Preliminary Review on Solvation Chemistry in Aqueous Solvents: Application to Amino Acids

Sanjay R¹* and Bijoy KD²

¹Department of Chemistry, Shibpur Dinobundhoo Institution (College), Howrah, West Bengal, India
²Department of Chemistry, Visva-Bharati, Santiniketan, Birbhum, West Bengal, India

*Corresponding author: Sanjay Roy, Department of Chemistry, Shibpur Dinobundhoo Institution (College), Howrah-711102, West Bengal, India, Tel: +91 9614855043; E-sanjayroyp@gmail.com

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Abstract
The present review deals with a literature survey on the amino acids solvation chemistry in aqueous solvent systems. The present study gives an idea about the classification of solvents, solvation thermodynamics of amino acids in aqueous solvent system and deals with detail aims and objectives of some works for amino acids solvation chemistry in aqua-organic solvent systems.

Keywords: Aqueous solvent; Solute; Amino acids; Solvation; Thermodynamic parameter

Introduction
The term “Solvation phenomenon” which is associated with dissolved state of matter has drawn the interest of physical chemists for quite a long time. This chemistry in fact forms the origin of careful investigations to understand the physicochemical properties of solution and to know the mechanistic paths of solvation of different solutes like amino acids particularly [1-6].

In fact, lot of chemistry pertains to and is conducted in liquid solutions and involves ionic and non-ionic species. The vast bodies of multi-component aqueous salt solutions of oceans, nature of physiological fluids, dissolution of proteins, nutrients, enzymes, sugars, etc., in body fluids, oxygen in blood, various industrial processes, use of different solvents in the fields of chemical, analytical, electrochemical, food, pharmaceuticals, ecological and photochemical chemistry all are the general subject of interest of solution chemists. In earlier experiments the chemists were attracted [3-10] about the role of different solutes on various physicochemical properties and processes in aqueous, non-aqueous and mixed solvents. The role of solvents was assumed to offer an inert and homogeneous medium for the chemical reactions. But later, it has been duly

recognized that solvent molecules play a significant role in dictating various aspects of physico-chemical properties, equilibrium, and kinetic behavior of reactions in solution phase.

Solvation phenomena have been studied in a wide range of aqueous, non-aqueous, electrolytes and mixed solvents from various properties viz. lowering of vapor pressure by solutes [10], order of ionic mobilities [6,10,11], viscosity B-coefficients [10-13], partial molar volume of ionic and non-ionic solutes [5,10], dielectric decrement produced by ions [14], solubility of substances [15], effect of ionic and non-ionic solutes on solvent spectra [14,16,17], etc. Several investigations [3,5,11,16,18,19-25] were made by via spectroscopic methods such as UV-VIS, IR, ESR, NMR, Raman, diffraction including X-ray, electron, and neutron diffraction, etc., simulation studies including Monte Carlo and molecular dynamic variants, dielectric relaxation and considering thermodynamic, kinetic, transport and electrochemical properties at infinite dilution. All these studies provide an idea about the solute/ion-solvent interactions [10,11,26].

Last few decades have witnessed an exponential growth on the fundamental research involving solute-solute, solute-solvent, and solvent-solvent interactions in aqueous and aquo-organic mixtures in particular but in pure or mixed organic solvents the research was not developed to that extent. In this context, much attention has been given also to determine the various thermodynamic properties such as molar volume [27], enthalpy and entropy of solutions [28-31], solubility [29-32] of various amino acids in different aquo-organic media. The purposes of such studies were to gain the ideas about various mechanisms of amino acid solvation and to reflect the structuredness [33,34] of the aquo-organic co-solvent systems as well as qualitative measurement of the hydrophobic hydration of the zwitter-ionic species with graded increase of \(-\text{CH}_2\)-group. Kundu et al. [29,30] have used previously as effective probes for the structuredness of solvents. Results of such proposed studies will have immense fundamental and physical implications in the realm of solution chemistry, biophysical chemistry, and pharmaceutical sciences. This will help to generate the basic knowledge of solute-solvent and solvent-solvent transfer energetics of solvation phenomena involved in the process and it will also help to understand the behavior of biologically important compounds in molecular levels.

Solvation and correlated factors

As the present my next works is concerned mainly with solvation of solutes; amino acids and their thermodynamic aspects, it would be pertinent to present here a few basic concepts of thermodynamics of solvation of solutes in order to facilitate the discussion of solvation models that will follow. The term ‘solvation’ can be defined as the more or less specific interaction between a solute molecule and one or more solvent molecule with a force intermediate between weak physical interaction and strong covalent bonding [35]. As we know solutes are generally two types; one is electrolytes and another is non-electrolytes. Electrolytes when dissolved in suitable solvent, called the ionizing medium, produce ions. Non-electrolytes don’t form ions even in the presence of solvent-induced polarization.

The basic difference between electrolytes and non-electrolytes then lies in the ability of the former to generate ions, which are distinguished by their integral charge, and the intense electric field associated with it. Various experimental facts indicate that in case of non-polar, non-electrolytes solutes in solution there is an increased order in vicinity of solute and restricted translational and vibrational motion of the solvent molecules. These are known variously as ‘structure making’ (SM) ‘hydrophobic hydration’ (H$_3$H) or ‘hydration of second kind’. On the other hand, if the non-electrolytes are progressively
charged, the order and correlation time of vicinal solvent get decreased, and this effect is known as ‘structure breaking’ (SB) or ‘negative hydration’. If the charging process leads to sufficiently higher charge: radius ratios, then the vicinal dipolar solvent molecules become strongly aligned by the ionic field to form ‘solvation shell’. This effect again increases the order and the correlation time and has been termed as ‘structures making’ and ‘positive solvation’ or solvation of first kind.

In case of ionic solute in polar solvents the solvation effects are strong enough resulting formation of solvation shell to act as an integral part of the ions. Mukherjee [36] followed by Gutmann [37] had explained the solute-solvent interaction in non-aqueous solvents in terms of donor-acceptor properties of solvent and thus Lewis acid-base description of solvent effect has also been proposed [38].

An important step towards a clearer understanding of solute-solvent interactions is the development of a ‘competitive preferential solvation’ theory [39]. This study [39] also has demonstrated that a continuum theory of solvation may be formulated in terms of modern electrodynamics of condensed media with spatial dispersion so as to rigorously take into account the structure of a polar solvent. The solvation has also extremely profound and diverse effects on the thermodynamic, kinetic and spectral behavior of solutions.

In fact, solute-solvent interactions guide all the properties of solutions. Solvation phenomena have been studied in a wide range of aqueous, non-aqueous and mixed solvents from various properties. These provide ample evidence that the phenomenon of solvation is very much a reality. Remarkable advancements have been made by a number of researchers providing answer to a wide range of relevant problems, concerning solute-solvent interactions from both experimental and theoretical stand points also.

**Thermodynamics parameters of solvation**

The heart of the present work centers on the Gibbs energy (G), the enthalpy (H) and also, the entropy (S). Also, the latter quantities in particular are very much sensitive to structural forms of the solvent, which tend to complicate a straightforward interpretation in terms of solute-solvent interactions. However, a compensation of these effects in the Gibbs energy makes it a direct measure of such interactions.

In considering the thermodynamics of solvation of an undissociated solute like amino acids the following two processes of transfer are of great importance.

\[
\Delta Y'\text{soln} \\
A \text{ (solid)} \rightarrow A \text{ (soln)}; \\
\Delta Y'\text{sub} \quad \Delta Y'\text{solv} \\
A \text{ (solid)} \rightarrow A \text{ (gas)} \rightarrow A \text{ (soln)}
\]

Here ‘A’ is a non-electrolye or un dissociated solute and \(\Delta Y'^o\) indicates changes in thermodynamic parameters like Gibbs energy (\(\Delta G'^o\)), enthalpy (\(\Delta H'^o\)) or entropy (\(\Delta S'^o\)) for one mole of the solute in the standard state i.e. at infinite dilution.

The thermodynamic quantities of the solution are given as:

\[
\Delta Y'\text{soln} = \Delta Y'\text{sub} + \Delta Y'\text{solv}
\]
Here $\Delta Y^{\circ}_{\text{soln}}$, $\Delta Y^{\circ}_{\text{sub}}$ and $\Delta Y^{\circ}_{\text{solv}}$ denote the change of thermodynamic quantities accompanying the dissolution, sublimation, and solvation of 1 mole of solute in the standard state respectively. $\Delta Y^{\circ}_{\text{soln}}$ and $\Delta Y^{\circ}_{\text{sub}}$ are directly measurable. But $\Delta Y^{\circ}_{\text{solv}}$ can be computed only.

**Structure of water and its role in amino acid solvation**

It is true that water is the most widely used versatile solvent in the realm of solution. It has been studied extensively and its properties examined critically for a long time at ordinary as well as at elevated and reduced temperatures and pressures [33,40,41]. It is believed that unique properties of water, including its structure is a result of strong intermolecular H-bonding interactions [42] leading to association [43]. It is known that O-atom of H$_2$O molecules imparts four-sp$^3$ hybridized orbital’s which can provide four water molecules and hence 5H$_2$O molecules form a unit of 3D-tetrahedral structure. These structure cluster are distributed in space giving rise to the “structuredness” [34] of water, as it is evident from neutron scattering studies at ordinary temperatures [40,44].

According to Frank and Wen and further developed by Nemethy and Scheraga [45] there exist at least two molecular species which can be distinguished on a time scale [10,11]; one is tetrahedrally hydrogen bonded “bulky” water while the other non-bonded monomeric “dense” water. These two forms of H$_2$O are believed to exist in a dynamic equilibrium represented by:

$$(\text{H}_2\text{O})_b \leftrightarrow ( \text{H}_2\text{O})_d$$

This equilibrium is dictated by temperature, pressure and other co-solutes and co-solvents. The structure of water has also been studied experimentally by Narten et al. using X-ray neutron and electron diffraction measurements [46,47]. According to Frank and Wen’s flickering cluster model of water, when a solute/ion is dissolved in water, structural changes occur and hence the equilibrium is shifted. Solute/ion which moves the equilibrium in the direction of non-bonded denser components is termed as ‘structure breaker’ (SB) and one that favours bulky form is called ‘structure maker’ (SM).

As in pure water, water structure is equally important in the case of binary mixtures of water with ionic and non-ionic organic co-solvents for equilibria and kinetic studies of various reactions. Organic compounds having hydroxyl groups being highly soluble in water are of particular interest till recent years. The observed peculiarities in some of the properties in aquo-alcoholic solutions are often adduced to the structural in origin and would be understood in the light of knowledge of structural behaviour of the components. Different studies [48-52] on alcohol water systems revealed that addition of low molecular weight alcohols to water produces at first an increase in the degree of three dimensional (3D) ‘structuredness’. Therefore, the heats of mixing with water for methyl alcohol (MeOH), ethyl alcohol (EtOH), 2-propyl alcohol (2-PrOH) and tertiary butyl alcohol (t-BuOH) show exothermic maxima in higher water-rich region followed by a downward structure breaking trend at higher alcoholic compositions. Also, the partial molar volumes of three mono-ols in highly aqueous solutions go through minima in almost identical composition of the respective co-solvents.

Ultrasonic absorption and velocity serve as a measure of compressibility and structuredness and the elevation of the temperature of maximum density (TMD) [52] of water also exhibit maxima in water-rich region of these mono-ols and water mixtures.
As the compositions of alcohol increases the structure making effect reaches gradually towards a saturation point and further addition of alcohols initiates a breakdown of water structure due to packing imbalance. The combined effects of these two tendencies produce the observed maxima.

Parallel investigations on other aquo-organic mixtures used are also too vast to be described here in detail. A brief account of it has been found in Frank’s Review series [1]. The different essential structural features of the different ‘classes’ of these aquo-organic solvents, which are related to their thermodynamic properties, particularly their molar excess functions are mentioned in TABLE 1.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Excess function</th>
<th>Co-solvent systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typically, aqueous (TA)</td>
<td>G⁺ Positive/T.S⁺/&gt;/H⁺</td>
<td>Monohydric alcohol (ROH) acetone (CH₂COCH₃), tetrahydrofuran (THF), dioxane (D)</td>
</tr>
<tr>
<td>Typically, non-aqueous Positive (TNAP)</td>
<td>G⁻ positive/H⁻/&gt;/T.S⁻</td>
<td>Acetonitrile (ACN), sulpholane (TMS), propylene carbonate (PC)</td>
</tr>
<tr>
<td>Typically, non-aqueous Negative (TNAN)</td>
<td>G⁻ negative/H⁻/&gt;/T.S⁻</td>
<td>Hydrogen peroxide (H₂O₂), dimethyl sulphoxide (DMSO), ethylene glycol (EG)</td>
</tr>
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</table>

In aqueous alcohols and other typically aqueous (TA) mixtures there is usually some enhancement of water structure when small amounts of the organic co-solvent are added to water. But the addition of greater amounts of the organic co-solvents eventually leads to a disruption of solvent structure. The composition corresponding to this change over is a characteristic of the co-solvents. The organic co-solvents with larger hydrophilic portion affect the water structure and related physical properties more extensively. At a lower characteristic composition of the organic co-solvents, there appear an extrema of the properties. On the other hand, in case of typically non-aqueous positive (TNAP) mixtures, there are no extrema of properties. Solvents like acetonitrile (ACN), propylene carbonate (PC), etc., merely disrupt water structure over the total range of composition. But typically, non-aqueous negative (TNAN) mixtures like dimethyl sulphoxide (DMSO), possess structure breaking properties because they take part for H-bonding like water. Therefore, this classification draws a fair guide to the structure making and breaking propensity of some organic co-solvents. But in some border line cases like glycol [53,54], glycerol [55], urea [55], dioxane [53,54,56] some difference of opinion arise which supported by various other investigations.

**Hydrophobic and hydrophilic hydration**

Our work about transfer energetics of amino acid solvation in protic ethylene glycol (EG), quasi-aprotic 2-methoxyethanol (ME) and aprotic 1, 2-dimethoxyethane (DME) having hydrophobic and hydrophilic moieties imparting hydrophobic hydration as well as hydrophilic hydration to influence solvation of solute concerned here, so it is very much relevant to discuss about these solvation phenomena.

Many decades of research have been devoted to the low solubility (unfavorable, positive Gibbs energy of transfer) of apolar compounds in water. This low solubility is essentially caused by the apolar solute being unable to compete with water itself for “positions” in the liquid phase [57]. However, the directional sensitivity of interactions between water molecules provides
a way of hydrating apolar molecules, called hydrophobic hydration that minimizes the (unfavorable) Gibbs energy change of solvation in water [57] and causes a pronounced thermodynamic signature.

Typically, the enthalpy of transfer is negative, but this is more than cancelled by strongly negative entropy of transfer. The heat capacity of transfer is positive making both the enthalpy and entropy of transfer positive at higher temperatures. However, not all apolar solutes show the same transfer parameters. The size and shape of solutes proves to be important as well. For example, increasing the size of noble gases decreases the Gibbs energy of transfer into water for Ben-Naim standard conditions [58,59] However, increasing the size of alkanes, the Gibbs energy of transfer into water for Ben Naim standard conditions first decreases but then increases again (resulting in a V-shaped plot). Also, the nature (aliphatic or aromatic) of the apolar compounds has a pronounced influence on the observed transfer parameters as obvious from the fact that transfer of aromatic solutes to water is spontaneous (ΔGt<0 J mol⁻¹) at room temperature for Ben-Naim standard conditions [58,59].

Central questions in studies of hydrophobic hydration are whether hydrogen bonds are stronger in the hydrophobic hydration shell and whether it is the size of the water molecule, the high directionality of the hydrogen bond or the particular strength of the hydrogen bonds that causes the unfavorable Gibbs energy of transfer. Recent examples of this debate still being very much alive were given by Kodaka and Graziano [60-63].

The simple hydrophilic ions cause hydrophilic hydration (H1H) or hydration of first kind or positive hydration [3,40,64-70] whereas hydrophobic solutes with apolar residues cause hydrophobic hydration or hydration of the second kind or negative hydration [3,71-78] resulting in a significant increase in free energies and decrease of entropy of the systems. The salient features of hydrophobic hydration have been derived from various studies [3,79-82] on thermodynamic and transport properties using R₄N⁺ salts (as model hydrophobic probes), the knowledge on salt and solvent effect on H₂H and study with other types of probes like RNH₃⁺ and RCOO- ions and amino acids are fairly scarce. Kundu and Talukdar [50] reported salt effect on hydrophobic hydration (H₂H) using R₄N-picrates in NaNO₃ salt solution. But the detailed study of solvent effect on hydrophobic hydration (H₂H), and the used of other types of model hydrophobic probes of the zwitterionic species having graded increase of hydrophobic moiety (-CH₂- group) are in order.

In hydrophobic interaction following thermodynamic effects are found

- An increase in the chemical potential of the solute, indicating of its low solubility
- A large negative entropy of mixing compared with the formation of a hypothetical ideal solution
- A decrease in the partial molar volume as the molecule fits into cavities in the water network
- An increase in heat capacity is observed

Hydrophobic interactions communicate the relations between water and hydrophobes (low water-soluble molecules). Hydrophobes are nonpolar molecules and usually have a long chain of carbons that do not interact with water molecules. In this context, nonpolar substance tends to clump up together rather than distributing itself in water medium because this fact allows the nonpolar molecules to have minimum contact with water.
In the presence of non-polar solute, water molecules are driven to either adopt more specific orientations to avoid losing hydrogen bonds, or to minimize the loss, depending on which alternative are allowed by the geometry of the hydrophobic moiety/surface. For better knowledge of amino acid side chain hydrophobicity, it is essential to know the origins of hydrophobicity. The actual molecular origins of hydrophobicity were shown by Lee et al. [83].

**Categorization of solvents**

This work is devoted mainly to the studies of interaction between zwitterionic species i.e. amino acids and solvent molecules in binary aqua-organic solvent mixtures and is primarily concerned with the interpretation of changes of thermodynamic quantities on transferring amino acids from water to some aqua-organic solvents, so a brief discussion on different types of solvent seems to be relevant at this stage.

According to Bronsted [84] there are four types of solvents on basis of their basic and acidic properties: (i) protogenic, which easily liberates proton;(ii) protophilic, proton acceptor;(iii) amphotropic, having both protogenic and prophilic character;(iv) aprotic, having neither protogenic nor protophilic character.

Bates [85] supposed that a solvent is clearly amphotropic when it has a well-defined and reproducible auto-photolysis constant greater than 10^{-20}. Davies extended this classification and renowned each class between solvent with dielectric constant (e) greater and less than 20. The following examples typify each class with the solvent having e>20 preceding that having e<20; protogenic (HCN, acetic acid), protophilic (N-methyl propionamide, pyridine); amphotropic (H_{2}O, t-butanol);aprotic (acetonitrile, benzene).

Parker recommended another classification [86-88] and modified by Gordon [89]. They divided the solvent into two broad groups: - protic (EG) and aprotic (Benzene) which are further subdivided into two main subgroups ionic and dipolar and third subgroup- nonpolar aprotic. Kolthoff [88,90] suggested a broad distinction into amphotropic (H_{2}O) solvent and aprotic solvent on the basis of acidic and basic properties. The amphotropic solvents are sub-grouped as neutral, protogenic and protophobic whereas the aprotic solvents are sub-grouped into dipolar protophilic (e.g. DMF);dipolar protophobic (e.g. acetonitrile) and inert (e.g. benzene) on the basis of properties as evident from these names. Each amphotropic subclass has been resolved into two groups according as e>20 or e<20. Gutmann and Lindqvist [91] classified the solvents as anionotropic, which are Lewis bases and cationotropic, which may be Bronsted or Lewis acids. However, the commonly referred different measures of solvent polarity, the dipole moment and the dielectric constant are not sufficient for characterization of the properties relevant for ion-solvation. The electron receiving and donating abilities of the solvents and their hydrogen bond formation capacities are of great importance in this respect.

**The importance of protic and dipolar aprotic solvent systems**

Parker [87,92] proposed that solvents possessing hydrogen bound to electronegative atoms like ‘F’, ‘O’ or ‘N’ will be protic, whereas solvents having hydrogen bound only to carbon will be dipolar aprotic. According to the above rule and parker’s modified solvent classification scheme the solvents like HF, H_{2}O, ROH, FA and NH_{3} are protic solvents (PS), while ME is quasi- aprotic solvent and DMF, DME, ACN etc. are dipolar aprotic solvents (DAS). Both the PS and DAS have high
dielectric constant values for performing thermodynamic studies of zwitterionic solution. These solvents can take part in dipole-dipole, acid-base, H-bonding and dispersion, hydrophobic/hydrophilic interactions in their binary mixtures.

PS readily acts as H-bond donors during interactions with hard negative charge i.e. anions, while DAS possess only very weak H-bond donating properties [2,85]. This means that PS is good Bronsted acid while DAS is not. Therefore, any negatively charged ion, which can be stabilized only through H-bonding with the solvent, is more highly solvated in PS than in DAS.

Furthermore, due to the higher dipole moment of DAS compared to PS the dipole-dipole interaction in DAS is generally stronger than that observed in PS. As the DAS molecules are more polarizable they undergo strong soft-soft and dispersion interactions with larger polarizable negative/positive or neutral molecules.

From these a great interest lies in the study of binary solvent mixtures containing a PS and a DAS with compositions ranging from the pure PS to the pure DAS. If possible as the proportion of the DAS in the mixed solvent is gradually increased the solvent character undergoes a gradual but material change, with H-bond donating ability weakening and giving way to radically different forces like soft-soft, dispersion interactions.

**Force and factors influencing solute-solvent interactions in aqueous and mixed aquo-organic systems**

The present review mainly related to solute and zwitterions solvation, it would be useful to present here a brief discussion on the forces and factors governing solute-solvent interactions. Forces governing the solute-solvent interactions are of two types (i) electrostatic-arising from the charge and the associated field around the ions and (ii) non-electrostatic dictating the solvation of neutral part.

According to the theory of electrostatic interactions Born [93] first considered an ion as a rigid charged sphere of definite radius and the surrounding solvent as structureless dielectric continuum. Electrostatic interaction is the sum of Born, ion-dipole, ion-quadruple, ion-induced dipole terms and the terms of mutual interactions of the solvents molecules near the ion among themselves, which depend on the geometry. Criss and Solomon [94] have listed the various types of electrostatic interactions involved in ion-solvation.

In case of non-electrolytes as well as for the neutral part of ions the non-electrostatic forces come into play and these are of the types: soft-soft interaction [95], London dispersion forces, H-bonding, solvent-structural effects and cavity forming interactions.

Obviously, in aqueous solution H-bonds play a major role. Conventionally, these have been considered to be of two types (i) the H-bond formation between water and polar group of the solute molecules in water and (ii) the H-bond taking place between the solvent molecules.

The cavity forming interaction is important for large hydrophobic solutes and related mainly with the solvent diameter and density. Guttmann and Lindquist [96] have drawn a scheme relating covalent contribution to solute-solvent interactions which stem from generalized acid-base interactions.
Feakins et al. [55], de Ligny et al. [97], Kundu et al. [29,30,51,98] and Khoo [57,99] and other have found it convenient to separate solute/ion-solvent interactions into (a) Primary interaction of the acid-base type, (b) Secondary interaction of Born type, (c) Dispersion and soft-soft interactions and (d) Structural interactions.

A successful theoretical approach to this problem that has gained wide acceptance is that of Pierotti [100] based on the scaled particle theory (SPT) of Reiss et al. [101]. This theory originally used for some non-ionic solutes to compute the ‘cavity effect’ in water is also increasingly used for solutes a polar [51,102], nonpolar [103,104], large [102,103,105] and small ions [51,103]. It is not only used in water but also in organic solvents and their aqueous mixtures and also in ionic solutions [106]. There are other two methods for the calculation of cavity forming interactions by Sinanoglu Riesse and Moura Ramos [54,107] and Mayer [53].

The dielectric constant of the solvent governs the magnitude of all electrostatic interactions; the dipole moment (µ) of the solvent and solute molecules dictates ion-dipole and dipole-dipole interactions [108].

**Solvation of amino acids**

The heart of the present work describes the solvation chemistry of homologous series of α-amino acids. So, it will be necessary to present here a details account about the solvation of amino acids and other biomolecules in different mixed aquo-organic solvent systems.

A good number of earlier studies that have been reported on the solubilities of amino acids and peptides in water and aquo-organic solvents have been well documented in some authoritative reviews on the subject [109,110]. Dalton and Schmidt [111] reported the solubility’s of certain amino acids in water and the corresponding heats of solution, Nozaki and Tanford [112] reported the free energies of transfer of some amino acids including Glycine from water to various solvents like urea, ethylene glycol and ethanol. Needhan et al. [113] had studied the effects of various solvents and pH on solubility’s of some amino acids in a series of aqueous alcoholic solution and also in mixed aqua organic solvent systems. Solubility’s of amino acids were studied in heavy water by Kresheck et al. [114] and also in different mixed solvents by Hutchens [115], Lahiri et al. [116-119] and Gekko [120].

It was concluded that ‘the protein stabilization by polyols is a manifestation of polyol induced strengthening of the hydrophobic interaction of protein molecules’. Erlander [121] applied previously developed theories for explaining the mechanism for the salting-in and salting-out phenomena of various amino acids from solubility measurements in presence of various salts. Bull et al. [122] reported the transfer energetics of some common amino acids from water to 1 M Na₂SO₄ and found that the transfer process was primarily enthalpy rather than entropic. Solubility studies [123] of amino acids and peptides in water indicated that solubility decreases with increasing number of hydrocarbon (-CH₂) groups, like those of homologous series of organic compounds.

Various researchers [32,124,125] suggested that while glycine behaves as structure breaker in water, higher homologous behave as structure makers. However, Sasaki et al. [126] contradicts this idea from their ultrasonic studies on aqueous
solutions of amino acids. Kundu et al. [29,30,127,128] have reported transfer energies of glycine, diglycine and triglycine in aqueous mixtures of glycerol, urea and NaNO₃ co-solvents and have drawn important conclusions about the effect of amino acids on the 3D-structuredness of co-solvents.

Heat capacity studies [129] on several amino acids indicated that the hydrophobic hydration (H₃H) of α-amino acids increases with alkyl side chain length as dipolar character remains constant and independent of alkyl chain length. Besides, the results on various isomers of amino acids show H₃H is unaffected by branching of alkyl groups.

Jolicoeur and Boileau [130] also studied heat capacities and limiting apparent molar volumes of some oligopeptides of glycine, alanine, and serine. Volumetric properties of amino acids in water were studied by several researchers [130,131], which were reviewed by Wadi et al. [132]. Various researchers [133,134] have studied hydration number of amino acids using various methods. They suggested that hydration behavior of amino acids also depends upon concentration, pH, and even dielectric constant of the medium.

Recently correlation between amino acid hydrophobicity scales had been done by Fulvia et al. [135] and Cornette et al. [136]. Recent studies on dissociation constant and solubility of amino acids in different aquo-organic and non-aqueous solvents have also been done by various researchers [119,137-151] which may help to determine thermodynamic properties of peptide solution [152] and relationship between amino acid properties and protein compressibility [153].

Lumry and Rajendar [154] found that there is a linear relationship between the enthalpy and entropy changes involved in many processes in water and that the linear relationship can be used as a diagnostic test for the participation of water in the process. Like Kundu et al. they also believe that the entropy of transfer of amino acids can be used as a structural probe to understand the structural changes taking place in various solvent systems in presence of amino acids. Pinho et al. [155] indicated that the solubility of amino acids studies is maximum in water and inversely related to the length of the non-polar portion of the molecules.

Thus, different studies on amino acids pointed out that amino acids possess an essentially dual character and which character will predominant depends on both the inherent structure of the amino acid and the environmental factors afforded by the experimental conditions employed.

**Our study and its success**

Aqueous solution draws much attention than non-aqueous solution even though it has been realized for a long time that water can’t be regarded as the sole prototype of electrolyte solvent. Thus, water despite being the cheapest, most abundant and versatile solvent is not always most efficient medium for organic reactions. In fact, the optimum requirement for a physico-chemical process can be achieved by mixed aquo-organic solvents. The physicochemical properties of aquo-organic solvents are important from the point of view of practical applications. For all these, entire attention should not be confirmed to pure solvent only. It is well known that standard transfer thermodynamic quantities of a solute in solution are related with the solvent effect on the physicochemical properties of the solute. As the thermodynamic properties are related to the solute-
solvent interactions, so determination of free energies of transfer $\Delta G^\circ_{t,i}$ (i) is desirable to understand relative stability of a solute in a solvent in terms of these interactions like hydrophobic, hydrophilic, H-bonding, acid/base and dispersion interactions. Again, it is well known that proteins play a key role in almost all the biological processes. The basic structural units of proteins are amino acids. The side chains of these building blocks differ in size, shape, charge, hydrogen bonding capacity, hydrophobicity, and chemical reactivity. Much attention has been given [27,31,156-163] to determine the various thermodynamic properties such as molar volume [157], enthalpy of solutions [28-30,162], solubility [28-30,32,162] of various amino acids in different aqua-organic media. Theoretical [98,116-132,164] as well as experimental studies on amino acid solvation in different protein stabilizing (i.e. glycerol) and denaturing media (i.e. urea) were also performed. In this context, the purposes of such studies were to explore various mechanisms of amino acid solvation.

Different mechanisms have been proposed to explain the protein stabilizing action of glycerol and destabilizing action of urea. Some of them are: (i) reduction of hydrophobic hydration [29,30], (ii) alternation of water structure [29,30], (iii) weakening the inter peptide hydrogen bond [120,165] and (iv) the preferential hydration of protein [118,119,166].

In order to gain an idea about solute-solute, solute-solvent and solvent-solvent interactions in depth, I have undertaken in this work to study the thermodynamics of solvation of a series of homologous $\alpha$-amino acids with graded increase of $(-\text{CH}_2\text{CH}_2\text{OH})$ (hydrophobic moiety) group like glycine (Gly.), DL-alanine (Ala.), DL-$\alpha$-amino butyric acid (Aba.) and DL-nor-valine (Val.) in aqueous mixture of protic ethylene glycol (EG), quasi-protic 2-methoxyethanol (ME) and aprotic 1, 2-dimethoxyethane (DME).

In this relation, the standard transfer Gibbs energies, $\Delta G^\circ_{t,i}$ and entropies, $\Delta S^\circ_{t,i}$ (i) of the above said series of homologous $\alpha$-amino acids from water to aqueous mixtures of EG, ME and DME are determined from solubility measurement at five equidistant temperatures from 288.15 K to 308.15 K by ‘formol titrimetry’. The chemical contributions, $\Delta P^\circ_{t,h} (i)$ obtained by subtracting the cavity effect, $\Delta P^\circ_{t,ch} (i)$ and dipole-dipole interaction effect, $\Delta P^\circ_{t,d-d} (i)$ (P=G or S) [164] from $\Delta P^\circ_{t,i} (i)$. $\Delta G^\circ_{t,ch} (i)$ values are dictated by hydrogen bonding interaction, hydrophilic/hydrophobic hydration, acidity-basicity and dispersion effects and $T \Delta S^\circ_{t,h} (i)$ are guided by superimposed structural interaction as well.

These values may also be helpful to compute the transfer energetic of the smallest hydrophobic moiety $(-\text{CH}_2\text{CH}_2\text{OH})$, $\Delta P^\circ_{t,ch} (i)$ $(-\text{CH}_2\text{CH}_2\text{OH})$, by subtracting the values of lower homologues from those of immediately higher homologues. Interestingly the proposed works are done by our group and results are published [143-146] and conclusions were made as ethylene glycol is a protic as well as structure maker solvent containing $(-\text{CH}_2\text{CH}_2\text{OH})$ organic moiety and two hydroxyl groups (-OH) with stronger H-bonding ability. On passing from protic EG to aprotic DME through quasi-protic ME, the number of $-\text{CH}_2$ group increases from zero in EG to two in DME. The electron donating $-\text{CH}_2$ group will induce a large negative charge density on the oxygen-center to which it is attached, therefore the capacity for hydrogen-bond formation and hydrophilic hydration increases in the order, EG<ME<DME. On the other hand, the increased number of $-\text{CH}_3$ group may also influence hydrophobic hydration in such solute-solvent systems.

From these results, one may get broader insight regarding the solute-solvent and solvent-solvent interactions in such aqueous mixtures of structurally related co-solvent systems in the context of amino-acid solvation.
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