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Solubility of DL-Serine and DL-Phenylalanine in Aqueous Mixtures of Dimethyl Sulfoxide and Solvation Thermodynamics

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ABSTRACT

The standard free energies ($\Delta G_t^0(i)$) and entropies ($\Delta S_t^0(i)$) of transfer of DL-serine and DL-phenylalanine from water (1) to aqueous mixtures of dimethylsulfoxide (DMSO) (2) at 298.15 K are reported in the present study. The transfer energies have been determined from solubility measurement of the amino acids. The solubility is measured at different temperatures i.e. from 288.15 to 308.15 K by 'analytical gravimetric method'. The chemical parts of free energies ($\Delta G_{t,ch}^0(i)$) and entropies ($T\Delta S_{t,ch}^0(i)$) of transfer of the amino acid have been computed by subtracting the cavity effects and dipole-dipole interaction effects from the total transfer energies. The characteristics of the solvation thermodynamics of the amino acids in aquo-organic solvent system are studied and discussed in the present manuscript.

Keywords: Aqueous solvent, amino acid, solvation thermodynamics, Transfer energetics

1. Introduction

It is well known that proteins play key roles in nearly all biological processes. The proteins are built of amino acids as its structural units. The side chains of these building blocks differ in size, shape, charge, hydrogen bonding capacity, acidity, basicity, hydrophilicity, hydrophobicity, chemical reactivity, etc. The zwitterionic behavior of amino acids is also an important guiding factor in building different proteins.

The native state of a protein is determined by the character and sequence of its constituent amino acids and also by the solvent environment in which it is present. Protein folding is an important process that affects nearly every aspect of their biological activities. The conformation of a protein in solution is generally a function of electrostatic, hydrogen bonding, van der Waals

forces, acid–base interactions, hydrophobic and hydrophilic interactions among the amino acid residues[1]. Denaturation or defolding of a protein is also an essential process for the dissolution and purification of proteins during their extraction from natural sources.

In this respect, the knowledge of the solvation thermodynamics of proteins as well as amino acids in different solutions is necessary[1-19]. For a long time researchers had drawn their attention to determine the solubilities as well as solvation thermodynamic data of amino acids in different solvent systems[1-19]. The purposes of such studies were to gain clear ideas about the various aspects of protein folding-unfolding and protein hydration [2, 3] with biological as well as pharmaceutical and industrial importance.[6-9] Various research groups in the world wide [2-22] are working on the solvation thermodynamics of some amino acids in aquo-organic, aqueous electrolyte and in non-aqueous solvent systems. Solvation thermodynamic data like free energy of transfer of the amino acids can help to predict the stability of different conformations of the biomolecules like amino acids[3-9], peptides[10, 17] as well as proteins[1, 15, 31]. Some authors [23-26] also believed that entropy of transfer of amino acids can be used as a structural probe to recognize the structural changes taking place in various solvent systems in presence of amino acids.

All these researcher also tried to explore the ideas about the relative stabilization of these amino acids and other biomolecules in aqua-organic,[2, 3, 5, 10-16] aqueous electrolyte [6, 7, 17, 18] and in non-aqueous mixtures [27-29] with respect to water and the complex solute-solvent and solvent-solvent interactions therein.

Presently, DMSO with immense biological importance [20] is chosen here as co-solvent with H_2O to get further broader insight about the aqua-organic chemistry for amino acid solvation.

DMSO possesses two hydrophobic methyl groups with +I effect and these hydrogen atoms of two CH_3- groups are of acidic character[37]. Also it has increased basicity as well as protophilic

dipolar aprotic character compared to H_2O. On the other hand between the amino acid DL-Serine and DL-Phenylalanine here under study the first and the second one is composed of hydrophilic –OH group and hydrophobic $–C_6H_5$ group respectively. Therefore study of solvation mechanism of these amino acids may be rewarding in H_2O-DMSO mixtures. Considering these point of views and followed by previous works[19], we are presenting the standard transfer free energy ($\Delta G_t^0(i)$) and entropies ($\Delta S_t^0(i)$) of amino acids like DL-serine and DL-phenylalanine from pure water to aqua-organic mixture of DMSO at 298.15 K.

In such situation in the present study we have tried to get some important ideas about structural eccentricities of water [23] and the role of highly complex aquo-organic chemistry in the context of stabilization of the same.

The solvation characters of this aqua-organic solvent mixture undergo gradual but material change compared to pure solvent system [10-16] with respect to amino acid solvation. The results found in the present study i.e. in this aqua-organic binary solvent system are likely to be very much useful to understand the solvation mechanism of amino acid and amino acid induced solvent-solvent interaction in aqua-organic binary solvent mixture and fill up the needs of the thermodynamic data in chemical, pharmaceutical, cosmetics, food and in industrial sciences.

2. Experimental Section

2.1 Materials and their Purifications

Amino acids, DL-serine (> 99.0 % E Merck) and DL-phenylalanine (> 99.0 %, E-Merck), were used after drying in a vacuum desiccator without further purification[11].

Dimethylsulfoxide (DMSO) [29, 30](> 99.8 %, Sigma Aldrich) was first dried over fused $CaCl_2$ for 3-4 days, decanted and then was distilled under reduced pressure. The distilled sample was

preserved in a well stoppered Jena bottle in desiccators and redistilled before use. The triple distilled water is used in the whole experimental solutions and for other needs.

2.2 Method.

Aqueous solvent mixtures of DMSO (2) that have been used were 0, 5.4, 13.3, 25.6, 47.9 and 100 mol % of DMSO. The mixed solvents were prepared by mixing triple distilled H_2O (1) and DMSO (2) by weight using a Mettler balance having a precision of ±0.1 mg.

The pure solvents and solvent mixtures were preserved in well stoppered glass bottles and all were protected by storing in desiccators when not in use.

The 'analytical gravimetric' method [26, 31] consists of the preparation of a saturated solution at the desired temperatures. The jacketed glass cell was charged with known masses (±0.1 mg) of the binary mixed solution and with each amino acid in a small excess to the expected saturation limit. To reach equilibrium conditions the solution was continuously stirred for 24 h and, after that, the solutions were allowed to settle for at least 12 h before sampling with preheated pipette. The samples (5 cm^3) were withdrawn from the supernatant phase, inserted into glass vessels and immediately weighted.

The next step was to evaporate all solution from the sample, and to dry completely in a drying stove for 2 days. Finally, the samples were cooled in a dehydrator with silica gel for 1 day and weighted; the process was regularly repeated until a constant mass value was achieved.

The mass of dissolved amino acids were calculated from the knowledge of the initial electrolyte concentration in the solution and the weight of the glass vessels empty, with the saturated solution and with the dried sample.

Four sets of measurements for the entire aqueous electrolyte mixtures were made for all temperatures by equilibrating the solutions from both above and below (± 0.1 K) the required

temperatures i.e. 288.15, 293.15, 298.15, 303.15 and 308.15K and the solubilities were found to agree with maximum 2.4 % uncertainties.

3. Theoretical

3.1 Calculations of thermodynamic parameters

The Gibbs energy of solutions ($\Delta G^0_{sol}(i)$) on molal scale were computed at different temperatures for each solvent mixture using eq 1 like previous studies.[11, 28, 29]

$$\Delta G^0_{sol}(i) = -RT \ln S\gamma \approx -RT \ln S \quad (1)$$

here γ is the molal activity coefficient and '*S*' is the experimental saturated solubility of the amino acids in mol·kg^{-1}.

Amino acids are likely to be zwitterions in solutions. So they are expected to have large dipole-dipole interaction among themselves. Therefore, the activity coefficient factor $-RT \ln \gamma$ may contribute to $\Delta G^0_{sol}(i)$. In some previous studies Held and coworkers[9] measured the activity coefficients of some amino acids like glycine, proline, hydroxyproline, L-Leucine, L-Methionine, etc., in aqueous systems. They found that the values of activity coefficient (γ) were nearly unity for such amino acids in lower concentrations. It is to be noted here that the mole fractions of amino acids present in different compositions of the present aqueous DMSO solvent system, as calculated from solubility values (shown in Table 3) are negligibly small. Therefore the activity coefficients of the present solute - solvent systems are taken as unity in calculating of $\Delta G^0_{sol}(i)$ as is usually done for non-electrolytes.[23, 24, 28, 29]

This assumption will not be difficult to understand because the factor containing the ratio of activity coefficient, $-RT \ln \gamma_s / \gamma_R$ ('s' for H_2O-DMSO and 'R' for reference solvent, H_2O), in

determining transfer free energies, $\Delta G_t^0(i)$ [$\Delta G_t^0(i) = {}_s\Delta G_{sol}^0(i) - {}_R\Delta G_{sol}^0(i)$], which is our main concern, is likely to be negligibly small.

To get the precise value of $\Delta G_{sol}^0(i)$ and to quantify the effect of temperature on $\Delta G_{sol}^0(i)$ the method of least squares is used in the form of eq 2.[29]

$$\Delta G_{sol}^0(i) = a + bT + cT\ln T \quad (2)$$

where T is the temperature in Kelvin scale. Transfer Gibbs energies, ΔG_t^0 and entropies ΔS_t^0 of the amino acids from H_2O to H_2O + DMSO mixtures were calculated at 298.15 K on mole fraction scale by using the following eqs 3, 4 & 5.

$$\Delta G_t^0(i) = {}_s\Delta G_{sol}^0(i) - {}_R\Delta G_{sol}^0(i) \quad (3)$$

i.e. $$\Delta G_t^0(i) = (a_s - a_R) + (b_s - b_R)T + (c_s - c_R)T\ln T - RT\ln(M_s / M_R) \quad (4)$$

and

$$\Delta S_t^0(i) = (b_R - b_s) + (c_R - c_S)(1 + \ln T) + R\ln(M_s / M_R) \quad (5)$$

here the subscript '*s*' for H_2O /DMSO mixtures, 'R' for reference solvent H_2O, M_s and M_R is the molar mass of the H_2O +DMSO and pure reference solvent, H_2O respectively. The computed $\Delta G_t^0(i)$ and $T\Delta S_t^0(i)$ values of the amino acids are presented in Table 5 & 6. The calculated values show uncertainties in $\Delta G_t^0(i)$ and $\Delta S_t^0(i)$ are about ±0.05 kJ·mol^{-1} and 2 kJ·mol^{-1}, respectively.

Now $\Delta X_t^0(i)$ (where X=G or S) may be ascribed as the sum of the following terms (assuming dipole induced dipole term to be negligibly small).[23, 26]

i.e. $\Delta X_t^0(i) = \Delta X_{t,cav}^0(i) + \Delta X_{t,d-d}^0(i) + \Delta X_{t,ch}^0(i)$ (6)

Here, $\Delta X^0_{t,cav}(i)$ means for the transfer energy contribution of the cavity effect which is involved due to creation of cavities for the species (amino acids) in H_2O and H_2O +DMSO mixed solvent system and $\Delta X^0_{t,d-d}(i)$ represents the dipole-dipole interaction effect involving interaction between dipolar-zwitter-ionic amino acids and the solvent molecules. On the other hand, $\Delta X^0_{t,ch}(i)$ includes that for all other effects such as those arising from acid-base or short- range dispersion interaction, hydrophilic or hydrophobic hydration and structural effects, etc. Here $\Delta X^0_{t,cav}(i)$ values are computed by well established Scaled particle theory (SPT) of R.A. Pierotti,[23, 25, 28, 32] assuming the solutes and solvent molecules as equivalent to hard-sphere models as dictated by their respective diameter [32]. Here the hard-sphere diameter for mixed solvent, σ_s for a particular composition of solvent mixture is calculated according to Graziano[38] (Table 2 & 6) as:

σ_s = mole fraction of water × hard-sphere diameter of water + mole fraction of DMSO × hard-sphere diameter of DMSO.

Keesom-orientation expression[30.32] is used to calculate $\Delta G^0_{d-d}(i)$ and ${}_s\Delta S^0_{d-d}(i)$ as:

$$\Delta G^0_{t,d-d}(i) = ({}_s\Delta G^0_{d-d}(i) - {}_R\Delta G^0_{d-d}(i)) \quad (7)$$

and $$\Delta S^0_{t,d-d}(i) = ({}_s\Delta S^0_{d-d}(i) - {}_R\Delta S^0_{d-d}(i)) \quad (8)$$

For ${}_s\Delta G^0_{d-d}(i)$ in a solvent S, as given below:

$${}_s\Delta G^0_{d-d}(i) = -(8\Pi/9)N^2\mu_s^2\mu_x^2\sigma_{s-x}^{-3}(kT)^{-1}V_s^{-1} = \mathrm{A/T}V_s \quad (9)$$

Where $\mathrm{A} = -(8\Pi/9)N^2\mu_s^2\mu_x^2\sigma_{s-x}^{-3}(k)^{-1}$

Π = 22/7, Vs=M_s/d_s = molar volume of solvent, M_s= molar mass of solvent, d_s = density of solvent, k is the Boltzmann constant. N for Avogadro's number, μ_s, μ_x are the dipole moment of mixed solvent and amino acid molecules respectively (Table 2 & 6).

The dipole moment of the mixed binary solvent system in a particular composition is calculated as[38]: μ_s = μ of reference solvent (H_2O) × mole fraction of reference solvent (H_2O) + μ of co-solvent (DMSO) × mole fraction of co-solvent (DMSO).

σ_{s-x} represents the distance at which the attractive and repulsive interactions between the solvent and solute molecules are equal and is generally equal to ½($\sigma_s + \sigma_x$) where σ_s and σ_x are the hard sphere diameters of co-solvent and solute amino acid molecules respectively (Table 2 & 6)

Here $\Delta S^0_{d-d}(i)$ can be written as follows:

$$_s\Delta S^0_{d-d}(i) = -\{\delta_s \Delta G^0_{d-d}(i)/\delta T\}_p \quad (10)$$

$$\text{i.e. } T_s\Delta S^0_{d-d}(i) = {}_s\Delta G^0_{d-d}(i)[1 + T\alpha]^{23,29} \quad (11)$$

where α is the isothermal expansibility [23] of the mixed solvent and represented by eq 12 as:

$$\alpha = (\delta \ln V_s/\delta T)_P = -(\delta \ln d_s/\delta T) \quad (12)$$

As in the earlier studies[32, 33] , in order to get the $\Delta X^0_{t,d-d}(i)$ term on the mole fraction scale, $\Delta X^0_{t,d-d}(i)$ was again multiplied by X_{sl}, which is the actual mole fraction of the organic co-solvent in the vicinity of the solute for the contribution of dipole-dipole interaction,[33] which was estimated using the eq 13 as follow[32];

$$X_{s1} = X_s(\mu_s/\sigma_s^3)/(\mu_R/\sigma_R^3) \quad (13)$$

On the other hand $\Delta X^0_{t,ch}(i)$ values of amino acids were calculated after the subtraction of $\Delta X^0_{t,cav}(i)$ and $\Delta X^0_{t,d-d}(i)$ from the total i.e. $\Delta X^0_t(i)$. The values of $\Delta X^0_{t,cav}(i)$, $\Delta X^0_{t,d-d}(i)$ and $\Delta X^0_{t,ch}(i)$ are presented in Table 6.

4. Result and Discussion

4.1. Analysis of solubility data.

The solubility of DL-Serine and DL-Phenylalanine increases with temperature in a particular composition of water-DMSO mixed solvent system. But the solubility of DL-Serine is higher than DL-Phenylalanine in 0, 20 and 40 wt % of water-DMSO composition and the reverse is true in 60, 80 and 100 wt % of the same at any temperature. This is due to the involvement of structural effect of solutes and solvents i.e. DL-Serine, DL-Phenylalanine, water and DMSO. Pure water has strong intermolecular hydrogen bonding capability. On the other hand the >S=O moiety of DMSO allows weak acid-base, anionophilic and cationophilic interaction for $–COO^-$ and NH_3^+ moieties of both the amino acids. In DL-Serine there is a hydrophilic –OH group (Scheme-1). In contrast there is a bulky hydrophobic moiety like $–C_6H_5$ instead of –OH moiety in DL-Phenylalanine (Scheme-1). The –OH group can take part in hydrophilic interaction with the solvent molecules through H-bonding and acid-base interactions which lead to more solubility for the amino acid DL-Serine, but in case of DL-Phenylalanine, the presence of such bulky hydrophobic moiety reduces the hydrophilic interaction with the solvent molecule, so that the solubility become higher for the former than the latter in water-rich composition of water-DMSO solvent system. The reverse is true due to the increased concentration of larger dipolar aprotic DMSO co-solvent from 60 to 100 wt % of the same in such aqueous DMSO binary solvent mixtures.

4.2. Solvation of the amino acids.

The specifications of chemical samples used in the experimental are given in the Table 1. The experimental solubility ($mol \cdot kg^{-1}$) of the amino acids (DL-Serine, DL- Phenylalanine) are measured on molal scale and are listed in Table 3. Standard uncertainties of solubilities at all temperatures and compositions are found to be ± 0.00004 and cited in the Table 3.

The values of $\Delta G_t^0(i)$ are cited in Table 5 which are represented by the Figure 1. The positive increment of $\Delta G_t^0(i)$ values for the both amino acids at 298.15 K with increased concentration (mol %) of DMSO in H_2O -DMSO mixed solvent system indicates destabilization of the same. But the positive increment is higher for DL-Serine than the DL- Phenylalanine. This indicates that the former amino acid gains lesser stability in H_2O -DMSO mixed solvent system than the latter due to different types of solute-solvent interactions like cavity forming, dipole-dipole and chemical interactions. The more or less gradual increase of components of $\Delta G_t^0(i)$ due to dipole-dipole interaction, $\Delta G_{t,d-d}^0(i)$ and cavity effect, $\Delta G_{t,cav}^0(i)$ are also responsible for this trend. Since the total transfer free energies, $\Delta G_t^0(i)$ of amino acid is mainly the sum of $\Delta G_{t,cav}^0(i)$, $\Delta G_{t,d-d}^0(i)$ and $\Delta G_{t,ch}^0(i)$ (Table. 6) and so it depends on many types of interactions. However, the actual stability order of the amino acids is somewhat complex to explain by considering total transfer free energies with the variation of solvent composition. So that the $\Delta G_{t,ch}^0(i)$ - composition profiles can be used to explain the results in terms of chemical interactional effects. The $\Delta G_{t,ch}^0(i)$ values of the amino acids with DMSO composition are presented in Table 6.

The $\Delta G_{t,ch}^0(i)$ values are obtained after elimination of $\Delta G_{t,cav}^0(i)$ and $\Delta G_{t,d-d}^0(i)$ from $\Delta G_t^0(i)$ of each amino acid. The amino acids become stabilized (Table 6) by the cavity forming interaction in the mixed aqueous DMSO solvent mixtures due to the involvement of larger

(σ_{DMSO} = 4.91 Å[32]) DMSO co-solvent molecules. But the dipole-dipole interaction between solute (amino acids) and mixed aqueous solvent (H_2O -DMSO) systems become unfavorable for the stabilization of both the amino acids. The stability due to dipole-dipole interaction, $\Delta G^0_{t,d-d}(i)$ of DL-phenylalanine is higher than DL-serine for the difference in size and dipole moment of the involved solutes and solvents under study.

The term $\Delta G^0_{t,ch}(i)$ represents the chemical interactions which is actually arises due to H-bonding, acid-base, dispersion, hydrophilic, hydrophobic and hard-soft interactions. The chemical interactions impart a gradual destabilization for both the amino acid i.e. DL-phenylalanine and DL-serine. In the main the extent of destabilization is comparatively greater for DL-serine than DL-phenylalanine.

DL-serine having hydrophilic side chain (-CH_2OH) along with –COO^- and NH_3^+ moieties are strongly interacted (greater association) by hydrogen bonding, acid-base, hydrophilic and hydrophobic hydration capability of reference solvent, protic H_2O molecule in the water-rich region of such protic and dipolar aprotic solvent mixtures.

But the gradual destabilization of the same occurs with the increase of concentration of co-solvent, DMSO having weaker capacity of hydrogen bonding, acid-base, hydrophobic and hydrophilic interactions. Here co-solvent, DMSO with its larger size [32] and hence polarizability (greater softness) will impart dispersion interaction for DL-serine (5.93Å). But the weakening of the polarity oriented former types of interactions plays dominant role over the latter type of interaction with the increased concentration of DMSO in such binary solvent mixtures and hence the nature of stability is reflected in Figure 2.

On the other hand DL-Phenylalanine having only bulky hydrophobic side chain (-$CH_2C_6H_5$) can take part in lesser extent of hydrogen bonding, acid-base, hydrophobic and hydrophilic

interactions. Therefore it will be destabilized in water-rich region of this water-DMSO solvent mixture. DL-Phenylalanine will take part in dispersion as well as soft-soft interaction with larger co-solvent DMSO molecules in greater extent than DL-serine due to the larger size of the former. Therefore, DL-Phenylalanine will comparatively be more stabilized than DL-serine with the increased concentration of DMSO in water-DMSO mixtures.

As the concentration of DMSO is increased, the association between H_2O and DMSO (Scheme 2(A)) may occur[20, 35] resulting comparatively larger associated solvent molecules. The self association (dimerisation) of DMSO (Scheme 2 (B)) [29] occurs in the higher concentration of DMSO in the mixed solvent system. Now the associated or self associated larger size molecule of mixed solvent takes part in dispersion interaction for both the α-amino acids.

The size of DL-phenylalanine (6.60 Å) is larger than DL-serine (5.93 Å). Therefore the dispersion interaction will be stronger for the former than the latter.

It is to be noted that the stability of DL-serine is greater than DL-Phenylalanine in 100wt % of DMSO. Here the dimerised $(DMSO)_2$ (Scheme 2 (B)) [29] exerts dispersion as well as acid-base, hydrogen bonding and cationophilic/anionophilic interaction for both the amino acids. These chemical interactions altogether will be stronger for DL-Serine than DL-Phenylalanine due to the presence of polar –OH group in the side chain of the former.

4.3 Role of amino acids for controlling solvent-solvent interaction in protic and dipolar aprotic binary solvent mixtures.

The variations of $T\Delta S_t^0(i)$ (Figure 3) values of the amino acids with the increased concentration of DMSO in H_2O -DMSO solvent system are presented in the Table 3 & 4.

The $T\Delta S_t^0(i)$ value is composed of cavity, dipole-dipole and chemical interaction effect as-

$$T\Delta S_t^0(i) = T\Delta S_{t,cav}^0(i) + T\Delta S_{t,d-d}^0(i) + T\Delta S_{t,ch}^0(i) \qquad (14)$$

The first two energy terms stand for the difference in the entropy change involved in creating appropriate cavities for accommodating the amino acids and dipole-dipole interaction between the amino acid dipole with the solvent dipole, respectively. $T\Delta S^0_{t,cav}(i)$ and $T\Delta S^0_{t,d-d}(i)$ values are presented in Table 6.

$T\Delta S^0_{t,ch}(i)$ term i.e. the chemical transfer entropy change, (Figure 4) stands for the combined effects of various chemical interactions between solvent molecules induced by the amino acids. The values of $T\Delta S^0_{t,ch}(i)$ of the amino acids are summarized in Table 6.

At water rich region with the introduction of DMSO molecules the hydrogen bonds between the water molecules are broken down and immediately the free water molecules are interacted with the solute molecules through hydrogen bonding. This type of interaction occurs strongly and easily with the molecules having polar side chain with stronger hydrogen bonding capacity. Therefore water molecules are involved in the interaction with DL-serine to show its lesser disorderness [negative $T\Delta S^0_{t,ch}(i)$] in the water-rich region (up to 60wt % H_2O) of this water-DMSO binary solvent system. DL-serine induces the association between H_2O and DMSO (Scheme 2(A))[20] resulting comparatively larger associated solvent molecules with lesser disorderness involving negative $T\Delta S^0_{t,ch}(i)$ as the concentration of DMSO is increased (80 wt % DMSO). The self association (dimerisation) of DMSO (Scheme 2 (B)) [29] is induced in the highest concentration of DMSO in the mixed solvent system imparting the lowest disorderness.

But in presence of DL-phenylalanine, having larger hydrophobic phenyl moiety the disorderness of the solvent molecules becomes more favorable up to about 60 wt % DMSO concentration due to weaker solute-solvent interaction. After that up to 100 wt % the disorderness is gradually decreased. With the increment of the concentration of DMSO in this mixed solvent system

dimerisation of DMSO (Scheme 2 (B)) [29] occurs progressively. Larger self-associated dimerised, $(DMSO)_2$ is induced to take part in the strongest dispersion interaction towards the amino acid, DL-Phenyl alanine.

The numbers of free DMSO molecules become lower due to such dimerisation of it. Therefore the overall entropy change due to DL-Phenylalanine induced chemical interactions results more negative values of transfer entropy [$T\Delta S^{0}_{t,ch}(i)$] that is the lowest disorderness in this aqueous DMSO solvent mixture (Figure 4).

5. Conclusion

From the above surveillance it may be concluded that the stability of both the amino acid, DL-serine and DL-phenylalanine is decreased in aqueous dimethylsulfoxide. DL-phenylalanine is comparatively more stable than DL-serine in such protic-dipolar aprotic aqua-organic binary solvent mixture. The cavity forming, dipole-dipole and chemical interactions influence the solvation mechanism of these two amino acids. The dispersion interaction and hydrogen bonding interactions play foremost role to control solvation mechanism of these amino acids. These types of interactions are also significant for controlling amino acid induced solvent-solvent interaction which is reflected in the change in disorderness that is in transfer entropy in the mixed binary solvent.

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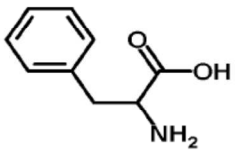
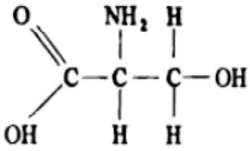
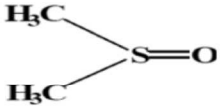
Table 1. Specification of Chemical Samples

Chemical Name	Chemical Structure	Source	Initial Purity[a] (fraction)	Purification Method	Final Purity (fraction)
DL-Phenylalanine		E. Merck	99.8 % (mass)	drying in vacuum desiccator	99.9 % (mass)
DL-Serine		E. Merck	99.8 % (mass)	drying in vacuum desiccator	99.9 % (mass)
Dimethylsulfoxide		Sigma Aldrich	99.8 % (mass)	Distilled under reduced pressure	99.98 % (mass) (analysis method: GC[b])
Sodium hydroxide	NaOH	GR, E. Merck	99 % (mass)	-	99 %
Water	H_2O			distillation	-
Formaldehyde	HCHO	GR, E. Merck	99 % (mass)	distillation	99 % (mass)

[a] Declared by the Supplier. [b] Gas−liquid chromatography

Table 2. Values of solvent parameters (Mol % of DMSO, Mole fraction of DMSO (z_s), water (z_R), Molar mass of aqueous solvent system (M_S), density (d_s), hard sphere diameter of co-solvent (σ_s) [(DMSO +H_2O))] and σ_{s-x} (= ½($\sigma_s + \sigma_x$)), Dipole moment of co-solvent (μ_s), and isobaric thermal expansibility constant (α) of DMSO +H_2O at 298.15 K

Mol % DMSO	Mole fraction (z_s)	Mole fraction (z_R)	Molar mass (M_S)	10^3 d_s (kg· m^{-3})	Molar Vol. (V_s)	σ_s (nm)	σ_{s-x} (nm)		Dipole Moment (μ_s)	α (x 10^{-3})
							Phe	Ser		
0.00	0.000	1.000	18.015	0.997#	18.06921	0.274	0.467	0.433	1.831	0.257*
5.40	0.054	0.946	21.260	1.002	21.21756	0.286	0.473	0.440	1.941	0.296
13.30	0.133	0.867	26.010	1.009	25.77800	0.303	0.482	0.448	2.105	0.353
25.60	0.256	0.744	33.400	1.021	32.71303	0.329	0.495	0.461	2.359	0.442
47.90	0.479	0.521	46.810	1.042	44.92322	0.378	0.519	0.486	2.821	0.602
100	1.000	0.000	78.130	1.091#	71.61320	0.491	0.576	0.542	3.900	0.982

#, * For the reference [31]

Table 3. Solubilities* (mol·kg^{-1}) of DL-Serine and DL-Phenylalanine in aqueous solvent mixtures of DMSO at (288.15, 293.15, 298.15, 303.15 and 308.15K#) temperatures (Experimental pressure p =0.1 MPa).

	Solubility(S)					
	mass fraction of DMSO (x)					
	0.00	0.20	0.40	0.60	0.80	1.00
T/ K	mol % of DMSO					
	0.00	5.40	13.30	25.60	47.90	100
	DL-Phenylalanine					
288.15	0.0657	0.0496	0.0304	0.0117	0.0084	0.0050
293.15	0.0690	0.0526	0.0342	0.0140	0.0096	0.0059
298.15	0.0726	0.0558	0.0366	0.0162	0.0104	0.0065
303.15	0.0762	0.0589	0.0392	0.0178	0.0118	0.0072
308.15	0.0798	0.0629	0.0418	0.0208	0.0130	0.0082
	DL-Serine					
288.15	0.4604	0.2142	0.0702	0.0180	0.0035	0.0017
293.15	0.4960	0.2252	0.0739	0.0206	0.0045	0.0022
298.15	0.5292	0.2365	0.0778	0.0227	0.0053	0.0025
303.15	0.5580	0.2456	0.0822	0.0254	0.0078	0.0031
308.15	0.5858	0.2504	0.0894	0.0285	0.0102	0.0039

u (T) = ± 0.1. u(x) ±0.01. * u(S) = ± 0.00004

Table 4. Standard Gibbs energies of solutions (ΔG^0_{sol}) (kJ•mol^{-1}) on molal scale in their respective solubilities (mol•kg^{-1}) of DL-Serine and DL-Phenylalanine in aqueous solvent mixtures of DMSO at different temperature (K[#])

288.15 K		293.15 K		298.15 K		303.15 K		303.18 K	
S	ΔG^0_{sol}	***S***	ΔG^0_{sol}	***S***	ΔG^0_{sol}	***S***	ΔG^0_{sol}	***S***	ΔG^0_{sol}
DL-Phenylalanine									
0.0657	6.5226	0.0690	6.5163	0.0726	6.5014	0.0762	6.4885	0.0798	6.4772
0.0496	7.1961	0.0526	7.1778	0.0558	7.1538	0.0589	7.1375	0.0629	7.0869
0.0304	8.3688	0.0342	8.2270	0.0366	8.1992	0.0392	8.1637	0.0418	8.1338
0.0117	10.6564	0.0140	10.4039	0.0162	10.2195	0.0178	10.1536	0.0208	9.9219
0.0084	11.4502	0.0096	11.3234	0.0104	11.3182	0.0118	11.1896	0.0130	11.1261
0.0050	12.6931	0.0059	12.5099	0.0065	12.4832	0.0072	12.4347	0.0082	12.3067
DL-Serine									
0.4604	1.8582	0.4940	1.7188	0.5292	1.5775	0.5580	1.4704	0.5858	1.3700
0.2142	3.6914	0.2252	3.6334	0.2365	3.5739	0.2456	3.5388	0.2504	3.5272
0.0702	6.3639	0.0739	6.3491	0.0778	6.3299	0.0822	6.2974	0.0894	6.1862
0.0180	9.6244	0.0206	9.4625	0.0227	9.3833	0.0254	9.2574	0.0285	9.1151
0.0035	13.5476	0.0045	13.1701	0.0053	12.9891	0.0078	12.2330	0.0102	11.7475
0.0017	15.2776	0.0022	14.9143	0.0025	14.8517	0.0031	14.5587	0.0039	14.2106

[#] Standard uncertainties of temperature u(T) = ± 0.1 K.

Table 5. Coefficients a, b and c of DL-Serine and DL-Phenylalanine in aqueous solvent mixtures of DMSO and Gibbs energies $\Delta G_t^0(i)$ and entropies $T\Delta S_t^0(i)$ of transfer of the amino acids (on mole fraction scale) in kJ·mol^{-1} from water to aqueous mixtures of DMSO at 298.15 K[#]

Solvent mass fractions (x_2)	a (kJ·mol^{-1})	b (kJ·mol^{-1}·K^{-1})	c (kJ·mol^{-1}·K^{-1})	$\Delta G_t^0(i)$ (kJ·mol^{-1})	$T\Delta S_t^0(i)$ (kJ·mol^{-1})
			DL-Phenylalanine		
0.000	3.14	0.0889	-0.01363	0	0
0.200	-20.20	0.6441	-0.09694	0.257	0.831
0.400	128.55	-2.6431	0.39304	0.777	2.885
0.600	101.82	-1.8612	0.27276	2.226	6.453
0.800	17.56	-0.0522	0.00545	2.408	5.487
1.000	62.53	-1.0279	0.15135	3.034	6.696
			DL-Serine		
0.000	65.87	-1.3047	0.19115	0	0
0.200	65.63	-1.3458	0.19967	1.569	-4.759
0.400	-95.93	2.3436	-0.35114	3.821	-4.437
0.600	12.86	0.0611	-0.01278	6.252	0.919
0.800	-361.94	8.9363	-1.34871	8.904	5.626
1.000	-71.95	2.2443	-0.34074	13.136	6.358

[#] u (T) = ± 0.1. u(x_2) ±0.01.

Table 6. Gibbs energies of transfer $\Delta G_t^0(i)$, $\Delta G_{t,cav}^0(i)$, $\Delta G_{t,d-d}^0(i)$, $\Delta G_{t,ch}^0(i)$ and enthalpy of transfer, $\Delta H_{t,cav}^0(i)$ and entropies of transfer $T\Delta S_t^0(i)$, $T\Delta S_{t,cav}^o(i)$, $T\Delta S_{t,d-d}^0(i)$ and $T\Delta S_{t,ch}^0(i)$ of DL-Serine and DL-Phenylalanine from water to in aqueous solvent mixtures of DMSO at 298.15 K[#] (on mole fraction scale in kJ·mol^{-1}).

Solvent mass fractions (x_2)	$\Delta G_t^0(i)$ (kJ·mol^{-1})	$\Delta G_{t,cav}^0(i)$ (kJ·mol^{-1})	$\Delta G_{t,d-d}^0(i)$ (kJ·mol^{-1})	$\Delta G_{t,ch}^0(i)$ (kJ·mol^{-1})	$T\Delta S_t^0(i)$ (kJ·mol^{-1})	$\Delta H_{t,cav}^0(i)$ (kJ·mol^{-1})	$T\Delta S_{t,cav}^o(i)$ (kJ·mol^{-1})	$T\Delta S_{t,d-d}^0(i)$ (kJ·mol^{-1})	$T\Delta S_{t,ch}^0(i)$ (kJ·mol^{-1})
				DL-Phenylalanine					
0.000	0	0	0	0	0	0	0	0	0
0.200	0.257	-1.580	0.011	1.826	0.831	-1.090	0.490	0.010	0.331
0.400	0.777	-3.200	0.050	3.927	2.885	-1.820	1.380	0.045	1.460
0.600	2.226	-4.870	0.121	6.975	6.453	-2.090	2.780	0.108	3.565
0.800	2.408	-6.670	0.236	8.842	5.487	-1.110	5.560	0.199	-0.272
1.000	3.034	-7.840	0.398	10.476	6.696	16.900	24.740	0.294	-18.338
				DL-Seine					
0.000	0	0	0	0	0	0	0	0	0
0.200	1.569	-1.450	0.307	2.712	-4.759	-0.892	0.558	0.294	-5.611
0.400	3.821	-2.960	1.310	5.471	-4.437	-1.500	1.460	1.120	-7.017
0.600	6.252	-4.550	3.170	7.632	0.919	-1.710	2.840	2.860	-4.781
0.800	8.904	-6.310	6.340	8.874	5.626	-0.879	5.431	5.470	-5.275
1.000	9.571	-7.620	10.700	6.491	6.358	14.300	21.920	8.270	-23.832

[#] u (T) = ± 0.1. u(x_2) ±0.01. Here σ_{H2O} = 2.74 Å[32], σ_{DMSO} = 4.91 Å[32], μ_{HOH} = 1.83 D[32] and $\mu_{DMSO=}$ 3.90 D[32] . The required hard sphere diameter of DL-Phenylalanine and DL-Seine is 6.60 and 5.93Å respectively. Dipole-moment values of Phenylalanine and DL-Seine are 2.480 D[35] and 11.10 D[36] respectively.

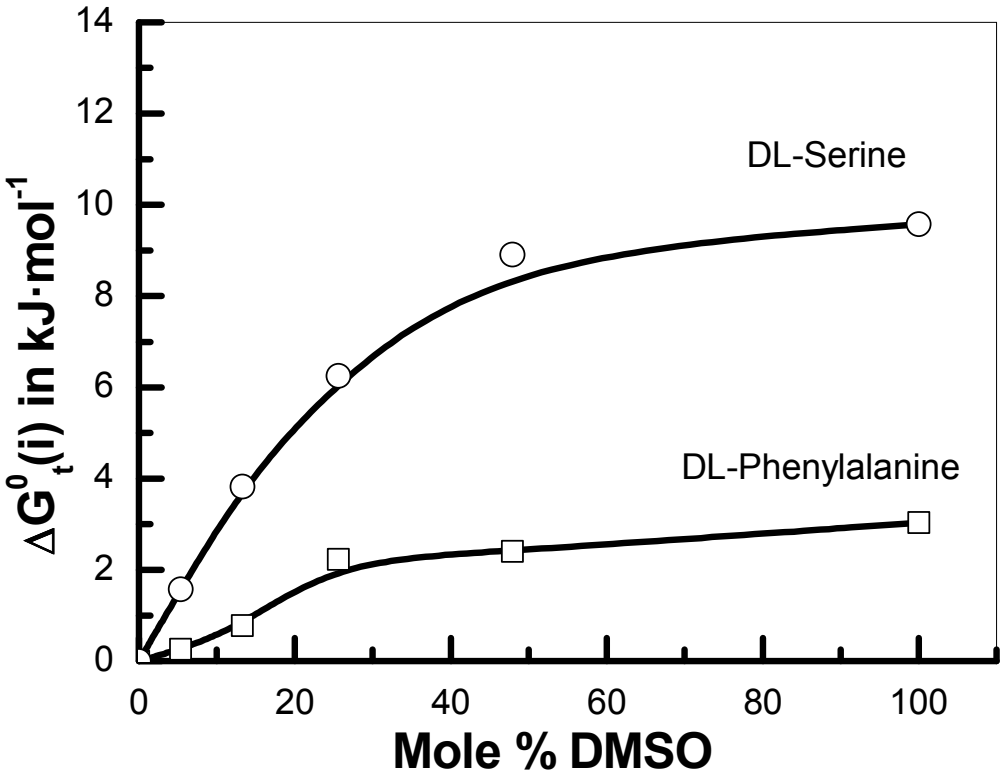


Figure 1: Variation of $\Delta G_t^0(i)$ in kJ•mol^{-1} of DL-Phenyl alanine and DL-Serine in aqueous mixtures of DMSO at 298.15 K

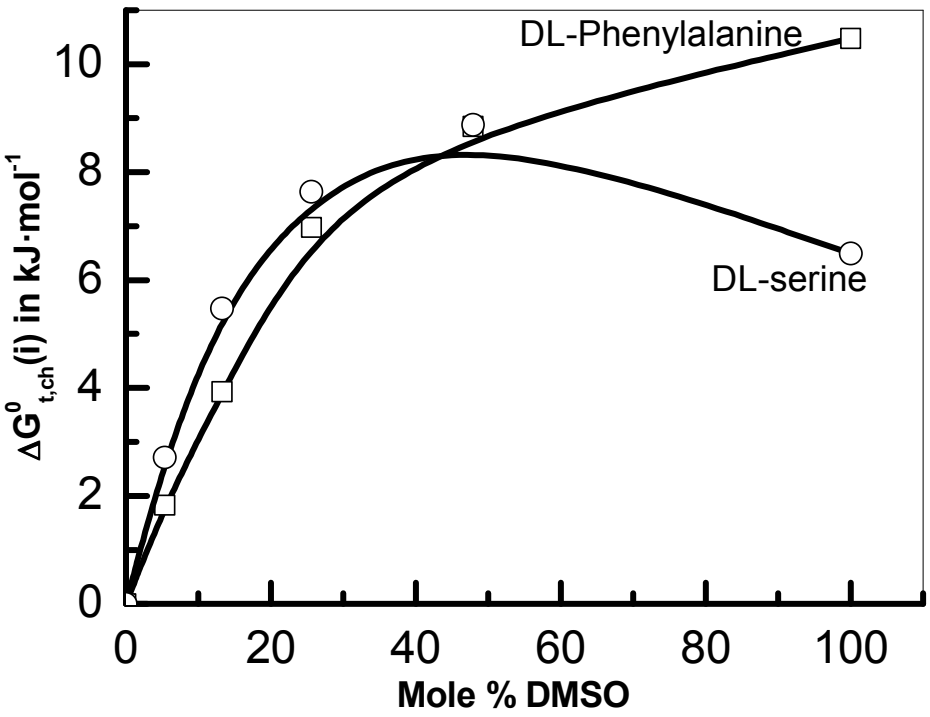


Figure 2: Variation of $\Delta G^0_{t,ch}(i)$ in kJ•mol^{-1} of DL-Phenyl alanine and DL-Serine in aqueous mixtures of DMSO at 298.15 K

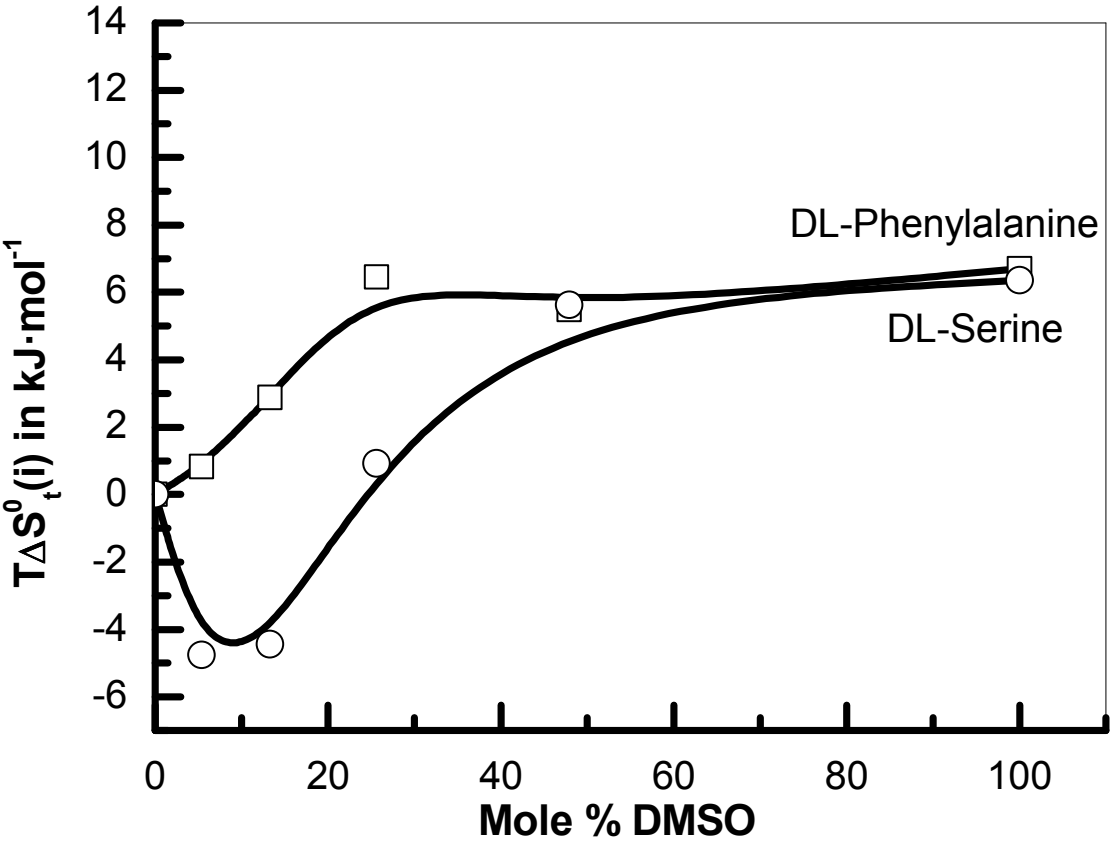


Figure 3: Variation of $T\Delta S_t^0(i)$ in kJ•mol^{-1} of DL-Phenyl alanine and DL-Serine in aqueous mixtures of DMSO at 298.15 K

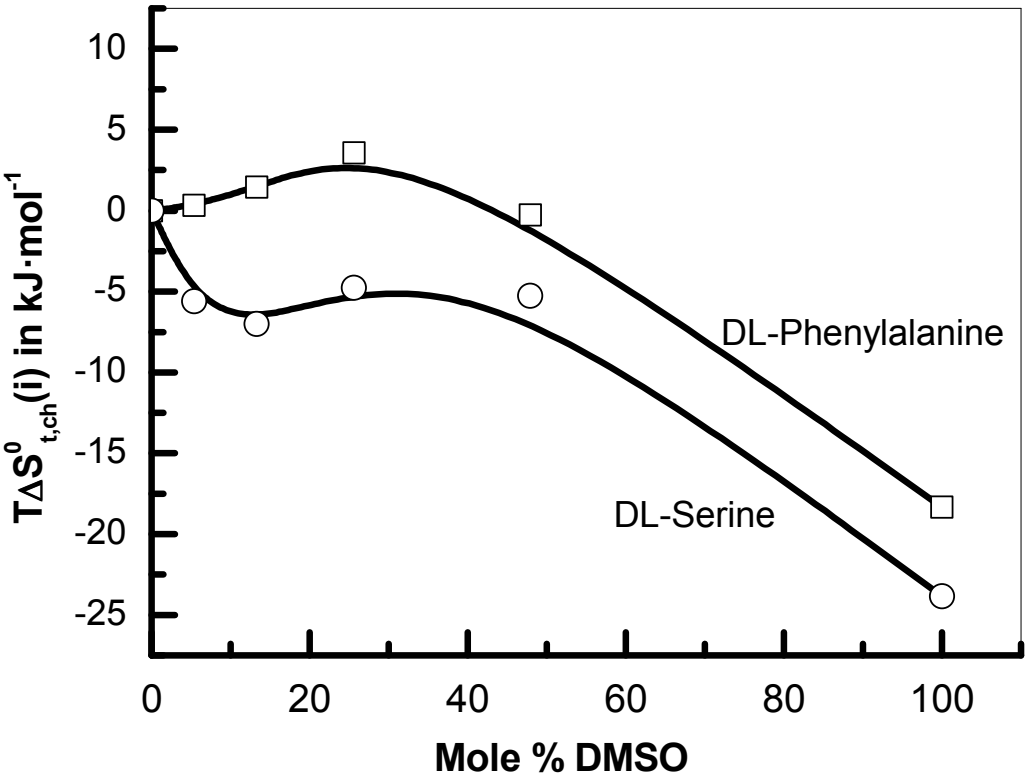
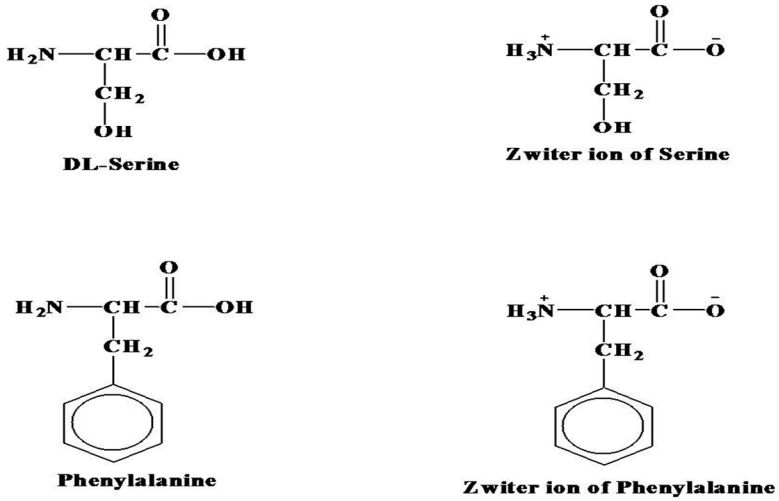
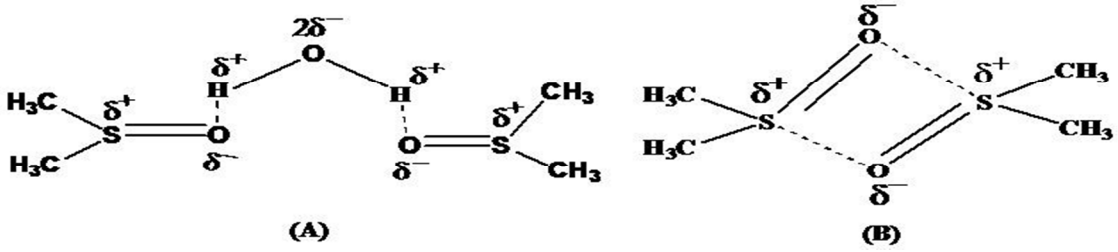


Figure 4: Variation of $T\Delta S^{0}_{t,ch}(i)$ in kJ•mol^{-1} of DL-Phenyl alanine and DL-Serine in aqueous mixtures of DMSO at 298.15 K



Scheme: 1



Scheme- 2: **(A)** Associated form of dimethylsulfoxide and water molecules; **(B)** Dimerised form of dimethylsulfoxide

“Graphical Abstract”

Solvation thermodynamic data of DL-serine and DL-phenylalanine in aqueous mixtures of dimethylsulfoxide at 298.15 K were determined from solubility measurement.