Aqueous L-alanine molecular interaction from Gibb’s free energy: CPCM and SMD in DFT and ultrasonic studies

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Abstract. L-Alanine (ALA) in water spontaneously forms stable zwitterions. It is observed in a present work that the stimulation to revert can be done by ultrasonic waves. It’s molecular interaction in aqueous system can be found from the Gibb’s free energy. It has been examined experimentally by estimating the Gibb’s free energy using the ultrasonic method for the verification of theoretical result. The theoretical work performed within the computational DFT framework for the different solvation models. This paper deals with two different solvation models, the CPCM and the SMD, which are implemented in a Density Functional Theory preferred with non-hybrid functional and analyzed interaction perspective. The weak interactions by NCI also analyzed for difference. Further, BP86 reported difference in both model. The SMD model is also tested by using B3LYP and PBEh-3 to compare ∆G.

Keywords. Gibb’s free energy, L-Alanine, interaction, Ultrasonic method, DFT, CPCM, SMD

1. Introduction
L-Alanine (CH3CHNH2COOH) (ALA) is a non-essential amino acid out of basic twenty [1]. In solid state at room temperature, it possesses in orthorhombic crystal structure. It involved in human body [2-5], and used as a dietary supplement [6]. It is also used in therapeutic [7], pharmaceutical products [8]. A recent studies are being reporting number of applications in many areas [1-8]. It is non-linear optical (NLO) material [9-14]. ALA has different solubility in different solvent [15] and it is water soluble. In water it starts the formation of zwitterions due to transfer of hydrogen ion from carboxylic group (-COOH) to amine group (-NH2) i.e. NH2 becomes NH3+ and COOH becomes COO-. This makes Carboxylic group negative and Amine group positive and making L-Alanine polar in aqueous so that overall resultant charges would become zero. Thermo-acoustical parameters are also found for aqueous L-Alanine [17-20]. The Zwitterions Trajectory and Dynamics of L-Alanine in a droplet of water using computer simulation method has been done by Degtyarenko et.al. [21]. The hydration shell properties and hydrogen bonding interaction also discussed for L-Alanine in water solution [21]. These different forms of geometries of L-Alanine molecule needed to study molecular interaction to correlate an experimental ultrasonic outcome in terms of change in Gibb’s free Energy (ΔG) with DFT using better solvation schemes. The change in Gibb’s free energy (ΔG) on an ionic interaction issue has been reported experimentally (ultrasonic method) and computationally. It has been computed by using the
hybrid and double-hybrid functional with the Conductor-like Continuum Polarization Model (i.e. CPCM) to HF contribution in DFT results [22]. There is another model scheme; the Solvation Model based on Density (SMD) is also available. Necessary details of CPCM and SMD are given in section 2.3. SMD with CPCM needed to be check for consistency of Gibb’s free energy and comparison with experimental outcome. For that, initially the non-hybrid functional is considered to use. Such CPCM and SMD comparison for ALA and its zwitterions for molecular interaction perspective are not found in literature.

Therefore, this paper mainly focuses on the molecular interaction using change in Gibb’s free Energy (ΔG) for aqueous L-Alanine and compare it in the CPCM and SMD models. The ΔG obtained from ultrasonic experimental method was compared with these and the reported values. The variations in it have been analyzed and discussed with respective to expected suitable possibilities of molecules interactions. The structure has been optimized and the obtained thermo-chemistry has been given in section 3.2.1

2. Material and Methods

2.1. Experimental Method

The experiment has been performed for the 0.008M concentration of L-Alanine in water solution at 298.15 K and the ultrasonic velocities, densities, viscosities, and attenuation by absorption were measured. Samples were prepared by using triple distilled water (Grade I) and AR grade L-Alanine (E-Merck) (concentrations 0.008M). Five samples have been randomly selected as the each from five-five's five groups of samples from the prepared 25 sample of 0.008M at 298.15K.

Densities were determined by using density bottle with plunger method whereas viscosities with Oswald Viscometer. Ultrasonic velocities and attenuation were measured with Pulse Echo Overlap method by using AUAR-102 (Automatic Ultrasonic Attenuation Recorder). Ultrasonic Interferometer cell (4 MHz) intended for precise measurement of ultrasonic velocity. The change in Gibb’s free energy (ΔG) and the relaxation time calculated by following formula. 

\[
\Delta G = -2.303RT \log_{10}\left(\frac{h}{k_B T \tau}\right) \text{mol}^{-1}
\]

\[
\tau = \frac{4}{3} \eta \beta_a
\]

In eq.(1), R is the real gas constant (8.314 J.mol\(^{-1}\).K\(^{-1}\)), T be the temperature (kept 303.15K in this study), \(k_B\) be the Boltzmann’s constant (1.38 x 10\(^{-23}\) J / K), \(h\) be the Plank’s constant (6.63 x 10\(^{-34}\)Js) and \(\tau\) be the relaxation time. In eq.(2), the unit of \(\tau\) is second, where \(\eta\) = viscosity and \(\beta_a\) = adiabatic compressibility. The adiabatic compressibility was calculated experimentally by finding ultrasonic velocity (u), density (\(\rho\)) and viscosity (\(\eta\)) for different molar concentration of L-Alanine in an aqueous solution. The corresponding observations and calculated values are reported in SI system

2.2. Computational Methods

The DFT method has been implemented in ORCA program [23] using GUI Avogadro [24]. Functional BP86 has been performed with RIJCOSX implemented along the two different solvation models. Calculations has been utilized the atom-pairwise dispersion correction with the Becke-Johnson damping scheme (D3BJ) using D3 [25-26]. All calculation utilized the basis set def2-SVP [27] and the auxiliary basis set def2/J [28]. For thermochemistry extraction, the vibrational entropy computed according to the QRRHO of S. Grimme [29]. Multiwfn [30] used for post processes.

Two Solvation Models have been implemented. First solvation model is the CPCM i.e. Conductor-like Polarizable Continuum Model (CPCM). According to this model, the solute is placed in a cavity of roughly molecular shape. [31] It is constructed using the GEPOL [32-34] algorithm. The free energy of solvation is calculated as per equation-(3) [35],

\[
\Delta G_S = (E + \Delta G_{CD}) - E_0
\]
Where, $E_0$ is the total energy of the molecule in vacuum and $\Delta G_{CD}$ is the non-electrostatic contribution (dispersion and cavity formation terms). If $A$ indicates the cavity surface area then it is calculated by equation (4) [36].

$$\Delta G_{CD} = 1.321 + (0.0067639 \times A) \quad (4)$$

The second model is SMD Solvation model which was proposed by the Cramer and Truhlar groups [37]. It is based on the quantum mechanical charge density of a solute molecule interacting with a continuum description of the solvent. Full solute electron density is used in this model without defining partial atomic charges. The solvent is not represented explicitly. It represents a dielectric medium with the surface tension at the solute (solvent boundary). SMD is applicable to any charged or uncharged solute in any solvent or liquid medium thus found suitable for present study. It needs few descriptors for e.g., dielectric constant, refractive index, bulk surface tension, and acidity and basicity etc. Neglecting the concentration contribution, the model separates the observable solvation free energy into two main components.

$$\Delta G_S = \Delta G_{ENP} + \Delta G_{CDS} \quad (5)$$

In program like ORCA, the first component $\Delta G_{ENP}$ is the bulk electrostatic contribution arising from a self-consistent reaction field treatment that involves the electrostatic interaction using the Conductor-like Polarizable Continuum Model (CPCM). However, the radii are set to intrinsic atomic Coulomb radii. The second component ($\Delta G_{CDS}$) is called the cavity-dispersion solvent-structure (CDS) term. It is the contribution resulting from short-range interactions between the solute and solvent molecules in the first solvation shell. It is a sum of terms that are proportional to the solvent-accessible surface areas of the individual atoms of the solute. The CDS contribution to the free energy of solvation is given by

$$\Delta G_{CDS} = \sum_{k} \sigma_k A_k(R, R_{zk} + r_s) + \sigma^{[M]} \sum_{k} \sigma_k A_k(R, R_{zk} + r_s) \quad (6)$$

where $\sigma_k$ and $\sigma^{[M]}$ are the atomic surface tension of atom $k$ and the molecular surface tension, respectively, and $A_k$ is the solvent accessible surface area (SASA). The SASA depends on the geometry $R$, the set $R_{zk}$ of all atomic Van-der-Waals radii, and the solvent radius $r_s$, which is added to each of the atomic van der Waals radii. In the program Bondi radii are used for CDS contribution.

3. Results

3.1. Ultrasonic Study

After measurement of velocity for these selected samples, the mean was calculated has been used shown in table 1. The change in Gibbs energy, truncated on 4th decimal (shown up to two decimal places in table), calculated as 20.070 KJ/mol from it along with all other parameters shown in table 1 for 0.008M. It matched closely with the reported experimental work 19.97 KJ/mol with deviation of 0.5% obtained for the molar concentration of 0.009M ALA. [22] This energy is the difference between two transition phases of ALA i.e., between normal ALA and zwitterions. Deviation is observed for the change in molar concentration by 0.001M. From this fact, the change in Gibbs can be said as a function of molarities. However the testing of this perhaps became another issue which is beyond the scope of present study. But it is confirmed that the $\Delta G$ by experiment is around 20KJ/mol.

| Experimental parameters | Values |
|-------------------------|--------|
| 1. Ultrasonic velocity(u) | 1496 m/s |
| 2. Density (ρ) | 1005.37 kg/m³ |
| 3. Viscosity (η) | 89.10×10⁻² Ns/m² |
| 4. Adiabatic compressibility (βa) | 4.44×10⁻¹⁰ N/m² |
| 5. Relaxation time (τ) | 5.28×10⁻¹⁰ s |
| 6. Gibb’s free energy (ΔG) | 20.07 KJ/mol |
3.2. DFT Study

3.2.1. Thermochemistry outcome. Thermochemistry has been obtained from the modes of vibration of the ALA and Zwitterions. For the IR plot of BP86 calculations, the full width at half maximum (FWHM) kept at 30 cm\(^{-1}\) and the obtained corresponding normal mode frequencies are illustrated in figure 1. In all cases (both models for ALA and zwitterions), first six acoustic non-IR modes (starting from 0th mode) out of 38 normal modes and remaining 33 are normal mode IR frequencies are being observed. Sixth mode is imaginary in zwitterions cases. The required thermochemistry parameters computed in DFT calculations at temperature 298.15 K and pressure 1.00 atm are given in table 2. The Gibb’s free energy of the reaction \(\Delta G_r\) (change in Gibb’s energy for conversion of source ALA to product zwitterions) can be obtained by

\[
\Delta G_r = \Delta G = G_{product} - G_{source}
\]

The negative Gibbs energy allows forming the product and gives the direction of spontaneous process. Here in DFT all negative \(\Delta G\) are obtained for the zwitterions as a final state and hence stable formation at STP in water confirms zwitterions represented by following reaction.

\[
\text{C}_2\text{H}_5\text{NH}_2\text{COOH (aq)} \rightarrow \text{C}_2\text{H}_4\text{N}^+\text{H}_3\text{COO}^- (aq)
\]

The free energies are given in the second last columns of both the natural and zwitterions of ALA (L-Alanine) of table 1. But the positive \(\Delta G\) are obtained in ultrasonic experiment which clarifying the stimulation reverts the zwitterions to ALA which is non-spontaneous process

![Figure 1. Comparison of frequencies of Two Forms of L-Alanine for different Functional](image)

**Table 2.** Thermo-chemistry of ALA in Normal and Zwitterion form at T = 298.15 K by DFT

|           | Natural/Normal ALA       | Zwitterions ALA          |
|-----------|--------------------------|--------------------------|
|           | CPCM SMD                  | CPCM SMD                 |
| 1. U      | -849175.6 -849173.05     | -849204 -849203.66      |
| 2. H      | -849173.12 -849170.57    | -849202 -849201.18      |
| 3. TS     | 101.20129 101.36807      | 94.7581 95.32776       |
| 4. \(G_N\)| -849274.33 -849271.94    | -849296 -849296.51      |
| 5. \(\Delta G_r\)| -22.12 -24.57       | - -                      |
| 6. \(G_{fZ}\) | 194.8627 192.2673 | 196.2268 196.0947      |

Note: i) All Energies unit are in KJ/mole. TS is in energy unit. (Suffixes meaning: el-electronic, kin-kinetic, n-nuclear, ZPE-zero point energy, vib-vibrational, rot-rotational, trans-translational. kB–Boltzmann’s constant, T-Temperature in K). ii) Formulae given in bracket are used to calculate: Internal Energy \((U = E_{el} + E_{ZPE} + E_{vib} + E_{rot} + E_{trans})\), Enthalpy \((H = U + kBT)\), Final Entropy \((TS = T(S_{el} + S_{vib} + S_{rot} + S_{trans}))\), Final Gibbs free enthalpy \((G_N = H - TS)\), For completeness \((G_N = G_N - E_{el})\) and the Change in Gibb’s free energy of reaction \(\Delta G_r = \Delta G = G_N (Zwit) - G_N (Nat)\). Here E is energy.
3.2.2. Interaction Perspective from $\Delta G$. The change in Gibb’s free energy for various chemical bonds can be categorized into four types; i) $\Delta G = -210$ to $-420$ kJ/mol indicates Covalent bond, ii) $\Delta G = -40$ to $-30$ kJ/mol indicates weak interactions, iii) $\Delta G = -20$ to $-30$ kJ/mol indicates ionic interactions and iv) $\Delta G = -3$ to $-4$ kJ/mol indicates Van der Waal’s interactions [38]. It was found that the value of change in Gibb’s free energy ($\Delta G$) comes around 20kJ/mol by Ultrasonic methods and -22kJ/mol and -24kJ/mol for the DFT method for CPCM and SDM respectively. This confirms the weak interaction exist between L-Alanine crystal and water solvent. Basically, L-Alanine is the only isomer of Alanine which is naturally found in protein.

It is observed in both models of DFT studies that the L-Alanine does not interact with water favorably due to side chain of CH$_3$. Formation of Zwitterions process is occurring spontaneously as the result shows the negative change in Gibb’s free energy ($-\Delta G$) using DFT method. The value of positive change in Gibb’s free energy ($+\Delta G$) using ultrasonic method (see table 1) also confirms the formation of stable Zwitterion which has been disturbed by ultrasonic waves. It reveals that we need external additional energy to reverse the reaction. From this result, we may predict that the non-polar form of L-Alanine can be converted to polar form (Zwitterions form) by giving energy of 20-30KJ/mol. It has been studied that the structural form of aqueous L-Alanine solution is also differ significantly from those of crystalline phase [20-21]. These differences being mainly attributed to hydrogen bonding interaction but as per our result of $\Delta G$ suggested the weak and ionic interaction. At least four to nine water molecules needed to begin stabilization of the ALA-zwitterions in water which was shown in the establishment of orientations of functional sites in earlier ab-initio studies [4, 6, 37-38].

![Figure 2](image-url). RDG as a function of $\text{sign}(\lambda_2)\rho$ for the non-covalent & the weak interactions. (a)(b) for CPCM models and (c)(d) for SMD [Blue colour shows hydrogen bonding interaction (attraction), red colour shows steric interaction (repulsion) and green rectangular shows Vander Wall interaction (positive sign for repulsion and negative sign for attraction). Lower the RDG, peak shows dominating interaction and darker in colour shows higher strength.]

3.2.3. Non-covalent Interaction (NCI). The Reduced Density Gradient (RDG) verses $\text{sign}(\lambda_2)\rho$ plot is shown NCI illustrated in figure 2. We already have seen the diversion in IR frequencies. In NCI study,
similar interactions are observed for natural for of L-alanine molecule in different solvation models. The hydrogen bonding and the steric repulsion are dominated, but it is not as stronger, strengthened and interactive as obtained for the zwitterions represented by the downward peaks at both sides far from the centre of sign($\lambda_2$)$\rho$. Green peak is showing Van-der-Waal’s attraction is also predicted to be found in all cases. In case of normal ALA (polar), the downward peaks of RDG observed between 0.2 to 0.4 isosurface for repulsion (steric) and attraction (Van der Waal’s) around $\frac{-0.013}{g_2870}$ and $\frac{-0.013a.u}{\sign(\lambda_2)\rho}$. In case of zwitterions (i.e polar form) the downward peaks of RDG observed between 0.02 to 0.3 isosurface for repulsion around the $\approx-0.034$ a.u. for CPCM and $\approx-0.036$ a.u. for SMD sign($\lambda_2$)$\rho$ and attraction around the $\approx-0.05$ in both CPCM and SMD. This study suggests domination of dipole-dipole, ion-dipole interaction than ion-ion interaction between ALA and water from DFT. This computational result has been confirmed with the experiment agreement.

On looking over-all pictures, it cannot be deny that, due to the absorbing an ultrasonic wave, the steric repulsion and hydrogen bonding interactions of zwitterions with water get disturbed and destabilized in to the natural L-Alanine’s form by utilizing the changing free energy like as an activation energy. One opinion can be made that charges on zwitterions are merely self induced to stabilize it in a non-acidic and non-basic equilibrium state of polar water medium. The relaxation is done by transferring Hydrogen from carboxylic group to amine group as shown in figure 3 and not interacting with Hydrogen from water molecule in neutral solution at pH =7.

![Figure 3. Illustration of Ultrasonic treatment and free energy relation](image)

![Figure 4. Comparison of an absolute value of $\Delta G$ in term of the three functional in DFT for CPCM and SMD models and the experimental method for different molarities](image)

4. Comparison of $\Delta G$s
In present work, we successfully reproduced the value of $\Delta G$ for CPCM model i.e. -22.12 KJ/mol using the non-hybrid functional BP86. The $\Delta G$ by using B3LYP (-13.08 KJ/mol) and PBEh-3 (-16.54 KJ/mol) hybrid functional have been reported for the CPCM in a literature [22]. Those values found much less compare to the reported experimental value. In added to reported $\Delta G$ for CPCM, we render our calculation for SMD in present work for those hybrid-functional. Using SMD models, the $\Delta G$ for B3LYP and PBEh-3c have been obtained -12.28 KJ/mol and -21.04 KJ/mol respectively. The comparative illustration of these data has been shown in figure 4. Well known B3LYP is failed again for the SMD model in our observation and decreased in comparison with CPCM. Whereas, for the PBEh-3c with SMD gave more approximated to experimental value compare to the CPCM model which is far from it. The PBEh-3c_BP86 result is even better compare to the CPCM model using BP86 non hybrid functional. We also found consistency for the reproducibility of $\Delta G$ for all results up to the two significant digits after all calculations and the variation has been found at the third digit under the change of different RI, version and machine.
5. Conclusion

The magnitude of ∆G obtained from DFT methods show dependencies on the solvation models in computation. The study confirms more accurate method with reference to the magnitude of ∆G ultrasonic experimental method. It is not deniable that the repulsive and attractive interactions of zwitterions with water get disturbed and forms ALA by utilizing the ∆G. Mechanism has predicted and given on the basis of different sign of ∆G, from it. The charges on zwitterions’ groups are merely self-induced to stabilize it in a non-acidic and non-basic equilibrium state of polar water medium i.e. neutral. The relaxations happen probably by transferring Hydrogen from carboxylic group to amine group instead-of (or in-added-with) from the water molecules according to ∆G, value. The non-survivability of meta-stable forms of ALA (cation, anion) is found most probable. Checking of the more different functional for close approximations to experimental results has been revealed the important fact for future studies. The BP86 is non-expensive and CPCM is closer to the experimental value of change in Gibb’s free energy compare to SMD. But SMD with double hybrid PBEh-3c found more approximate to experimental value.

6. References

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