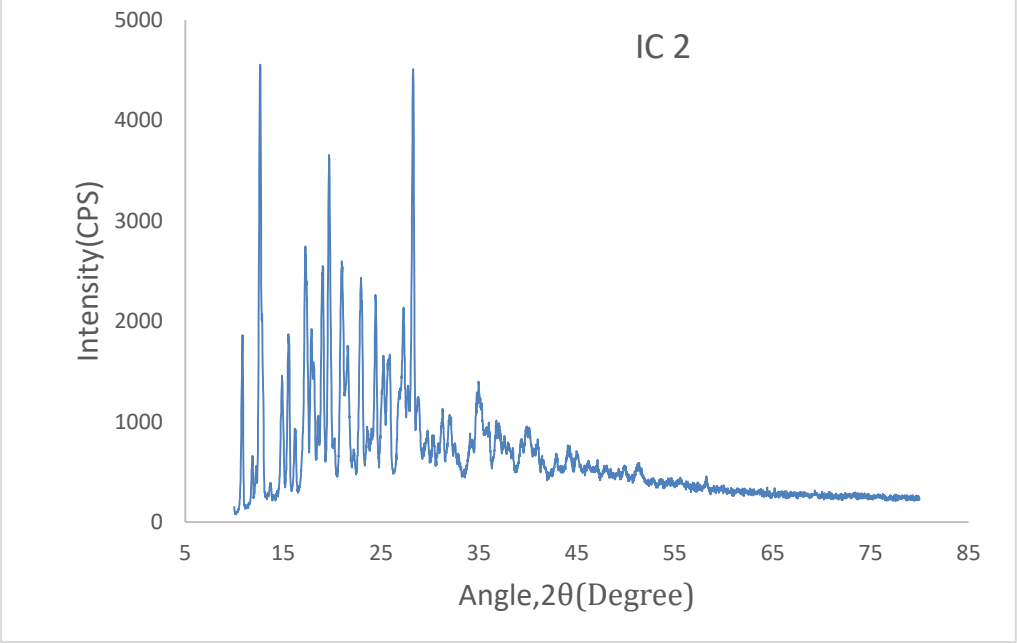

Figure 6.10(c). Powder X-ray diffraction pattern of ALP+β-CD

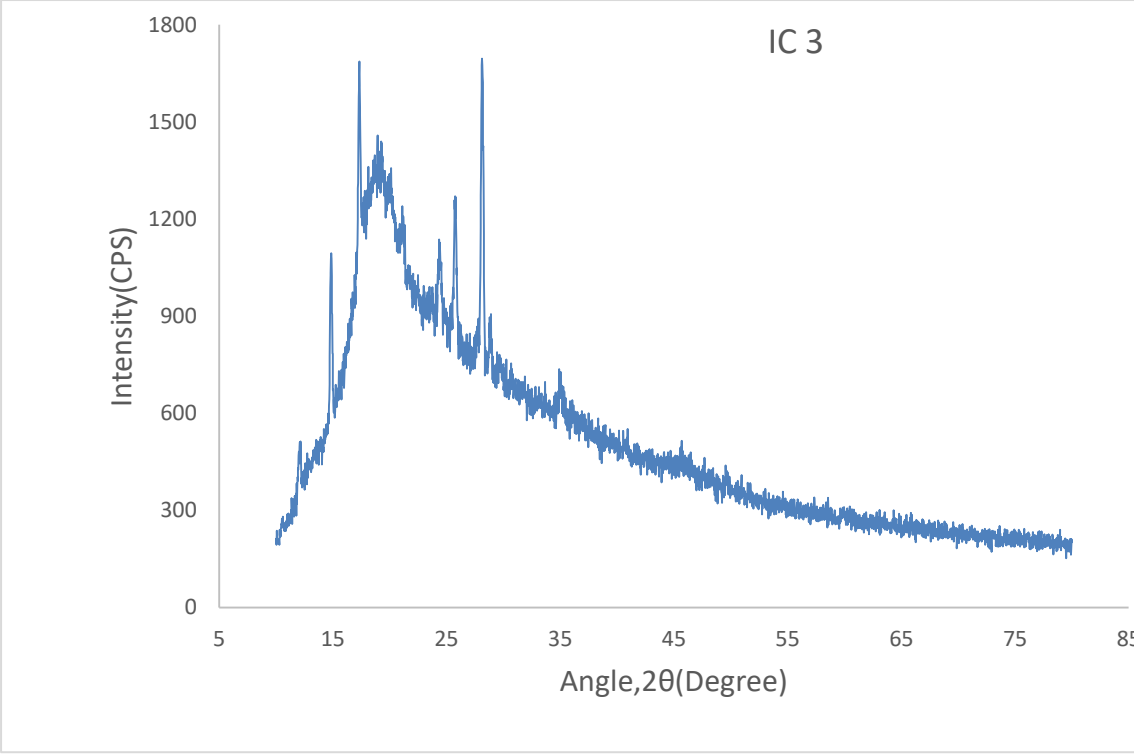

Figure 6.10(d). Powder X-ray diffraction pattern of ALP+HP-β-CD

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6.3.9 ESI-MS

The 'ESI-mass spectrometric analysis' were additionally used to recognize the formation of IC synthesized by procedure described above in the solid state of experimental procedure and have been shown in (Figure. 6.11(a), (b), (c)). Observation of peaks have been put, which verifies that in each cases the desired IC's have been formed in solid state and stoichiometric ratio of (host: guest) is (1: 1). The 'Positive electrospray ionization mass spectrometry' [ESI-MS] is enormously important process that has been used to examine host guest complexation with the two studied cyclodextrins. Mass spectrums of (1:1) stoichiometries of [α-CD: {ALP}], [β : {ALP} and [HP-β-CD: {ALP}] systems are evaluated by [ESI-MS] represents every preferred mass that one can expect. These experimental facts of the chosen [[ALP]/α-CD], [[ALP]/β-CD] and [[ALP] / HP-β-CD] complexes recommended that the [[ALP] + cation] simultaneously inserted in cyclodextrin's hollow space with (1:1) stoichiometry. [37]

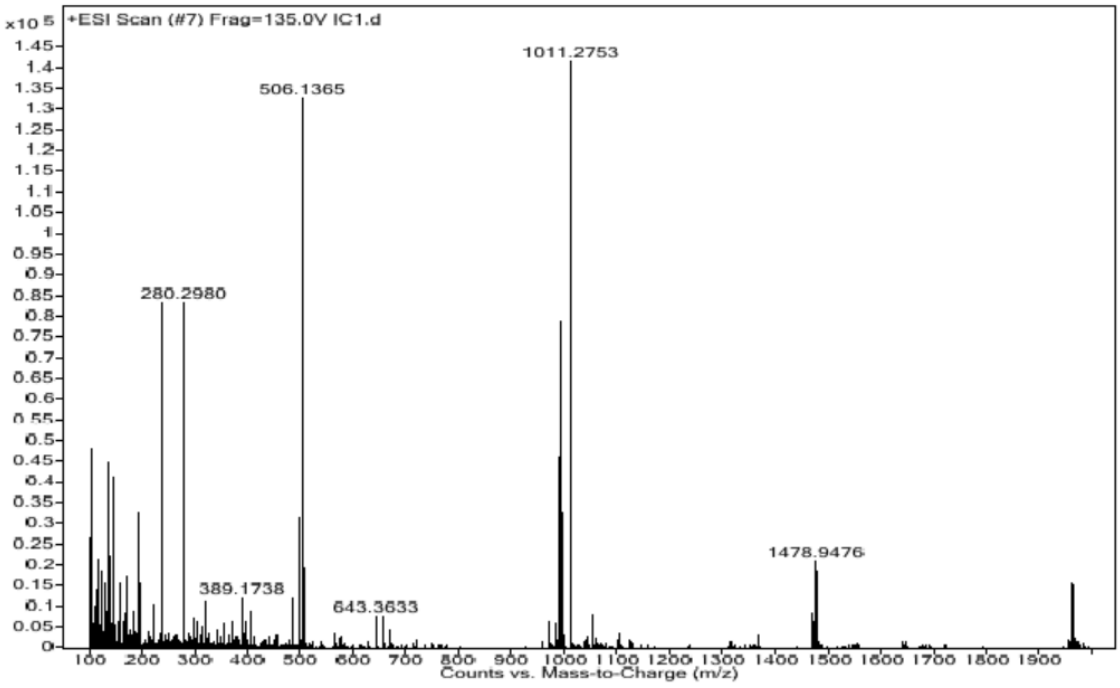

Figure 6.11(a). ESI mass spectra of [ALP]-α-CD inclusion complex

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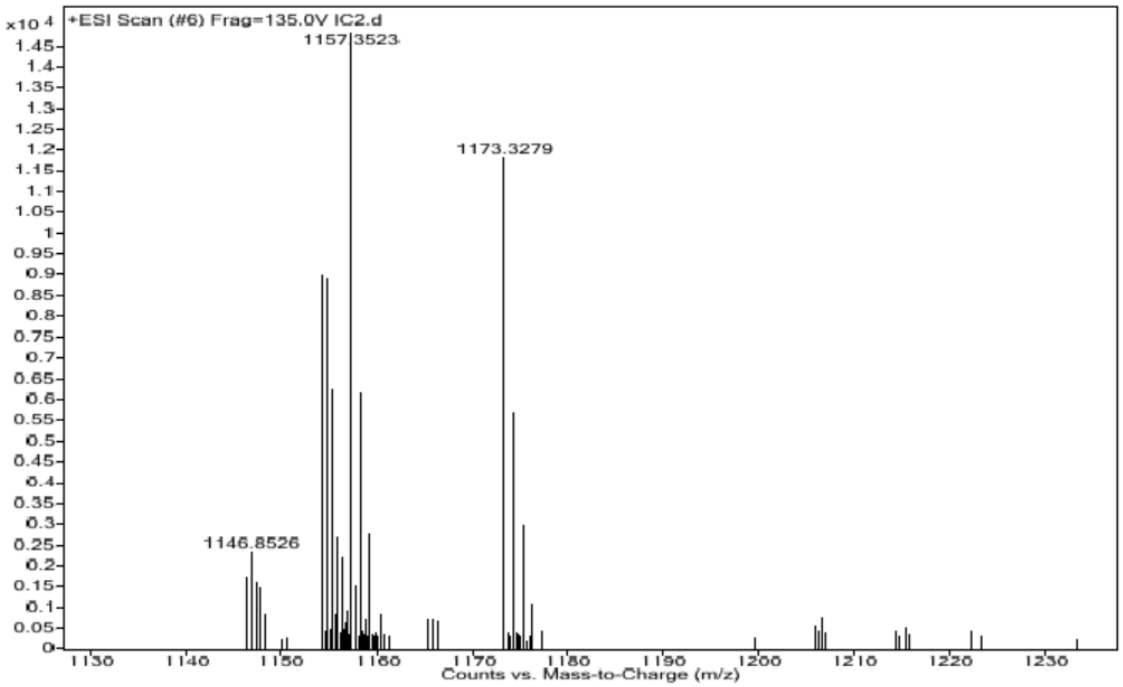

Figure 6.11(b). ESI mass spectra of [ALP]-β-CD inclusion complex

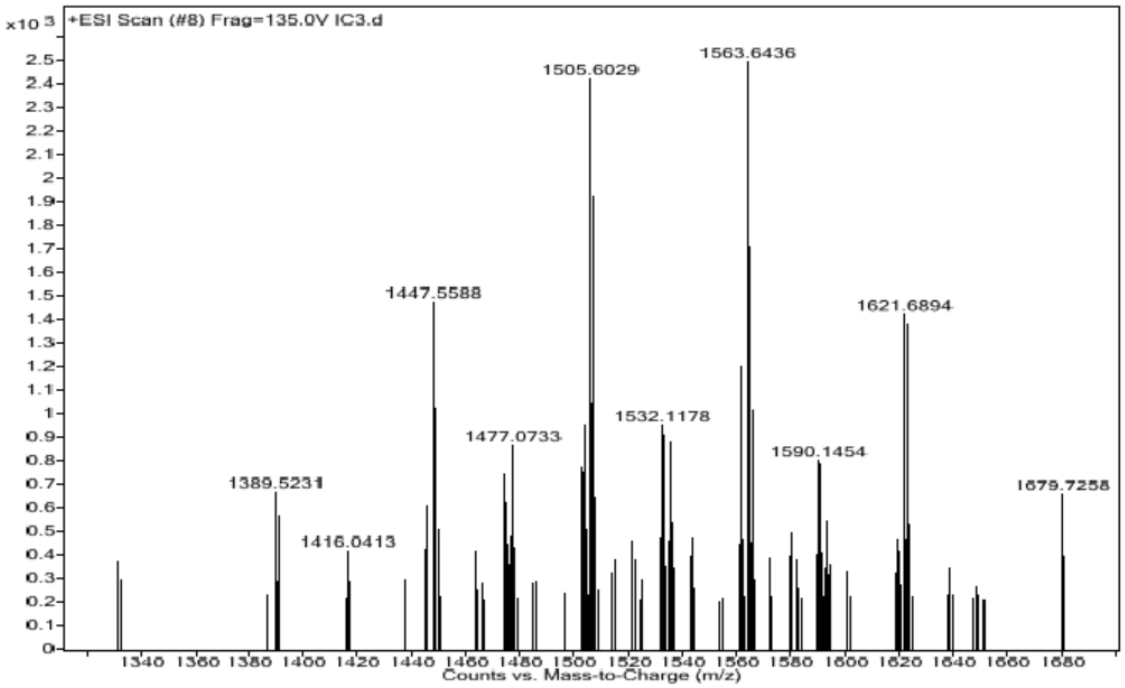

Figure 6.11(c). ESI mass spectra of [ALP]-HP-β-CD inclusion complex

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6.4. Biological activity

ALP itself is non-toxic to cut micro flora. No zone of inhibition, in case of both the gram positive and gram negative organisms. There was no growth inhibition compared to control. These results recommend that ICs (IC1 = [ALP + α – CD], IC2 = [ALP + β-CD], IC3 = [ALP + HP-β-CD] doesn't have any antimicrobial activity shown in Figure 6.12 (a), (b), (c). So it is nontoxic for the cells experiment based on the sensitivity towards cut micro flora. There is no effect on cut-microbes- host interaction. [38]

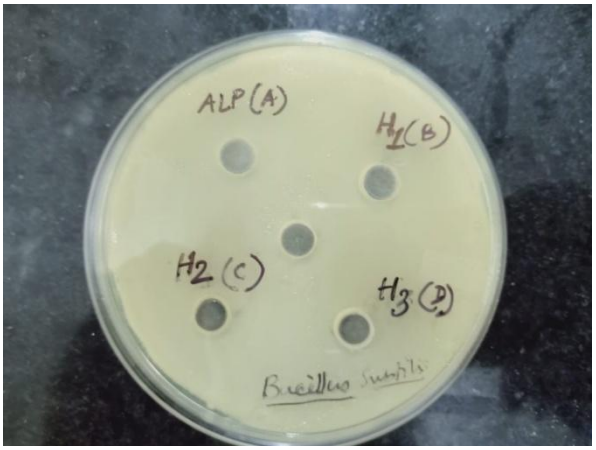

Figure 6.12(a). Antimicrobial activity analysis ALP on Gram-positive B. subtilis. No zone of inhibition was observed. Double distilled water was taken as the control.

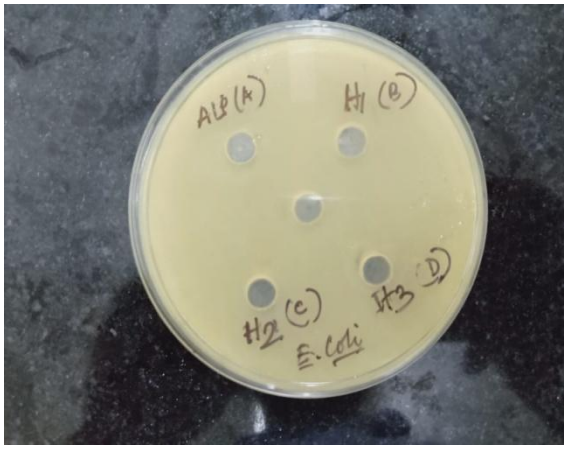

Figure 6.12(b). Antimicrobial activity analysis ALP on Gram-negative E. coli. No zone of inhibition was observed. Double distilled water was taken as the control.

Figure 6.12(c). Antimicrobial activity analysis on ALP on Gram-positive B. subtilis. No zone of inhibition was observed with IC1, IC2, and IC3. Double distilled water was taken as the control.

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Conclusion

Allopurinol sketch host-guest inclusion complexes together with (α-, β-, HP-β-) CD win the (1:1) stoichiometry which is recognized by UV, NMR, Steady state Fluorescence, SEM, HRMS imply that the selected guest (ALP) molecule, shaped IC's with nano hydrophobic core of efficiency. As a result the present work adjoins a new dimension in the diversified field of existing science of controlled release of allopurinol through appropriate host molecules like (α-, β-, HP-β-) CD.

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CHAPTER VII

Studies on the Solvation Consequences of N,N-dimethylformamide and Dimethyl sulphoxide on Salicylaldehyde anil zinc(II)

7.1. Introduction

Zinc is biologically one of the most important essential metals, because it is a constituent of over 200 metalloproteinase and about 300 enzymes, *e.g*., carboxy peptidase, carbonic anhydrase and alcohol dehydrogenase, *etc*.[1] It is also one of the most essential micronutrients for plant growth.[2] A large number of biochemical processes in plants require Zn.[3,4] Some biological processes, *viz*., protein and carbohydrate metabolism, anti-oxidative defence and various enzymatic activities[5] involve zinc. On the other side, Schiff base complexes are very much valuable in transition metal coordination chemistry due to their preparative accessibility and structural variety. Such complexes have various contributions to both basic and applied fields due to their various applications such as in catalysis, magnetism, material chemistry, molecular architecture, as anti-microbial, anti-tumor and dying agents, *etc*.[6-11] Salicylidene-aniline (abbreviated as SA) is an important Schiff base because of its uses in optical memory devices and optical switches. Liu *et al*.[12] synthesized salicylaldehyde anil zinc (SAZ) that can form nano-scale thermally stable amorphous films. Most of the reactions are generally occur in the solution phase and solvents influence the reactions in various ways. The presence of solvent influences the outcome of a reaction via the interaction of local environment with the individual species that undergo the reactions. The solvents are important part of the chemical or biochemical processes. The solvents give an alternative energy path for stabilization of energetic products and perturb the potential energy curves of the reactions.[13] Such solvent effects can be understood with the help of experimental physical and chemical data of the solvents and intermolecular forces operating within the solution.[14] The thermodynamic properties of the solute constituents in dilute solution, in short solvation consequences are of immense importance to reveal the behavior of solute molecule in solution (like size, structure, packing). That's why in this chapter an attempt was undertaken to study these properties for SAZ in two pure solvents (N, N-dimethyl formamide, dimethyl sulphoxide) at 298.15, 303.15, 308.15, 313.15 and 318.15 K.

7.2. Experimental Section

7.2.1. Chemicals used

Analytical reagent (A.R.) grade aniline, salicylaldehyde, zinc acetate dihydrate and spectroscopic grade N,N-dimethyl formamide, dimethyl sulphoxide (all with purity >99%) were purchased from Sd Fine chemicals, India. All the chemicals were used as received from the commercial sources. Table 7.1 contains the measured physical properties of these pure solvents and compared to the literature values.[15–22]

Following a literature method the Schiff base ligand (SA) and its corresponding zinc(II) complex were prepared.[23] The ligand (SA) was prepared by condensing salicylaldehyde with aniline (in 1:1 molar ratio). The reaction mixture when stirred for about an hour at around 140-150 °C yielded SA as a yellow precipitate. It was filtered and washed successively with little MeOH, diethylether and recrystalized from MeOH. Next a methanolic solution of SA and zinc acetate (in 1:2 molar ratio) was stirred for an hour at around 60-80 °C to yield the complex (SAZ) as yellowish green solid. It was filtered, dried in vacuum and recrystallized from methanol. Its purity was checked by elemental analysis (Found: C, 63.20; O, 12.91; N, 5.64; H, 4.08; Zn, 13.22; Calc: C, 63.23; O, 12.96; N, 5.67; H, 4.09; Zn, 13.24) and IR spectroscopy (bands at 1609.5 (1616.1[23]), 1584.2 (1589.2[23]), 1255 (1253.1[23]), 1174, 602 (596[23]), 547, 3438 (3435[23]). Elemental micro-analyses were obtained from Perkin–Elmer (Model 240C) analyzer and IR spectrum was recorded on Perkin–Elmer FT-IR spectrophotometer (Spectrum RX1). The molecular structure of the Schiff base ligand (SA) and its metal complex (SAZ) are presented in Figure 7.1.

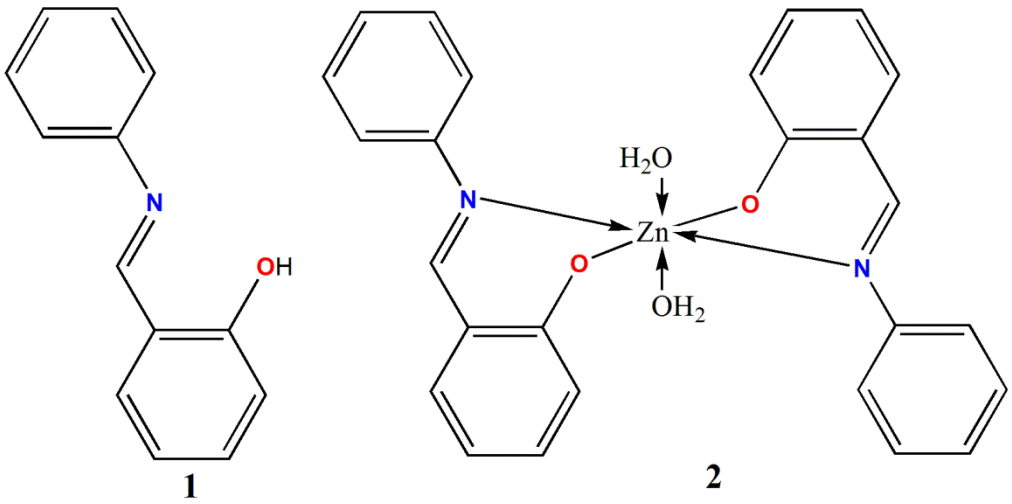

Fig 7.1. Molecular structure of: 1, Salicylidene-aniline (SA); 2, salicylaldehyde anil zinc (SAZ).

Table 7.1. Densities (ρ) and viscosities (η) of DMF and DMSO at T = (298.15 to 318.15) K.

Solvent	T /K	$\rho \cdot 10^{-3}$/kg · m^{-3}		η/mPa · s	
		Expt.	Lit.	Expt.	Lit.
DMF	298.15	0.94404	0.9445[15]	0.8025	0.802[16]
	303.15	0.93939	0.9398[15] 0.94009[19]	0.7512	0.752[17]
	308.15	0.93462	0.9351[15]	0.7103	0.710[15]
	313.15	0.92968	0.9302[15] 0.9298[18] 0.93074[19]	0.6637	0.673[15] 0.664[17]
	318.15	0.92486	-	0.6333	-
DMSO	298.15	1.09570	1.09629[22]	1.9914	1.9960[22]
	303.15	1.09040	1.09037[19] 1.09041[20] 1.09144[22]	1.8080	1.786[19] 1.8357[22]
	308.15	1.08476	1.08641[22]	1.6431	1.6689[22]
	313.15	1.07974	1.08058[19] 1.08159[22]	1.5126	1.506[19] 1.516[21] 1.5351[22]
	318.15	1.07474	1.07646[22]	1.3815	1.3935[22]

7.2.2. Apparatus and procedure

All the stock solutions of the complex in both the solvents were prepared by mass using an analytical balance (Mettler, AG 285, Switzerland) with a precision of ±0.01 mg. Molalities were converted into molarities using experimental density values. Densities (ρ) were measured with a vibrating-tube density meter (Anton Paar, DMA 4500M). Viscosities (η) were measured by means of a suspended Canon-type Ubbelhode viscometer. In all determinations, an average of triplicate measurements was used for various data calculations. Adequate precautions were adapted to keep evaporation losses minimum during the measurements. The standard uncertainties in the molality of SAZ solutions, densities and viscosities were $\pm 1 \times 10^{-4}\,\mathrm{mol \cdot kg^{-1}}$,

$\pm 2\times10^{-5}\,\mathrm{g\cdot cm^{-3}}$, $\pm 4\times10^{-4}$ mPa·s, respectively. The details of the calibration and measurement techniques have been described in Chapter III.

7.3. Results and discussion

The experimental molalities (*m*), densities (ρ), viscosities (η), and apparent molar volumes (ϕ_V) of SAZ in both the solvents at experimental temperatures are reported in Table 7.2.

7.3.1. *Apparent and partial molar volumes*

The apparent molar volumes (ϕ_V) were obtained using the following relation:[24]

$$\phi_V = \frac{M}{\rho} - \frac{1000(\rho - \rho_1)}{m\rho\rho_1} \qquad (1)$$

where *m* is the molality of the SAZ solution, *M* is the molar mass of SAZ, ρ and ρ_1 are the densities of the solution and solvent respectively. Standard uncertainties in ϕ_V values were within the range of $0.17-0.22\times10^{-6}\,\mathrm{m^3\cdot mol^{-1}}$. ϕ_V values were observed to correlate linearly with the square root of solution molalities (*m*) at different temperatures (shown in Figure 7.2), hence standard partial molar volumes (ϕ_V^0) were obtained from the following equation known as Masson equation:[25]

$$\phi_V = \phi_V^0 + S_V^* \sqrt{m} \qquad (2)$$

where ϕ_V^0 is partial molar volume at infinitesimal dilution and S_V^* is the experimental slope. The values of ϕ_V^0 and S_V^* along with standard deviations at different temperature are reported in Table 7.3. Standard uncertainty of molality and apparent molar volume were $\pm1\times10^{-4}\,\mathrm{mol\cdot kg^{-1}}$ and $\pm 0.15-0.25\times10^{-6}\,\mathrm{m^3\cdot mol^{-1}}$, respectively. An inspection of it suggests that ϕ_V^0 values are positive in both the solvents and increases as experimental temperatures increase. The ϕ_V^0 values are comparatively greater in DMF than those in DMSO. This suggests the presence of the solute-solvent interactions[23,24] and such interactions may be attributed to increase in solvation of the complex in these solvents even at elevated temperatures.[26] These interactions are higher in case of DMF when compared to those in DMSO.

Table 7.2. Molalities (m), densities (ρ), viscosities (η), and apparent molar volumes (ϕ_V) of SAZ in DMF and DMSO at T = (298.15 to 318.15) K.

m/mol·kg^{-1}	$\rho \cdot 10^{-3}$/kg·m^{-3}	η/mPa·s	$\phi_V \cdot 10^6$/m^3·mol^{-1}
DMF			
T = 298.15 K			
0.0133	0.94551	0.8221	398.51
0.0267	0.94705	0.8391	395.39
0.0403	0.94862	0.8561	393.71
0.0540	0.95022	0.8757	392.16
0.0678	0.95189	0.8928	389.99
0.0818	0.95357	0.9072	388.50
T = 303.15 K			
0.0133	0.94088	0.7683	398.15
0.0267	0.94247	0.7880	393.72
0.0403	0.94409	0.8052	391.62
0.0540	0.94581	0.8250	388.36
0.0678	0.94751	0.8421	386.68
0.0818	0.94927	0.8541	384.82
T = 308.15 K			
0.0133	0.93613	0.7274	397.80
0.0267	0.93773	0.7499	393.76
0.0403	0.93940	0.7645	390.63
0.0540	0.94111	0.7843	388.13
0.0678	0.94286	0.8015	385.88
0.0818	0.94467	0.8187	383.64
T = 313.15 K			
0.0133	0.93121	0.6810	397.47
0.0267	0.93288	0.6983	391.21
0.0403	0.93459	0.7183	388.21
0.0540	0.93638	0.7329	384.90
0.0678	0.93823	0.7503	381.81
0.0818	0.94005	0.7676	380.31

	T = 318.15 K		
0.0133	0.92642	0.6534	396.20
0.0267	0.92809	0.6680	391.20
0.0403	0.92983	0.6853	387.73
0.0540	0.93169	0.7027	383.30
0.0678	0.93354	0.7228	380.75
0.0818	0.93549	0.7428	377.73
	DMSO		
	T = 298.15 K		
0.0114	1.09652	2.0138	390.53
0.0230	1.09740	2.0364	388.57
0.0347	1.09831	2.0590	387.16
0.0465	1.09924	2.0816	386.08
0.0585	1.10021	2.1018	384.83
0.0706	1.10122	2.1246	383.49
	T = 303.15 K		
0.0114	1.09089	1.8279	390.02
0.0230	1.09181	1.8532	387.68
0.0347	1.09279	1.8759	385.40
0.0465	1.09383	1.8988	383.15
0.0585	1.09489	1.9164	381.48
0.0706	1.09597	1.9420	380.12
	T = 308.15 K		
0.0114	1.08564	1.6658	389.36
0.0230	1.08660	1.6912	386.64
0.0347	1.08761	1.7141	384.47
0.0465	1.08865	1.7422	382.81
0.0585	1.08981	1.7653	380.02
0.0706	1.09099	1.7884	377.90
	T = 313.15 K		
0.0114	1.08065	1.5381	388.60
0.0230	1.08166	1.5583	385.11
0.0347	1.08273	1.5813	382.43

0.0465	1.08387	1.6044	379.76
0.0585	1.08503	1.6329	377.85
0.0706	1.08633	1.6589	374.82
	T = 318.15 K		
0.0114	1.07568	1.4044	387.80
0.0230	1.07672	1.4248	384.29
0.0347	1.07784	1.4480	381.08
0.0465	1.07899	1.4712	378.90
0.0585	1.08030	1.4946	375.16
0.0706	1.08166	1.5207	372.03

DMF is a colourless water miscible liquid amide and DMSO is also a colourless water miscible organo sulfur compound. Although DMSO (Dielectric constant = 49) is more polar than DMF (dielectric constant = 37), DMF has a resonance structure that carries positive charge over its N-atom and negative charge over its O-atom. That is why the complex probably interacts more via the polar-polar and polar-ionic group interactions in DMF than those in DMSO. On the contrary, S_V^* indicates the extent of the solute-solute interactions. Negative values of S_V^* and its trend opposite to ϕ_V^0 values indicate weak solute-solute interactions.[23,24] So it can be said that the solute–solvent interactions dominate over the solute–solute interactions in both the solvents, *i.e.*, the complex exists in highly solvated form in both these solvents.

7.3.2. ***Apparent molar expansibilities***

The apparent molar expansibilities (ϕ_E) of SAZ in two different solvent were determined by using following the relation:[27]

$$\phi_E = \alpha\phi_V + \frac{1000(\alpha - \alpha_1)}{m\rho_1} \tag{3}$$

where $\alpha = -\rho^{-1}(\partial\rho/\partial T)_P$ is the coefficient of isobaric thermal expansion of the solvent and $\alpha_1 = -\rho_1^{-1}(\partial\rho_1/\partial T)_P$ is of solution, and other symbols have their usual significance. The standard uncertainty in the coefficients of isobaric thermal expansion was $\pm 4\times10^{-6}\,\mathrm{K}^{-1}$ and in case of ϕ_E, the uncertainty values was within

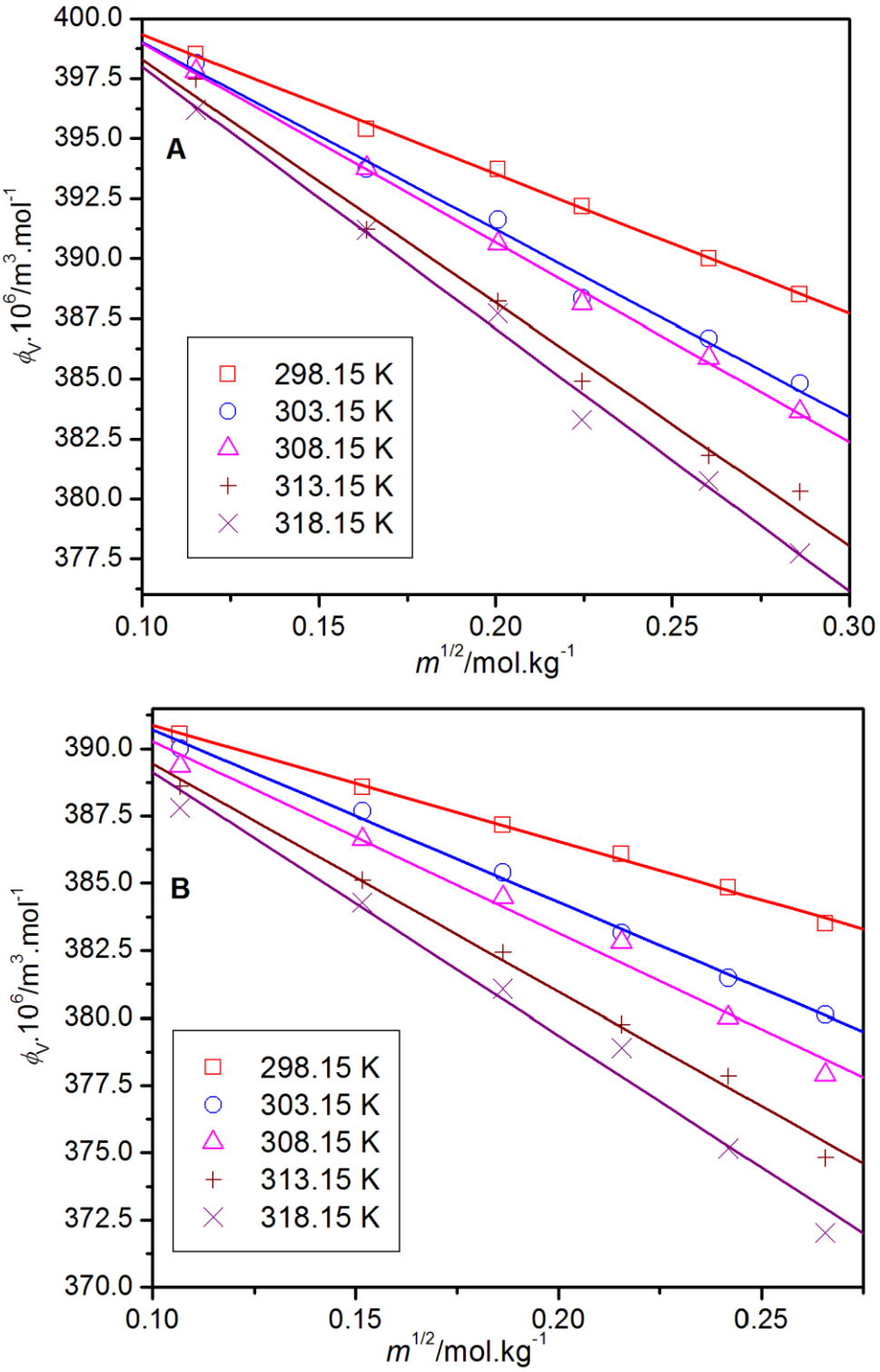

Fig 7.2. Apparent molar volumes (ϕ_V) of the complex against its square root of molalities ($\sqrt{m}$) in: A, DMF and B, DMSO at various experimental temperatures.

Table 7.3. Partial molar volumes (ϕ_V^0), the slopes (S_V^*) and standard deviations (σ) of linear regression of Eq. (2) for SAZ in DMF and DMSO at T = (298.15 to 318.15) K.

T/K	$\frac{\phi_V^0 \cdot 10^6}{\mathrm{m^3\ mol^{-1}}}$	$\frac{S_V^* \cdot 10^6}{\mathrm{m^3\ kg^{1/.2}\ mol^{-3/2}}}$	$\frac{\sigma \cdot 10^6}{\mathrm{m^3\ mol^{-1}}}$
	DMF		
298.15	405.10 (±0.37)	-57.49 (±1.71)	2.64
303.15	406.86 (±0.49)	-77.73 (±2.27)	3.51
308.15	407.27 (±0.09)	-82.46 (±0.40)	0.62
313.15	407.42 (±0.81)	-100.60 (±3.70)	5.74
318.15	408.94 (±0.48)	-108.67 (±2.22)	3.45
	DMSO		
298.15	395.20 (±0.21)	-43.30 (±1.02)	1.47
303.15	397.12 (±0.31)	-64.16 (±1.52)	2.18
308.15	397.40 (±0.71)	-71.24 (±3.52)	5.06
313.15	397.94 (±0.53)	-84.88 (±2.64)	3.80
318.15	398.93 (±1.03)	-97.92 (±5.09)	7.32

Standard errors are given the parenthesis.

$\pm 0.001\times10^{-6}\,\mathrm{m^3\,mol^{-1}\,K^{-1}}$, respectively. The partial molar expansibilities (ϕ_E^0) were obtained from the given relation:[27]

$$\phi_E = \phi_E^0 + S_E\sqrt{m} \qquad (4)$$

The $(\partial\phi_E^0/\partial T)_P$ values were found from the slope of linear fit of ϕ_E^0 values against temperature T (as shown in Figure 7.3) with the correlation coefficient ($R^2 \approx$ 0.963-0.999). The ϕ_E^0 values of SAZ in different solvent at different temperature are presented in Table 7.4. A pursue of it shows that ϕ_E^0 values are negative in both the solvent and decreases as the temperature increases. These may be because of structural perturbation caused by the

Table 7.4. Partial molar expansibilities (ϕ_E^0), the slopes (S_E) and the $(\partial\phi_E^0/\partial T)_P$ values for the complex in DFM and DMSO at the experimental temperatures.

Parameters	T	DMF	DMSO
ϕ_E^0	298.15	-0.242 (±0.002)	-0.219 (±0.001)
	303.15	-0.244 (±0.003)	-0.222 (±0.002)
	308.15	-0.249 (±0.002)	-0.226 (±0.002)
	313.15	-0.253 (±0.002)	-0.229 (±0.001)
	318.15	-0.258 (±0.004)	-0.233 (±0.003)
S_E	298.15	-2.21 (±0.01)	-2.34 (±0.01)
	303.15	-2.25 (±0.02)	-2.38 (±0.04)
	308.15	-2.27 (±0.01)	-2.40 (±0.03)
	313.15	-2.31 (±0.02)	-2.44 (±0.04)
	318.15	-2.34 (±0.04)	-2.47 (±0.01)
$(\partial\phi_E^0/\partial T)_P$		-0.814 (±0.002)	-0.696 (±0.003)

Units: T, K; ϕ_E^0, $10^{-3}\,m^3\cdot mol^{-1}\cdot K^{-1}$;
S_E, $10^{-3}\,m^3\cdot kg^{1/2}\cdot mol^{-1}\cdot K^{-1}$ and $(\partial\phi_E^0/\partial T)_P$, $10^{-6}\,m^3\cdot mol^{-1}\cdot K^{-2}$

gradual appearance of caging/packing effect[28,29] as the temperature increases. According to Hepler,[30] sign of $(\partial\phi_E^0/\partial T)_P$ is a better criterion in characterization of long-range structure making and breaking ability of the solutes in solution. If the values of $(\partial\phi_E^0/\partial T)_P$ are negative the solute behaves as a structure breaker,

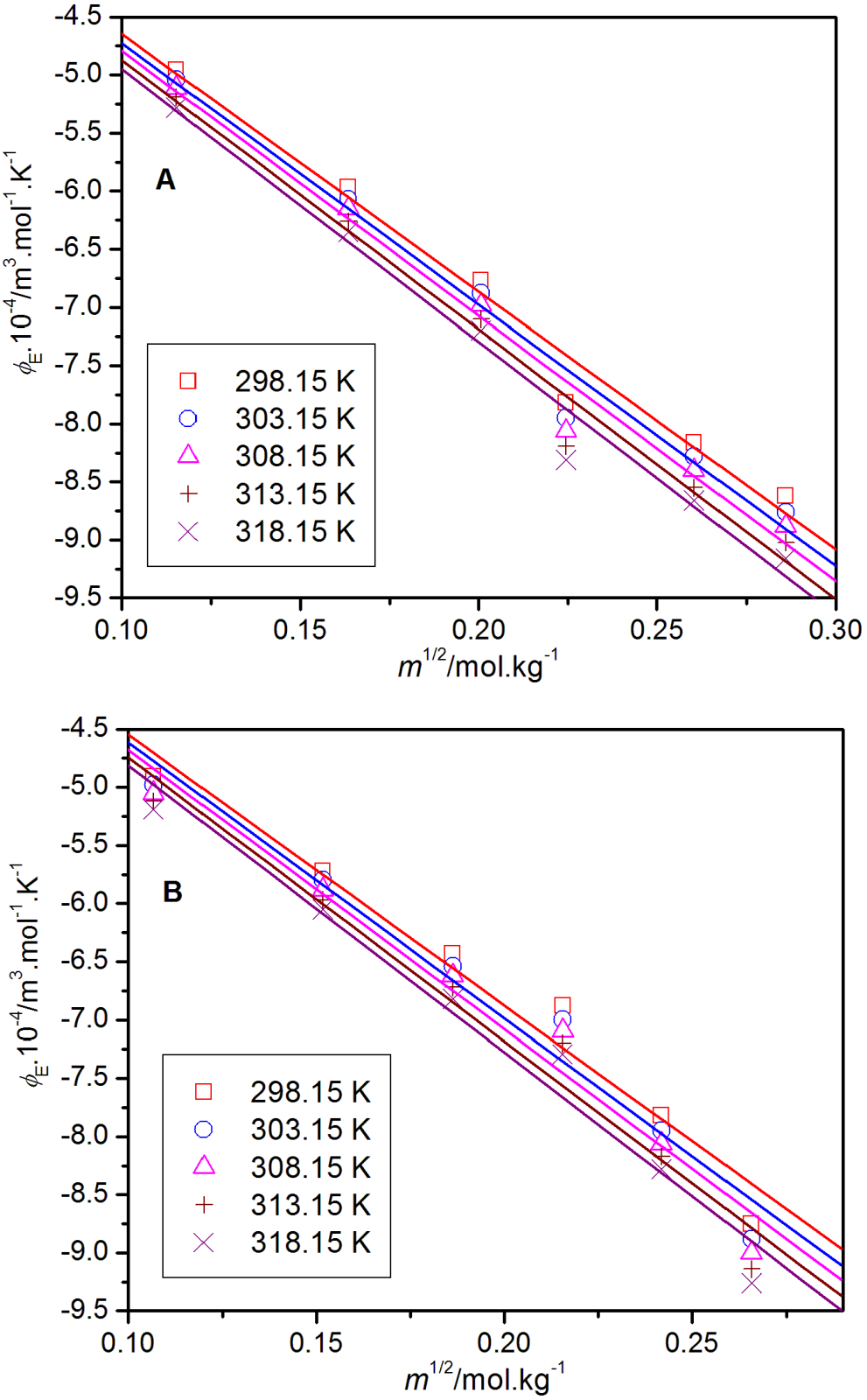

Fig 7.3. Apparent molar expansibilities (ϕ_E) of the complex against its square root of molalities ($\sqrt{m}$) in: A, DMF and B, DMSO at various experimental temperatures.

otherwise it is a structure maker. The negative values of $(\partial\phi_E^0/\partial T)_P$ (given in Table 7.4) for SAZ in both the solvent indicate SAZ behaves as a net structure breaker.

7.3.3. ***Viscometric results***

Viscosity *B*-coefficient depends on solute-solvent interaction and structural factors; it gives a clear idea regarding structural modification caused by the solute-solvent interactions and can be obtained from the relation:

$$\eta_r = 1 + Bc \tag{5}$$

where $\eta_r = \eta/\eta_1$; η_1, η are viscosities of the solvents and of the solutions; c is molar concentration of the solute. Values of viscosity *B*-coefficient depend on several factors like solute-solvent interaction, structural factors. Viscosity *B*-coefficients were obtained by least squares linear regression analysis with correlation coefficient ($R^2 \approx$ 0.992-0.999). An investigation of Table 7.5 shows that viscosity *B*-coefficients for SAZ in the studied solvent systems are positive and their values increase with increasing temperature. Solvation numbers (S_n) were calculated using the relation:[31] $S_n = B/\phi_V^0$ that provides useful information about the primary solvation sphere around the solute; The value of solvation numbers for an unsolvated spherical solute lie between 0 to 2.5 but higher S_n values is an indication of solvated state with a primary solvation sphere. Study of S_n values, presented in Table 7.5 indicated that SAZ remains highly solvated in both the solvent media especially in DMF and its solvation is likely to be favored at high temperature.

On the basis of Feakins' transition state theory of relative viscosity,[32, 33] the viscosity *B*-coefficients were used for the calculation of Gibbs free energy of activation per mole of solvent ($\Delta\mu_1^{0\neq}$) and solute ($\Delta\mu_2^{0\neq}$):

$$\Delta\mu_1^{0\neq} = \Delta G_1^{0\neq} = RT\ln(\eta_1\phi_{V,1}^0/hN_A) \tag{6}$$

$$\Delta\mu_2^{0\neq} = \nu\Delta\mu_1^{0\neq} + [B - (\nu\phi_{V,1}^0 - \phi_{V,2}^0)](\phi_{V,1}^0/RT) \tag{7}$$

where $\phi_{V,1}^0$ is the partial molar volume of the solvent and $\phi_{V,2}^0$ is of the solute. The other symbols have their usual significances. The values of $\Delta\mu_1^{0\neq}$ and $\Delta\mu_2^{0\neq}$ are given in Table 7.6. An inspection of it shows that $\Delta\mu_1^{0\neq}$ is almost invariant with temperatures in a particular solvent, suggesting that $\Delta\mu_2^{0\neq}$ is dependent mainly on

viscosity *B*-coefficient values and $\phi_{V,1}^{0}$, $\phi_{V,2}^{0}$ terms. $\Delta\mu_1^{0\neq}$ values are positive but much smaller

Table 7.5. Viscosity *B*-coefficients for SAZ with standard deviations σ for linear regression of Eq. (5) and solvation number (S_n) in DMF and DMSO at T = (298.15 to 318.15) K.

Parameters	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
			DMF		
$B/\mathrm{m}^3\cdot\mathrm{mol}^{-1}$	1.728	1.868	2.050	2.108	2.312
	(±0.027)	(±0.052)	(±0.040)	(±0.030)	(±0.053)
$\sigma/\mathrm{mPa}\cdot\mathrm{s}$	0.002	0.003	0.002	0.002	0.003
S_n	4.27	4.59	5.03	5.16	5.66
	(±0.071)	(±0.135)	(±5.162)	(±0.083)	(±0.136)
			DMSO		
$B/\mathrm{m}^3\cdot\mathrm{mol}^{-1}$	0.887	0.995	1.212	1.304	1.372
	(±0.006)	(±0.018)	(±0.013)	(±0.031)	(±0.019)
$\sigma/\mathrm{mPa}\cdot\mathrm{s}$	0.001	0.001	0.001	0.002	0.001
S_n	2.24	2.51	3.05	3.27	3.44
	(±0.016)	(±0.049)	(±0.038)	(±0.082)	(±0.493)

Standard errors are given the parenthesis.

with respect to $\Delta\mu_2^{0\neq}$ values in both the solvent at all the experimental temperature indicating that the interaction of SAZ molecule with both the solvent are much stronger in the ground state than that of transition state. So in free energy terms, solvation of SAZ is less favored in transition state. Values of $\Delta\mu_2^{0\neq}$ increases with increasing temperature indicate that viscous flow becomes more difficult at higher temperature because of greater solute-solvent interaction. So, positive temperature dependence of both viscosity *B*-coefficients and $\Delta\mu_2^{0\neq}$ values suggest structure breaking ability of solute which is also supported by negative values of $(\partial\phi_E^0/\partial T)_P$.

Table 7.6. Values of $\Delta\mu_1^{0\neq}$, $\Delta\mu_2^{0\neq}$ and $(\Delta\mu_2^{0\neq} - \Delta\mu_1^{0\neq})$ for SAZ in DMF and DMSO at T = (298.15 to 318.15) K

T /K	$\Delta\mu_1^{0\neq}$ / kJ mol^{-1}	$\Delta\mu_2^{0\neq}$ / kJ mol^{-1}	$(\Delta\mu_2^{0\neq} - \Delta\mu_1^{0\#})$ / kJ mol^{-1}
		DMF	
298.15	12.51	78.31	65.80
	(±0.01)	(±0.03)	(±0.02)
303.15	12.57	83.71	71.14
	(±0.03)	(±0.05)	(±0.04)
308.15	12.65	90.55	77.91
	(±0.05)	(±0.04)	(±0.04)
313.15	12.69	93.41	80.72
	(±0.01)	(±0.03)	(±0.03)
318.15	12.78	101.21	88.43
	(±0.02)	(±0.04)	(±0.03)
		DMSO	
298.15	14.56	56.66	42.09
	(±0.01)	(±0.01)	(±0.01)
303.15	14.57	61.00	46.43
	(±0.01)	(±0.02)	(±0.02)
308.15	14.58	69.27	54.69
	(±0.01)	(±0.01)	(±0.01)
313.15	14.62	73.25	58.63
	(±0.01)	(±0.03)	(±0.03)
318.15	14.62	76.40	61.78
	(±0.01)	(±0.02)	(±0.02)

Standard errors are given the parenthesis.

7.4. Conclusion

So different parameters such as partial molar volumes (ϕ_V^0) at infinite dilution, and viscosity *B*-coefficient values for SAZ suggest the presence of strong

solute-solvent interactions in both the solvents and these interactions are greater in DMF than in DMSO. The negative $\left(\partial\phi_E^0/\partial T\right)_P$ values for SAZ in both DMF and DMSO indicate structure breaking ability of the complex and this fact is also supported by viscosity *B*-coefficients and $\Delta\mu_2^{0\neq}$ values.

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CHAPTER VIII

Concluding Remarks

The main objectives of this research work is to find out how the biologically active molecules are get affected the by the different types of ionic liquid and heart stimulant like caffeine molecules. Because there is close resemblance found among the biologically active molecules and their molecular conformation and biological phenomena`s. Since most of the biological activity are found to be happened in the water medium, so maximum no. of my work focused on it. During this study it was found that temperature and the concentration of the solvent plays most important role in predicting the different type of interaction taking place in between biologically active molecules and other compound. Therefore in this research work some viscometric properties, volumetric properties, different types of transport property, ultrasonic measurement ,refractive index, etc., have been studied in order to understand such interaction.

In chapter IV, from the comparative study of the L-Leucine and L-Proline in aqueous Tetrabutyl Phosphonium *p*-Toluene Sulphonate solutions at 298.15, 303.15 and 308.15K gives a deep insight about the different types of solute-solute, solute-solvent interaction. In addition to this how the various interaction takes place in the aqueous solution between solute and solvent or solute-cosolute, solute-solute depends upon the molecular structure of the solute and the solvent is also discussed. Here the values of the limiting apparent molar volume (ϕ_V^0) and viscosity *B*-coefficients for L-Leucine and L-Proline in aqueous TBPPTS shows the existence of strong solute-solvent interactions that rises with the increase in amount of TBPPTS in solvent mixture and with the rise in the experimental temperature. The refractive index and the molar refraction values also suggest that L-Leucine molecules are interact more with the solvent molecule i.e tightly packed in the solution leading to higher solute-solvent interaction than L-Glycine.

In chapter V, It has been found that the partial molar volumes (ϕ_V^0) and viscosity *B*-coefficients of both the solutes in the aqueous uracil solutions are positive. These results unveil that the solute-solvent interactions are strong and there is structural enhancement at even higher temperatures. Again for the studied aqueous

solutions, S_V^* values are found to be negative and always lesser than the ϕ_V^0 values, *i.e*, the solute-solvent interactions spur the solute-solute interactions. Standard transfer volumes ($\Delta_t\phi_V^0$) are all positive for the solutions with paracetamol and such values increase when uracil molalities in the ternary solutions increase at all the experimental temperatures. $\Delta_t\phi_V^0$ values for the solutions with caffeine are positive initially; however, such values decrease as the uracil molalities in the ternary solutions increase and finally they become negative. These values are suggestive of the presence of polar-hydrophobic, hydrophilic-hydrophobic and hydrophobic-hydrophobic interactions and theses interactions result into volume contraction by the increased electrostriction of water by caffeine. These results are also well reflected by ϕ_E^0 and $\left(\partial\phi_E^0/\partial T\right)_P$ values of these solutes and they act as an overall structure maker in aqueous uracil solutions. Further the fact that $\Delta\mu_2^{0\neq} > \Delta\mu_1^{0\neq}$ and the viscosity *B*-coefficients are all positive for the aqueous solutions investigated support the view that the degree of solute-solvent interactions are greater in the ground state than those in the transition state and the solvation of the solutes is less favoured energetically in the transition state. The absorption spectra for the solutes in various aqueous uracil solutions also well corroborate with the above results.

In Chapter VI, the drug molecule Allopurinol sketch host-guest inclusion complexes together with (α-, β-, HP-β-) CDwin the (1:1) stoichiometry which is recognized by UV, NMR, Steady state Fluorescence, SEM, HRMS imply that the selected guest (ALP) molecule, shaped IC's with nano hydrophobic core of efficiency. As a result the present work adjoins a new dimension in the diversified field of existing science of controlled release of allopurinol through appropriate host molecules like (α-, β-, HP-β-) CD.

In Chapter VII, the different parameters such as partial molar volumes (ϕ_V^0) at infinite dilution, and viscosity *B*-coefficient values for SAZ suggest the presence of strong solute-solvent interactions in both the solvents and these interactions are greater in DMF than in DMSO. The negative $\left(\partial\phi_E^0/\partial T\right)_P$ values for SAZ in both

DMF and DMSO indicate structure breaking ability of the complex and this fact is also supported by viscosity *B*-coefficients and $\Delta\mu_2^{0\neq}$ values.

However, the molecular interactions are too much complex in nature and quite hard to investigate and explain, obviously those involving biologically active molecules. There are various forces may executed between the molecules present in a solvent and it is tough to isolate or identify and assign them all. By careful implementing of various experimental procedure and theoretical equation some valuable conclusions may be drawn depending on the nature of structure solute and solvent present in the solution. It also depends upon the order or the arrangement of the systems in solution phase. By realizing the nature and structure of the complex compound present in solution is important for the choosing of solvents to be used in a definite reaction. It may further add an excellent way to give the quantitative explanation of the various interactions taking place in the solution and the influence of the solvent and solute on these interactions in the solution mixture. It also provides a way for realizing different type of phenomena that attached to the solution chemistry. Though the many research work found in this field that enriched the solution chemistry but it still have wide scope to be explore.

APPENDIX I

List of Publications

[1] Probing Subsistence of Host Guest Inclusion Complexes of Oligosaccharides with Allopurinol for Regulatory Release with the Manifestation of Solvation Consequences , ***J. Adv. Chem. Sci. – Volume 5 Issue 1 (2019) 621–628***

APPENDIX II

Seminar, Symposium & Convention Attended

- **Trend in surface science and related areas(TSSRA)V**, organized by Department of Chemistry, University of North Bengal, Darjeeling, India & Indian society for surface science & technology, Jadavpur university, Kolkata-700023 , India on December 06,2008 as Delegate.

- **National Seminar on Frontiers in Chemistry**, organized by Department of Chemistry, University of North Bengal, 11th and 12th March 2014 as delegate.

- **17th CRSI National Symposium in Chemistry**, organized by Department of Chemistry, National Chemical Laboratory, Pune, India on 6-8 February, 2015; presenting poster.

- **National Seminar on Frontiers in Chemistry**, organized by Department of Chemistry, University of North Bengal, Darjeeling and CRSI North Bengal Local Chapter on February, 2017 as Delegate.

- **UGC- ASSISTED INTERNATIONAL INTERDISCIPLINARY SEMINAR**-Contemporary Development in social and basic sciences in times of global crisis. Organized by Surya Sen Mahavidyalaya, March 28th -29th, 2017 (oral presentation).

- **International Seminar on "International year of the periodic table of chemicals"** 22nd, 23rd November2019" .organized by Department of Chemistry, University of North Bengal, Darjeeling. Presenting Poster.

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Probing Subsistence of Host Guest Inclusion Complexes of Oligosaccharides with Allopurinol for Regulatory Release with the Manifestation of Solvation Consequences

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ABSTRACT

The inspection of molecular interaction widespread in allopurinol and in aqueous solutions of α-, β- and HP-β-cyclodextrin have been probed by thermophysical properties. The established complexes obtained with 1:1 stoichiometry. Role of solvent (aqueous solution of α-CD, β-CD, HP-β-CD) and contribution of solute–solute and solute–solvent interactions to solution complexes, have also been analyzed via stability constant-NMR, UV, steady state fluorescence, FTIR, HRMS, SEM, PXRD, cytotoxicity, hydrophobic effect, hydrogen-bonding, structural effects in creation of inclusion complexes.

1. Introduction

Uric acid is end-product of the purine catabolic path. Enzyme xanthine oxido reductase is concerned in formation of uric acid from hypoxanthine and xanthine. Xanthine oxidoreductase exists in two distinct functional forms including xanthine dehydrogenase and xanthine oxidase [1-7]. Allopurinol or 1,5-dihydro-4H-pyrazolo [3,4-d] pyrimidin-4-one, is a purine inhibitor of the enzyme xanthine oxidase. This material as a significant drug for hyperuricemia can inhibit the synthesis of uric acid [8-11]. Ever in the last 50 years ago, it has been administered for treatment of gout. In the year of 1946, allopurinol was developed by Elion and colleagues, at Burroughs-Wellcome Company. Allopurinol (ALP) is quickly oxidized by xanthine oxidase to hypoxanthine and xanthine, respectively. ALP after oral administration is rapidly absorbed and has a short half-life in plasma (about 2-3 hours). Therefore, we have used all the supramolecular molecules with various cavity sizes to show its controlled release and increase its longevity in the plasma. Xanthine oxidase is a noteworthy biological source of free radical generation and ALP, as an antioxidant, has direct and indirect antioxidant activity on these free radicals. Furthermore, it can scavenge free radicals such as hydroxyl radical and superoxide anion and numerous studies have shown these effects of ALP. This drug revealed advantageous effects in the treatment of some renal disorders both in experimental and clinical trials [12-17].

Macrocyclic cyclodextrins (enzymic conversion products of starch) were exposed in 1891, and structures were elucidated in the mid-1930s. Their industrial implication become obvious in the 1970s, by now thousands of tons of the three cyclodextrins (α-, β-, and HP-β-CD) and of their chemical derivatives and inclusion complexes are produced industrially. Outer surface of these doughnut-shaped molecules is hydrophilic, but they have an axial open cavity, which is of hydrophobic character and capable of including other apolar molecules (or their moiety) in case of geometric compatibility. This is the real meaning of molecular encapsulation by inclusion complex formation. Taking into account that one, and probably largest, field of practical utilization of CDs is based on their solubilizing capacity (mainly in pharmaceutical industry) due attention must be paid to the above-mentioned, and many other CD-related, apparent anomalies by solution chemistry [18-25]

The goal of this paper is to give comprehensive information about therapeutic effects and the controlled delivery of allopurinol as an antioxidant agent in some diseases including hyperuricemia, renal IRI, nephrotoxicity, gout, contrast-induced nephropathy etc.

2. Experimental Methods

2.1 Source and Purity of Materials

Allopurinol and CD's purchased from Sigma-Aldrich. Mass fractions purity of both was ≥0.99. The used reagents were placed in the desiccators over P_2O_5 to keep them in dry atmosphere. These chemicals were used as received without extra purification (Fig. 1).

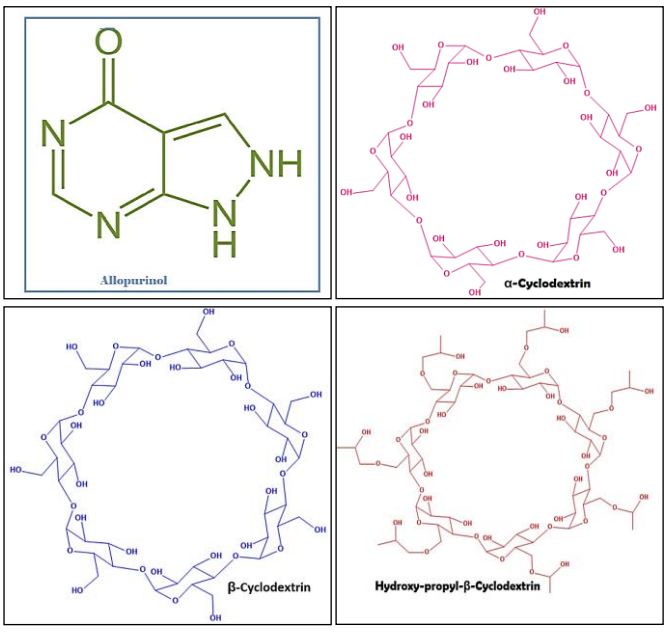

Fig. 1 Molecular structures of the hosts and guest

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2.2 Apparatus and Procedure

Prior to start of the experimental work we observed that allopurinol soluble in all proportion of aqueous CD solutions. Therefore, mother solutions of Allopurinol were prepared by mass (Mettler Toledo AG-285 with uncertainty 0.0003 g) and then the working solutions were prepared by mass dilution. Conversions of molarity into molality had been done using experimental density values of respective solutions and adequate precautions were taken to reduce evaporation losses during mixing in the experiment.

^{1}H NMR and 2D ROESY spectra of the solid inclusion complex prepared were recorded in D_2O using Bruker AVANCE 400 MHz instrument. The signals are presented in ppm using residual protonated solvent signal at 4.79 ppm in D_2O as internal standard and all the Data are reported as chemical shift. UV–visible spectroscopic data was carried out using JASCO V-530 UV/VIS Spectro-photometer with wavelength accuracy of ±0.5nm. Spectra were recorded at (297.15±1) K. FTIR spectras of solid ICs were recorded by Perkin Elmer FT-IR Spectrometer using KBr desk procedure with scanning range of 200 to 4000 cm^{-1}. Mass spectroscopic study was taken by JEOL GC MATE II quadruple double focusing mass analyser using electron impact ionization.

2.3 Preparation of Solid Inclusion Complex

Preparations of solid inclusion complex 1.34 g of CD's were dissolved in 30 mL of triply distilled and degassed water in round bottom flasks. Mixture was stirred to make homogeneous solutions over magnetic stirrer. Alternatively, solutions of [ALP] was prepared taking 0.295 g of [ALP] in a separate beaker with 15 mL water and stirred until homogeneous mixtures were formed. Subsequent to both the homogeneous mixtures are prepared, the ALP solution was then added into CD solution slowly with continuous stirring and after completion of the addition the ALP solution the mixture was stirred for 48 h continuously.

Following completion of 48 hours, mixture was allowed to cool at lower temperature when a white solid was observed. Then the precipitate was filtered and washed for several times. Lastly, the dry white powder was obtained after drying in oven at 50 °C for 24 h. The solid inclusion complex with all CD's was prepared following the same procedure. The resulting solids of inclusion complex between ALP and CD were found to dissolve in pure distilled water freely. These solids were further analyzed and characterized by means of FTIR, UV-VIS, NMR and ESI-Mass spectroscopic methods.

3. Results and Discussion

3.1 JOB Plot

Job's continuous variation method was applied to determine stoichiometry of the inclusion complexes formed. By the measurement of absorbance of a set of solutions prepared of the ALP and CD in water mixture in the mole fraction range of 0–1 (Tables 1-3). Here we calculate (ΔA × R) values against R, where ΔA signifies the difference in absorbance of ALP in the pure form and complexed form and R is [ALP]/ ([ALP] + [CD]).

λ_{max} was found at 250 nm at 298.15 K. Ratio of guest and host i.e., stoichiometry is obtained from value of R at maxima on the Job' Plot such as R ≈ 0.33, for 1:2 IC, R≈ 0.5 for 1:1 IC, R≈ 0.66 for 2:1 IC etc. In the experiment of ALP and CD's the maxima in the Job' plots were obtained at R ≈ 0.5 which is the indication of 1:1 stoichiometry of ALP and CD ICs (Figs. 2a-c) [26-29].

Table 1 Data of Job's plot between ALP and α-CD obtained from UV spectroscopy

ALP (mL)	α-CD (mL)	ALP (μM)	α-CD (μM)	[ALP]/([ALP]+[αCD])	ABSORBANCE	ΔA	ΔA*[ALP]/([ALP] + [αCD])
4	0	100	0	1	3.543	0	0
3.6	0.4	90	10	0.9	3.743	0.2	0.18
3.2	0.8	80	20	0.8	3.416	0.327	0.2616
2.8	1.2	70	30	0.7	3.416	0	0
2.4	1.6	60	40	0.6	2.909	0.507	0.3042
2	2	50	50	0.5	2.563	0.346	0.173
1.6	2.4	40	60	0.4	2.133	0.43	0.172
1.2	2.8	30	70	0.3	1.783	0.35	0.105
0.8	3.2	20	80	0.2	1.272	0.511	0.1022
0.4	3.6	10	90	0.1	0.877	0.395	0.0395
0	4	0	100	0	0.299	0.578	0

Table 2 Data of Job's plot between ALP and β-CD obtained from UV spectroscopy

ALP (mL)	β-CD (mL)	ALP (μM)	β-CD (μM)	[ALP]/([ALP]+[βCD])	ABSORBANCE	ΔA	ΔA*[ALP]/([ALP]+[β-CD])
4	0	100	0	1	3.997	0.324	1.345
3.6	0.4	90	10	0.9	3.998	0.456	1.461
3.2	0.8	80	20	0.8	3.999	0.567	1.562
2.8	1.2	70	30	0.7	3.999	0.782	1.721
2.4	1.6	60	40	0.6	3.096	0.903	2.503
2	2	50	50	0.5	2.588	0.508	2.508
1.6	2.4	40	60	0.4	2.302	0.286	2.686
1.2	2.8	30	70	0.3	1.73	0.572	3.372
0.8	3.2	20	80	0.2	0.821	0.909	4.109
0.4	3.6	10	90	0.1	0.778	0.043	3.643
0	4	0	100	0	0.417	0.361	3.175

Table 3 Data of Job's plot between ALP and HP-β-CD obtained from UV spectroscopy

ALP (mL)	HP-β-CD (mL)	ALP (μM)	HP-β-CD (μM)	[ALP]/([ALP]+[HP-β-CD])	ABSORBANCE	ΔA	ΔA*[ALP]/([ALP]+[β-CD])
4	0	100	0	1	3.573	0	0
3.6	0.4	90	10	0.9	3.959	0.386	10.386
3.2	0.8	80	20	0.8	3.965	0.006	20.006
2.8	1.2	70	30	0.7	3.999	0.034	30.034
2.4	1.6	60	40	0.6	3.337	0.662	39.338
2	2	50	50	0.5	1.844	1.493	48.507
1.6	2.4	40	60	0.4	1.435	0.409	59.591
1.2	2.8	30	70	0.3	1.225	0.21	69.79
0.8	3.2	20	80	0.2	0.959	0.266	79.734
0.4	3.6	10	90	0.1	0.751	0.208	89.792
0	4	0	100	0	0.58	0.171	0

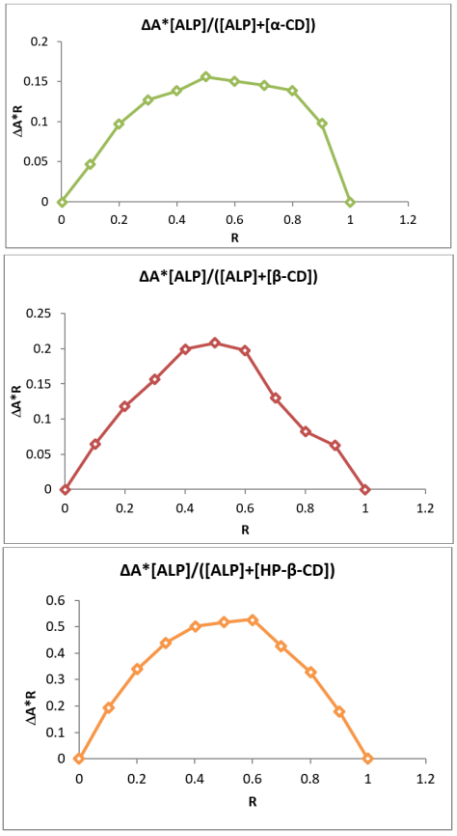

Fig. 2 Job's Plot for [ALP] with a) α-CD, b) β-CD and c) HP-β-CD

3.2 Determination of Binding (or Association) Constant by UV–Vis Spectroscopy

The binding constant between α-CD, β-CD, HP-β-CD and ALP has been evaluated via UV–Vis spectroscopy. The Benesi–Hildebrand technique represents one of the most common strategies to determine binding constants based on absorption spectra for inclusion complex. With the help of Benesi–Hildebrand method for 1:1 host–guest ICs, double-reciprocal plots of 1/ΔA against 1/ [CD] were plotted using the following equation (Figs. 3-5).

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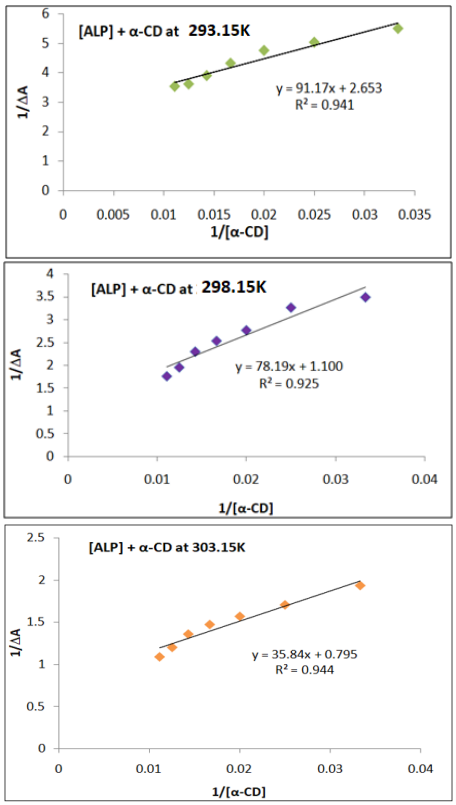

Fig. 3 Benesi-Hildebrand double reciprocal plots for the effect of α-CD on the absorbance of [ALP] at a) 293.15 K, b) 298.15 K and c) 303.15K

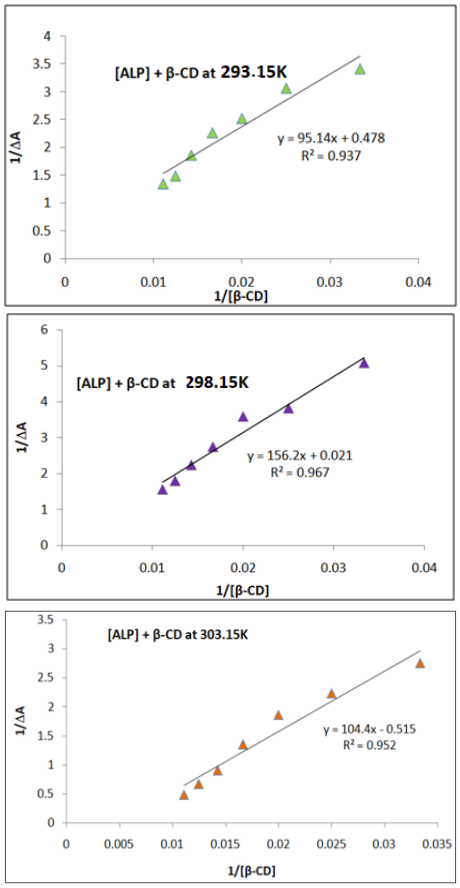

Fig. 4 Benesi-Hildebrand double reciprocal plots for the effect of β-CD on the absorbance of [ALP] at a) 293.15 K, b) 298.15 K and c) 303.15K

$$\frac{1}{\Delta A} = \frac{1}{\Delta\varepsilon[V]K_a} X \frac{1}{[CD]} + \frac{1}{\Delta\varepsilon[V]} \qquad (1)$$

Association constants (K_a^c) were also calculated for the inclusion complexation of ALP and CD by means of conductivity study with the help of a nonlinear program. Basing upon the fact that the insertion of the ALP inside the CD cavity changes the conductivity of the solutions. The equilibrium between ALP and CD can be represented as:

$$ALP + CD \xleftrightarrow{K_a} IC \qquad (2)$$

The equilibrium constant, K_a is represented as,

$$K_a = [IC] / [ALP] [CD] * f(IC)/f(ALP) f(CD) \qquad (3)$$

where, [IC], [ALP] and [CD] are molar concentrations of inclusion complex, allopurinol and cyclodextrin's at equilibrium accordingly. (f) is activity coefficients of the respective species (Tables 4-6). The activity coefficient of CD, f (CD), can be assumed as unity as system was dilute. In order to have an accurate estimation of binding constants of the inclusion complexes under investigation, changes in the absorption intensity of the ALP at different wavelength, were monitored as a function of the CD's concentration and non-linear regression estimation of the K_a was chosen.

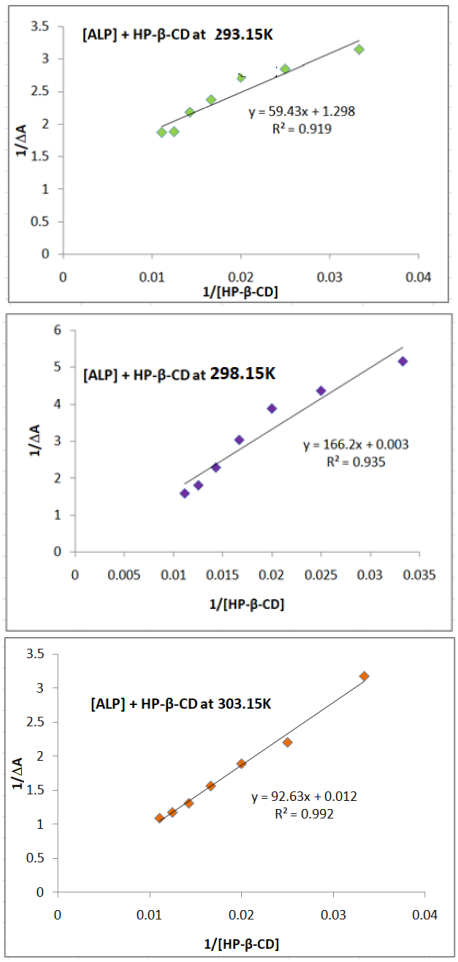

Fig. 5 Benesi-Hildebrand double reciprocal plots for the effect of HP-β-CD on the absorbance of [ALP] at a) 293.15 K, b) 298.15 K and c) 303.15K

Table 4 Data for the Benesi-Hildebrand double reciprocal plot performed by UV-VIS spectroscopic study for [ALP]-α-CD systems at (293.15, 298.15, and 303.15) K

temp/ K	[ALP]/ μM	[α-CD]/ μM	A_o	A	ΔA	1/[α-CD]/M^{-1}	1/ΔA
	50	30	0.9926	1.1745	0.1819	0.03333	5.49752
	50	40	0.9926	1.1913	0.1987	0.025	5.03271
293.15 K	50	50	0.9926	1.2028	0.2102	0.02	4.75737
	50	60	0.9926	1.2239	0.2313	0.01667	4.32339
	50	70	0.9926	1.2484	0.2558	0.01429	3.90930
	50	80	0.9926	1.2684	0.2758	0.0125	3.62582
	50	90	0.9926	1.2747	0.2821	0.01111	3.54484
298.15 K	50	30	0.9926	1.2789	0.2863	0.03333	3.49284
	50	40	0.9926	1.2986	0.306	0.025	3.26797
	50	50	0.9926	1.3535	0.3609	0.02	2.77085
	50	60	0.9926	1.3867	0.3941	0.0167	2.53743
	50	70	0.9926	1.4269	0.4343	0.0142	2.30256

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	50	80	0.9926	1.5034	0.5108	0.0125	1.95771
	50	90	0.9926	1.5594	0.5668	0.01111	1.76429
303.15 K	50	30	0.9926	1.5096	0.517	0.03333	1.93424
	50	40	0.9926	1.5791	0.5865	0.025	1.70503
	50	50	0.9926	1.62991	0.6373	0.02	1.56909
	50	60	0.9926	1.6715	0.6789	0.01667	1.47297
	50	70	0.9926	1.7286	0.736	0.01429	1.35870
	50	80	0.9926	1.8247	0.8321	0.0125	1.20178
	50	90	0.9926	1.9105	0.9179	0.01111	1.08944

Table 5 Data for the Benesi-Hildebrand double reciprocal plot performed by UV-VIS spectroscopic study for [ALP]-β-CD systems at (293.15, 298.15, and 303.15) K

temp/ K	[ALP]/ μM	[β-CD]/ μM	A_o	A	ΔA	1/[β-CD]/M^{-1}	1/ΔA
	50	30	0.9926	1.2854	0.2928	0.03333	3.41530
	50	40	0.9926	1.3185	0.3259	0.025	3.06842
293.15 K	50	50	0.9926	1.3883	0.3957	0.02	2.52716
	50	60	0.9926	1.4331	0.4405	0.01667	2.27015
	50	70	0.9926	1.5281	0.5355	0.01428	1.86741
	50	80	0.9926	1.6621	0.6695	0.0125	1.49365
	50	90	0.9926	1.7315	0.7389	0.01111	1.35336
298.15 K	50	30	0.9926	1.1892	0.1966	0.03333	5.08647
	50	40	0.9926	1.2538	0.2612	0.025	3.82848
	50	50	0.9926	1.2706	0.278	0.02	3.59712
	50	60	0.9926	1.3555	0.3629	0.01667	2.75558
	50	70	0.9926	1.4366	0.444	0.01428	2.25225
	50	80	0.9926	1.5434	0.5508	0.0125	1.81554
	50	90	0.9926	1.628	0.6354	0.01111	1.57381
303.15 K	50	30	0.9926	1.386	0.3934	0.03333	2.54194
	50	40	0.9926	1.4405	0.4479	0.025	2.23264
	50	50	0.9926	1.3297	0.3371	0.02	2.96648
	50	60	0.9926	1.5344	0.5418	0.01667	1.8457
	50	70	0.9926	2.0923	1.0997	0.01428	0.90934
	50	80	0.9926	2.1743	1.1817	0.0125	0.84624
	50	90	0.9926	2.3721	1.3795	0.01111	0.7249

Table 6 Data for the Benesi-Hildebrand double reciprocal plot performed by UV-VIS spectroscopic study for [ALP]-HP-β-CD systems at (293.15, 298.15, and 303.15) K

temp/ K	[ALP]/ μM	[HP-β-CD]/μM	A_o	A	ΔA	1/[HP-β-CD]/M^{-1}	1/ΔA
	50	30	0.9926	1.3111	0.3185	0.03333	3.13971
	50	40	0.9926	1.3448	0.3522	0.025	2.83929
293.15 K	50	50	0.9926	1.3612	0.3686	0.02	2.71297
	50	60	0.9926	1.4141	0.4215	0.01667	2.37248
	50	70	0.9926	1.4519	0.4593	0.01428	2.17722
	50	80	0.9926	1.5249	0.5323	0.0125	1.87864
	50	90	0.9926	1.5283	0.5357	0.01111	1.86671
298.15 K	50	30	0.9926	1.1863	0.1937	0.03333	5.16262
	50	40	0.9926	1.2217	0.2291	0.025	4.36490
	50	50	0.9926	1.2501	0.2575	0.02	3.88349
	50	60	0.9926	1.3222	0.3296	0.01667	3.03398
	50	70	0.9926	1.4299	0.4373	0.01428	2.28676
	50	80	0.9926	1.5463	0.5537	0.0125	1.80603
	50	90	0.9926	1.6234	0.6308	0.01111	1.58529
303.15 K	50	30	0.9926	1.3078	0.3152	0.03333	3.17259
	50	40	0.9926	1.4467	0.4541	0.025	2.20216
	50	50	0.9926	1.5219	0.5293	0.02	1.88929
	50	60	0.9926	1.6324	0.6398	0.01667	1.56299
	50	70	0.9926	1.7565	0.7639	0.01428	1.30907
	50	80	0.9926	1.8435	0.8509	0.0125	1.17522
	50	90	0.9926	1.91	0.9174	0.01111	1.09003

3.3 Fluorescence

Fluorescence was extensively studied for static and dynamic properties of the aggregated system such as the derivatives of the drug. In amphiphile molecules, CD's (quencher) are preferentially solubilized in their core hydrophobic regions. Change in the microenvironment of solution is experienced by (ALP), where the shift in the absorbance is located. Hence is used to aggregate properties in the form of inclusion. Vibronic band spectra endure major perturbation on transferring from non-polar to a polar environment. Fluorescence measurements are used to determine the association and complexation, of studied complex and also in understanding interaction between the host-guest inclusion processes (ICs). Steady-state fluorescence measurements were done at room temperature. Concentration of solutions used in all the system was approximately up to 10^{-6} moldm^{-3}. The lower the florescence intensity more is the binding with CD's, moreover it is found that in the α-CD inclusion with ALP the controlled release of the drug is more prominent ((Figs. 6a-c) [30, 31].

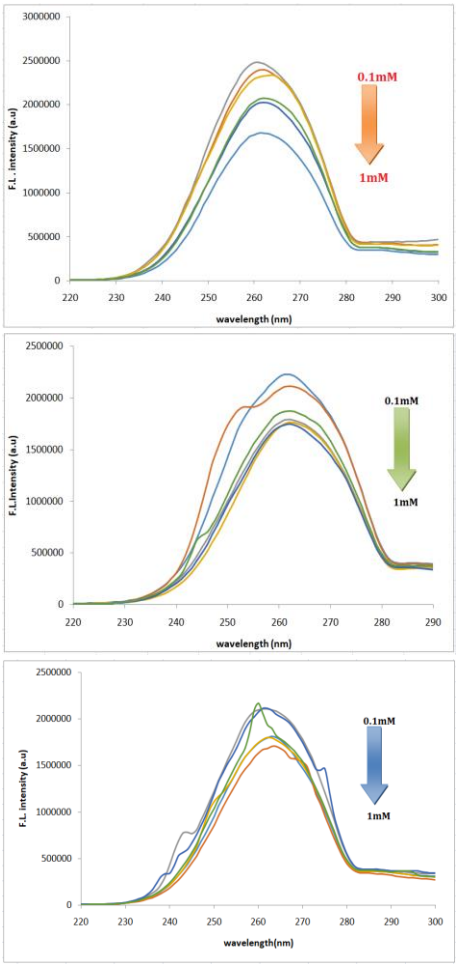

Fig. 6 Fluorescence emission spectrum of aqueous a) α-CD, b) β-CD and c) HP-β-CD in presence of (0.1mM—1.0 mM) of ALP (λ_{ex} =250 nm, slit width =5/5).

3.4 FTIR Study

FT-IR study of the solid ICs formed was performed to investigate the formation of the solid ICs. There are changes in frequencies of bands of the inserted guest molecules as well as some bands are absent in the spectra of complex. This may be due to the formation of the ICs. Data for pure compounds and inclusion complexes are recorded and spectroscopic change in wave number before and after inclusion are shown in Figs. 7a-d. Due to non-covalent interactions the changes of bands are observed. In the spectra of α-CD, β-CD and HP-β-CD the broad bands obtained at 3410 cm^{-1}, 3408 cm^{-1} and 3415.82 cm^{-1} are due to the valence vibrations of -O-H groups linked by H-bond. The O-H stretching for α-CD and β-CD obtained at 3410 cm^{-1}, 3408 cm^{-1} and 3415.82 cm^{-1} were obtained in the complexes 3410.85 cm^{-1}, 3415.94 cm^{-1} and 3414.44 cm^{-1} respectively, may be due to the interaction of the positively charged nitrogen atom of the pyrazole ring and the oxygen atom of (C=O) group which is again reflected in the shifted band of C=N stretching for 1701.40 cm^{-1} for the pure ALP to 1601.17 cm^{-1} in IC of α-CD, 1623.67 cm^{-1} in IC of β-CD and 1626.80 cm^{-1} in IC of HP-β-CD respectively. The C-H stretching and bending are obtained at 2941 cm^{-1} and 1404 cm^{-1} for pure β-CD and 2919. 19 cm^{-1} and 1366.67 cm^{-1} and HP-β-CD shift is almost the same. For pure α-CD, which are shifted in the ICs to 2886.26 cm^{-1} from 2927 cm^{-1}, 1367 cm^{-1} for α-CD. The out of plane C-H bending for [ALP] obtained at 814 cm^{-1} and 768 cm^{-1} for α-CD, 761 cm^{-1} for β-CD and 762 cm^{-1} for HP-β-CD respectively. This may be due to the closeness of C-H of CD and the aromatic C-H of the ALP. The aromatic stretching bands for pure [ALP] observed at 3165 cm^{-1}, stretching band due to alkyl C-H at 3081 cm^{-1} and 3042 cm^{-1}, are absent in the spectra of ICs. The peak due to stretching of C-H from -CH_2- at 2941 cm^{-1} for [ALP] are absent or shifted to 2886 cm^{-1}, 2919 cm^{-1} and 2927cm^{-1}, 2922 cm^{-1} in the spectra of ICs of α-CD, β-CD and HP-β-CD respectively, may be due to interaction inside the cavity of cyclodextrin. In ICs no additional signal is obtained which deny the chance of chemical reaction. Thus, the study

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provides major information about the formation of the ICs in the solid state [32].

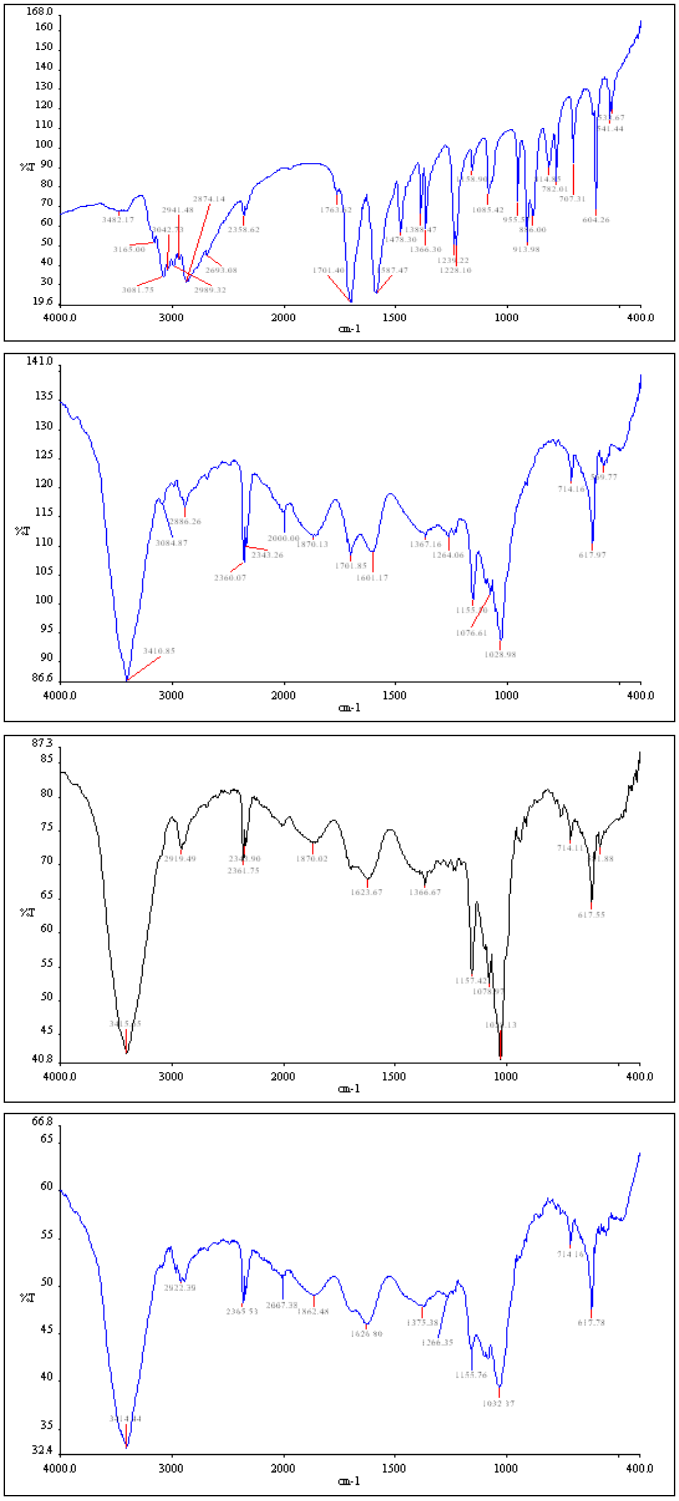
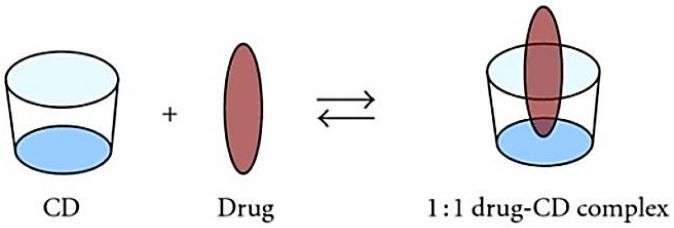


Fig. 7 FT-IR spectra of 1:1 inclusion complexes a) [ALP] +b) [ALP] +α-CD, c) [ALP] +β-CD and d) [ALP] +HP-β-CD) at 298.15K

3.5 ^{1}H NMR Spectroscopy

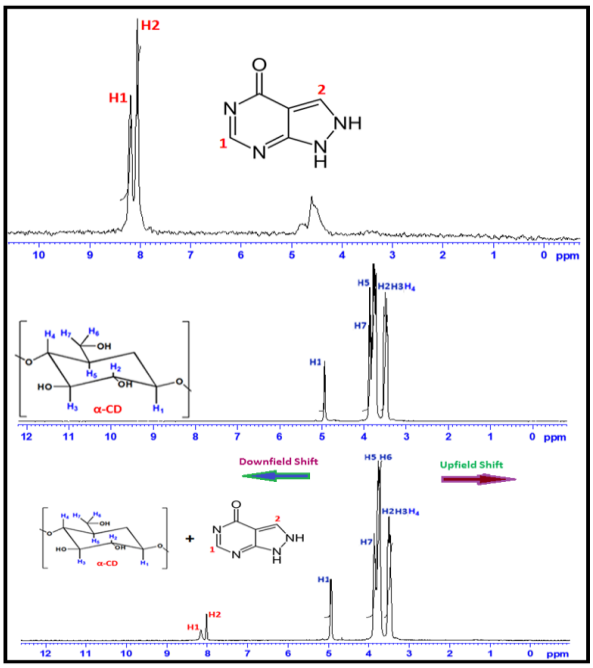
NMR spectroscopic study in aqueous solution at 298.15 K. Figs. 6a-c represents ^{1}H NMR spectra of the complex of ALP with α-CD, β-CD and HP-β-CD which describes slight downfield shift of the aliphatic protons of guest molecule. The signal due to aryl protons are nearly shifted and little broadening. Conversely protons of guest molecules of the aliphatic chain illustrate a slight change in their signals while present in the complex (α, β and γ protons of free ALP appears downfield shift respectively, then complex. This result clearly reveals the existence of some sort of association between the electron rich oxygen atoms of the CD's and the nitrogen atom (Scheme 1). The aromatic part of the ALP shows no change of their signals indicating their free state in the solvent medium.

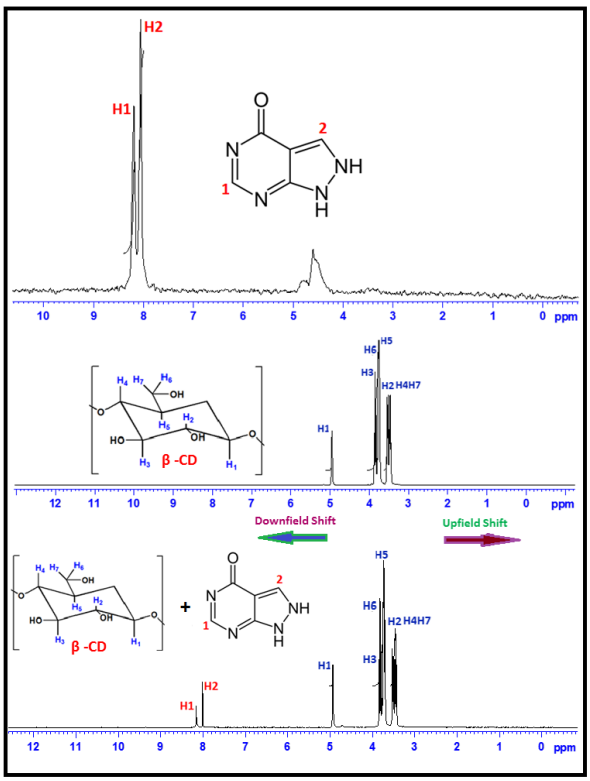


Scheme 1 Diagrammatic representation of the probable complexes obtained

Upon inclusion, upfield chemical shift values (Δδ) of the H3 and H5 protons of α and β-Cyclodextrins and H3 protons for HP-β-CD have been shown in Fig. 8, which confirm that the interaction of the guest ALP with H3 is greater than that with H5, signifying that the inclusion has taken place through the wider rim of the α, β and HP-β-Cyclodextrins.

It is to be mentioned that upon inclusion some non-aromatic peak of the ALP was completely disappeared in the proton NMR spectra of ALP, leave strong evidence of inclusion complexation [33].





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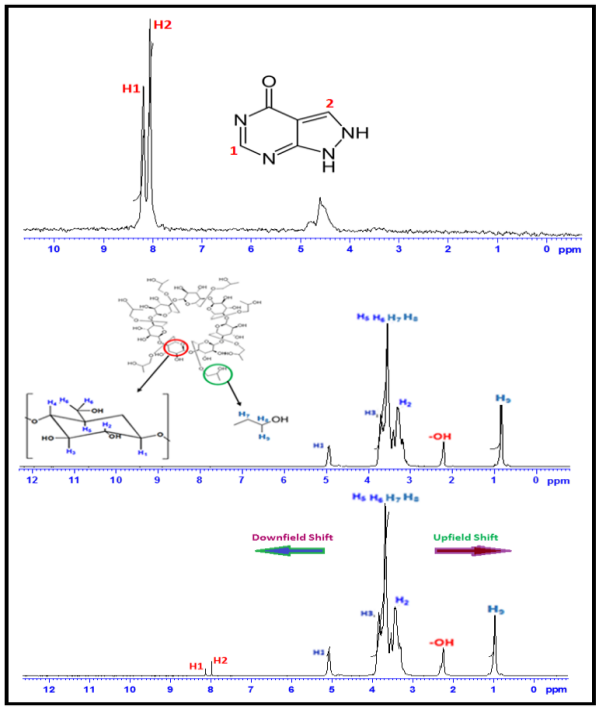

Fig. 8 ^{1}H-NMR spectra of the pure compounds and inclusion complexes with a) [ALP], b) [ALP] +α-CD, c) [ALP] +β-CD and d) [ALP] +HP-β-CD) at 298.15K (400MHz, D_2O)

3.6 2D-ROESY Spectroscopy

The principle of '2D ROESY' is the interaction of protons which are present in close proximity of 0.4 nm range to each other to produce NMR cross peak. In our study, we investigated the inclusion of ALP inside the α-CD, β-CD, and HP-β-CD hydrophobic cavity. NMR study was carried out in D_2O. It is clear H-3 and H-5 protons of CDs are present inside the cavity and hence if inclusion happens, there should be presence of such close proximity of 0.4 nm of the ALP protons with H-3 and H-5 protons of CD which can produce rotating-frame nuclear overhauser effect spectroscopy (ROESY) to give cross peaks.

In the Figs. 9a-c, there is the presence of cross peaks of H3 and H5 protons of β-CD with H-3 and H-5 protons of the aromatic ring and H-4' protons of [ALP]; with the H3 and H5 protons of α-CD and H-1', H-1"and H-4'of [ALP] and negligible cross peaks in HP-β-CD. In the dynamic process of inclusion, the cross peaks are generated due to insertion of the pyrazole part of the ALP as well as the aromatic ring of the ALP but it is sterically unfavourable. Hence in some cases benzylic part and in some cases pyrazole enters inside the cavity. This signifies inclusion phenomena of the said ALP into CD cavity [34].

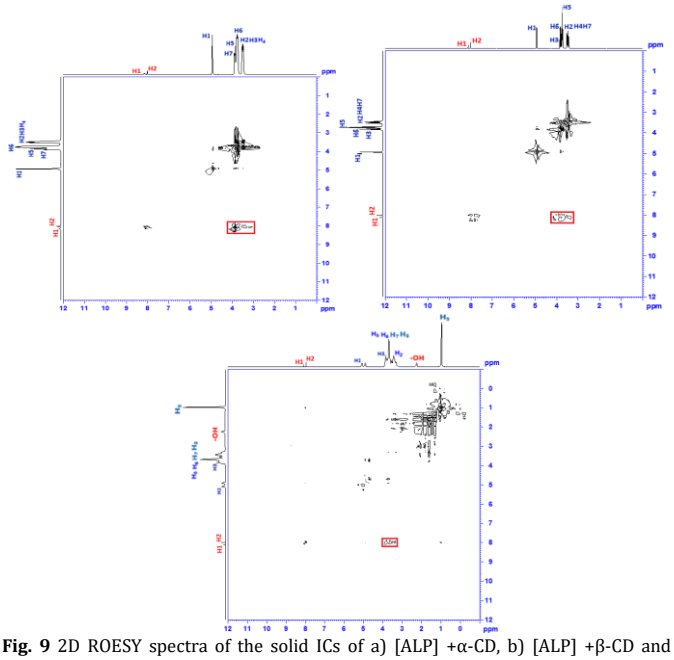

Fig. 9 2D ROESY spectra of the solid ICs of a) [ALP] +α-CD, b) [ALP] +β-CD and c) [ALP] +HP-β-CD)in D_2O (Cross correlations are indicated by red circles)

3.7 SEM

A very illustrious technique for analyzing the surface texture and particle size of solid materials. The exterior surface morphological structures of (α-, β-, HP-β-) CD and solid IC (ALP: α-CD, ALP: β-CD, ALP: HP-β-CD) are shown in respectively. From Figs. 10a-c, it is obvious that morphological structures of each are totally different from each other. Moreover, as the complexation by α-, β- and HP-β-CD can be viewed distinctly. This provides clear evidence that [ALP] fits adequately into the hydrophobic cavity of CD's to figure solid IC with different morphology. [35].

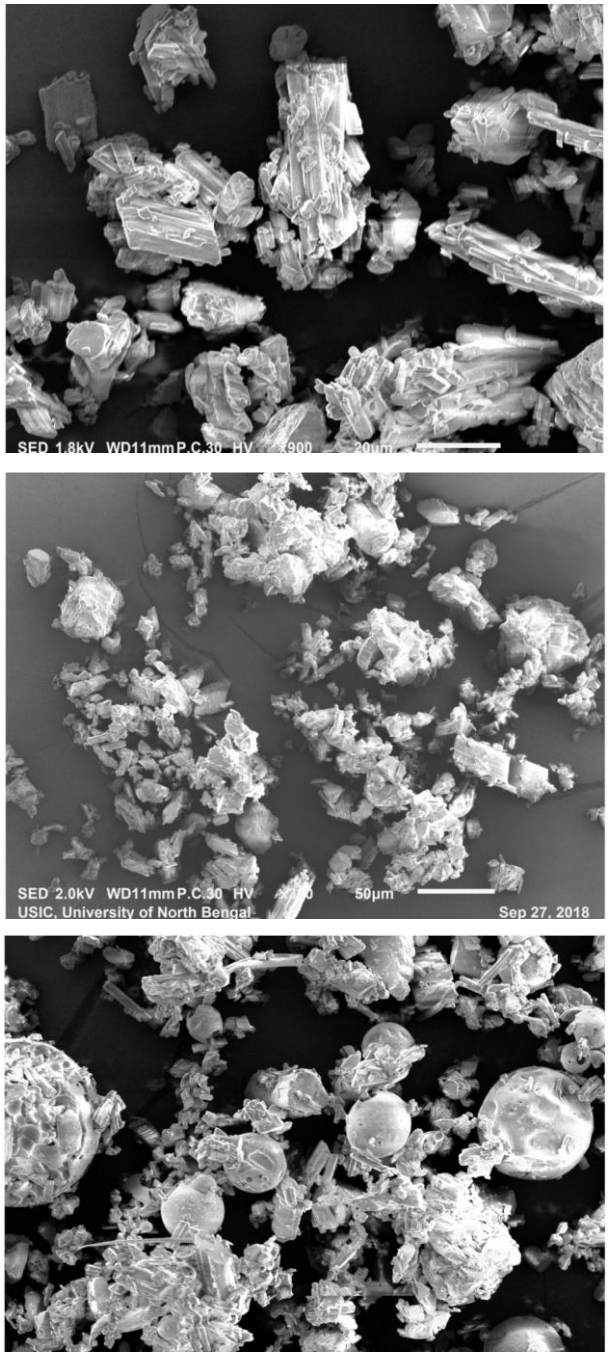

Fig. 10 SEM showing morphologic study of a) [ALP] +α-CD, b) [ALP] +β-CD and c) [ALP] +HP-β-CD) in (1:1 M ratio) of inclusion complex

3.8 PXRD – Powdered X-Ray Diffraction Spectroscopy

X-ray diffraction (XRD analysis or XRPD analysis) is an exclusive method in determination of crystallinity of a compound. It is primarily used for crystalline material of different polymorphic forms. Distinguishing among amorphous and crystalline material, quantification of the percent crystallinity of a sample is the mandatory criteria. We find (Figs. 11a-d) the crystallinity changes in the complexes by definite angles [36].

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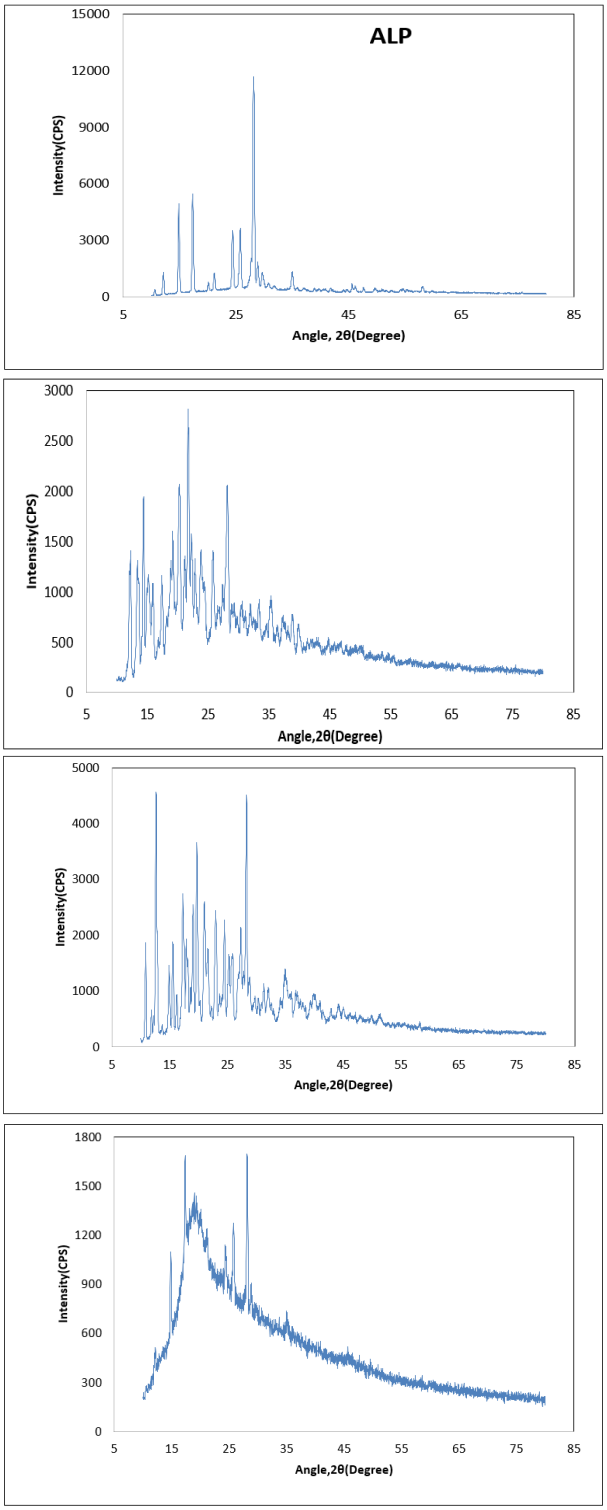

Fig. 11 Powder X-ray diffraction pattern of a) [ALP], b) [ALP] +α-CD, c) [ALP] +β-CD and d) [ALP] +HP-β-CD)

3.9 ESI-MS Analysis

The 'ESI-mass spectrometric analysis' were additionally used to recognize the formation of IC synthesized by procedure described above in the solid state of experimental procedure and have been shown in Figs. 12a-c. Observation of peaks have been put, which verifies that in each cases the desired IC's have been formed in solid state and stoichiometric ratio of (host: guest) is (1: 1). The 'Positive electrospray ionization mass spectrometry' [ESI-MS] is enormously important process that has been used to examine host guest complexation with the two studied cyclodextrins. Mass spectrums of (1:1) stoichiometries of [α-CD: {ALP}], [β : {ALP} and [HP-β-CD: {ALP}] systems are evaluated by [ESI-MS] represents every preferred mass that one can expect. These experimental facts of the chosen [[ALP]/α-CD], [[ALP]/β-CD] and [[ALP] / HP-β-CD] complexes recommended that the [[ALP] + cation] simultaneously inserted in cyclodextrin's hollow space with (1:1) stoichiometry [33].

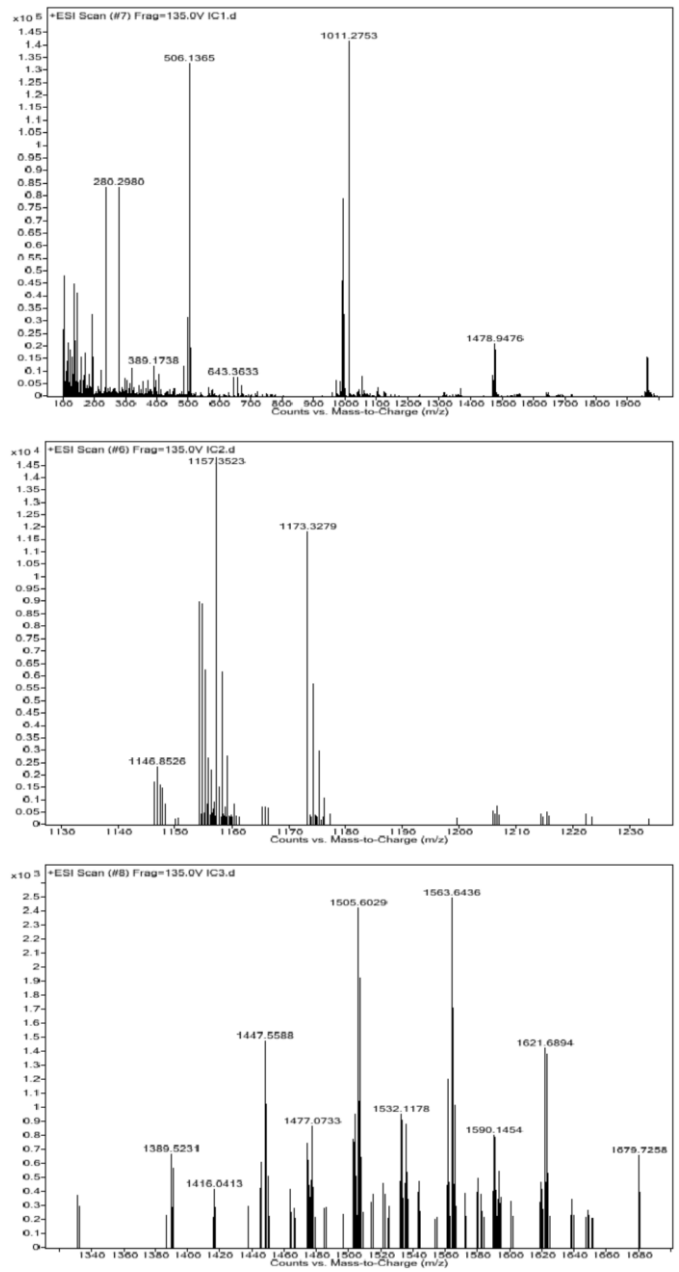

Fig. 12 ESI mass spectra of a) [ALP] +α-CD, b) [ALP] +β-CD and c) [ALP] +HP-β-CD) inclusion complex

3.10 Biological Activity

ALP itself is non-toxic to cut micro flora. No zone of inhibition, in case of both the gram-positive and gram-negative organisms. There was no growth inhibition compared to control. These results recommend that ICs (IC1 = [ALP + α – CD], IC2 = [ALP + β-CD], IC3 = [ALP + HP-β-CD] doesn't have any antimicrobial activity shown in Figs. 13a-b. So, it is nontoxic for the cells experiment based on the sensitivity towards cut micro flora. There is no effect on cut-microbes- host interaction [37].

Fig. 13 Antimicrobial activity analysis on ALP on a) gram-positive *B. subtilis* and b) gram-negative *E. coli*. No zone of inhibition was observed with IC1, IC2, and IC3. Double distilled water was taken as the control

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4. Conclusion

Allopurinol sketch host-guest inclusion complexes together with (α-, β-, HP-β-) CD win the (1:1) stoichiometry which is recognized by UV, NMR, steady state fluorescence, SEM, HRMS imply that the selected guest (ALP) molecule, shaped IC's with nano hydrophobic core of efficiency. As a result, the present work adjoins a new dimension in the diversified field of existing science of controlled release of allopurinol through appropriate host molecules like (α-, β-, HP-β-) CD.

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