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# Investigation of Solid Formation Enthalpy and Molecular Mechanics Energies of Amino Acids via Force Field Approach

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**Abstract**

Amino acids which are organic compounds directly affect gene expression and control of the function of proteins. Their enthalpy values and molecular mechanical energies of them profoundly influence the protein folding mechanism. Molecular modeling simulations are one of the methods used to obtain their properties. In this study, the enthalpy values and molecular mechanics parameters of 17 amino acids have been investigated by the classical molecular dynamics simulation based on the force-field potential approach. Enthalpy values obtained from the simulation study for ALA, ASN, ASP, CYS, LYS, and PHE are in good agreement with the experimental data. In addition, molecular mechanics parameters such as Coulomb, bond, angle, dihedral, and Van der Waals have been calculated for all amino acids. It is represented that the Coulomb energy is quite low compared to the rest of the molecular mechanical energies. Their enthalpy and molecular energy values are crucial for molecular biology studies such as electronic interaction in protein-lipid modification, ligand binding to the cell surface, and correct protein localization.

## 1. Introduction

Amino acids are organic compounds that are consisted of Amino (COOH) (-COOH) which is basic and Carboxyl (COOH) (-COOH) which is possessed an acidic character. They have directly affected gene expression and control of the function of proteins [1].Proteins are linear polymers that fold into specific and ordered three-dimensional conformations based on their amino acid sequences[2], [3]. Their folding is a vital parameter that determines protein effectiveness in biological processes and this folding process is driven by thermodynamic stability. It is directly related to the enthalpy value that is dependent on the thermodynamic properties of both individual amino acids and their interactions among them[4], [5]. These enthalpy values can be obtained by both experimental methods and theoretical approaches[5]–[7]. Using this thermodynamic parameter, their probable folding concerning the protein sequence that is consist of amino acids can be predicted by approaches such as deep learning[8]. However, for these predictions to be accurate and reliable, it is necessary to find the enthalpy values of the amino acids.

To understand the effects of amino acids on biological activity, studies investigating thermochemical data are carried out extensively.Considering the literature, there are experimental studies on the thermodynamic properties of amino acids. For instance, Cole et al. have determined the enthalpy of the solid formation of alanine as -134.5 Kcal/mole experimentally [9]. Nguon (1977) et al., [10]have calculated it as -133.72 Kcal/mole, and Contineanu and Marchidan[11]have found out it as -134±0.41. This has also been studied by Petrauskas et al. using isothermal titration calorimetry to determine the average standard values of the thermodynamic parameters (Gibbs free energy, enthalpy, entropy, and heat capacity) of the interaction between positively charged amino acid homopolymers[12]. Hossian and colleagues have examined the current solubility of amino acids in different binary solvent systems and their thermodynamic behavior with different salt and organic solvent concentrations [13]. Pandit and De

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have investigated the trends in thermodynamic properties in the interaction of amino acids and graphene oxide and conducted a study showing the correlation between enthalpy-entropy compensation analysis and flexibility [14]. Gheorghe et al. have calculated the enthalpy value of tryptophan by the calorimetric method [15].

The application of computer-based models using analytical potential energy functions within the framework of classical and quantum mechanics has proven its power to used in biochemistry and organic chemistry studies. Classical MD,ab-initio MD, and Monte Carlo methods are used for energy minimization on analytical potential energy surfaces in molecular mechanics applications[16]. These methods have been used to study a wide variety of phenomena, including the internal tension of organic molecules, the structure and dynamics of simple and complex liquids, the thermodynamics of ligand binding to proteins, and conformational transitions in nucleic acids [18]. Physical events in biological systems occur on a wide time scale, from 10-12 seconds to 10-18 seconds. For instance, in fully folded protein structures, bond vibrations take place in the femtosecond, while their side-chain rotamers occur in nanoseconds.Gas formation enthalpy of amino acids has been investigated by Dorofeeva and Ryzhova via the ab-initio study [17]. It has been exhibited that the calculated enthalpies of 10 out of 14 corresponded with experimental. In addition, Nie et al. theoretically have computed the evaporation enthalpies of 20 amino acids with Molecular Dynamics (MD) simulation[18].

In this study, the thermodynamic parameters of 17 amino acids have been obtained by the MD Simulation method. Force field approach, which is frequently used for biomolecules and allows us to produce the parameters very close to the experimental results, has been employed in this study. Finally, MD results have been compared with the experimental data. It is concluded that they are in agreement.

## 2. Material and Method

In this study, the classical MD method is employed to obtain the enthalpy values and molecular mechanical energies of amino acids[16]. The interactions of the atoms constituting amino acids have been described by the force-field potential. The equation of molecular mechanical force field potential and its parameters are given in equation 1. It consists of bond, angle, improper, torsion among the atoms of molecules, as well as, Lennard-Jones (LJ) and Coulomb energy coming from its electrical charge [19].

$$\cup = \sum_{\text{bounds}} k_i^{\text{bound}} (r_i - r_0)^2 + \sum_{\text{angles}} k_i^{\text{angle}} (\theta_i - \theta_0)^2 + \sum_{\text{improper}} k_\varphi (\varphi - \varphi_0)^2 + \sum_{\text{torsions}} k_i^{\text{torsion}} \left[1 + \cos\left(n_i \phi_i + \delta_i\right)\right] + \sum_i \sum_{j \neq i} 4\varepsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\varepsilon r_{ij}} \quad (1)$$

20 essential amino acids structure information in cartesian coordinates has been obtained from the Protein Data Bank (PDB) [20]. All simulations carry out via LAMMPS [21] software since it can calculate physical properties more efficiently than other counterparts. Their potential files have been generated by applying CHARMM topology (CHARMM36) to the Visual Molecular Dynamics (VMD) program [22]–[25]. However, 3 amino acids (Glutamine, Glutamate, and Glycine) have been not included in this study since potential parameters generated for them via CHARMM36 are problematic. To avoid surface interactions, the periodic boundary condition has been applied in all simulations. The Nosé-Hoover thermostat [26], [27], and Parrinello-Rahman [28]barostathave been employed to control both temperature and pressure. In the study, simulations have been made for each of the amino acids separately and no solvent was employed in them. System temperatures have been set to 298 K. Also, all models have been run for 0.5 nanoseconds to reach thermal equilibrium and 1 nanosecond to obtain the thermodynamics parameter with 0.2 femtoseconds time steps.

## 3. Results and Discussion

Protein chains can self-organize and transform into their natural structures in the appropriate environment. Thermodynamic investigations are excellent tools to explain these biological processes macroscopically [5]. Although thermodynamic control is widely accepted as the default behavior for correct folding, it is still difficult to understand in detail how the forces and atomic interactions involved in thermodynamic control relate the amino acid sequence to the folding and stability of the native structure [29]. Spectroscopic and calorimetric experiments have revealed that the increase in stability in protein folding, which is directly depend on amino acids, is mainly driven by enthalpy [30]. Enthalpy values are significant parameters for chemical reactions. The solid-state enthalpy of formation, calculated by MD simulation, is relational

energy, i.e. internal energy, based on the force field term [31]. The enthalpy values derived from the simulations and the measured values in the literature [32] are comparatively represented in Table 1. All enthalpies obtained from simulations have been averaged over the total simulation time that is 1 nanosecond. Although temperatures of the systems have fluctuated between 297K and 299K, the average temperature is around 298 K. It is concluded that the fluctuation of temperature results of potential energy functions. As it can be demonstrated in Table 1, the enthalpy of cysteine resulting from MD calculation is -124.37 Kcal/mole and the experimental value is -127.65 Kcal/mole[32]. The discrepancy between them is approximately 2.57%. While the enthalpy value obtained for alanine is -128.88 Kcal/mole, the value measured by the experimental method is -134.45 and the difference between them is 4.14%. In addition, the MD simulation and experimental enthalpy values for Phenylanin are -103.03 Kcal/mole, and -110.09 Kcal/mole, respectively. The enthalpy data of all amino acids included in the study are given in Table 1. Less than 10% difference between simulation results and experimental measurements supports the accuracy of simulation results. Weiss et al.[33] found that, with the thermochemical experimental approach, the enthalpy of solid-state formation is -127.63 Kcal/mole for Cysteine, -232.55 Kcal/mole for Aspartate, -188.58 Kcal/mol for Arginine, -148.9 Kcal/mole for Arginine, for Histidine, -111.62. However, for Prolinethere is quite a difference between the experimental and the simulation values. It is considered that below 10% difference between simulation results and experimental measurements can be acceptable. The difference between simulation and experimental results greater than %10 will be due to the potential energy parameters (CHARMM36) which cannot be acceptable.

Recent studies in cell biology and biophysics have created a new paradigm in protein targeting and function. The electrostatic charge on the surface of a biological membrane is emerging as a key determinant of signal protein localization and activity [34]. Therefore, electronic interaction is important for protein-lipid modification studies for ligand binding and accurate protein localization to the cell surface. Moreover, molecular mechanical energy directly influences the enthalpy and structural properties of amino acids. These energies are bond strain, angular, and torsional energies, which are the parameters of intramolecular interactions. Coulomb and Van der Waals energies are effective in intermolecular interaction. Van der Waals energy represents the long and short-distance electronic effect and is known as the electrodynamic energy used to explain bonding. Van der Waals terms utilizing theoretical protein-ligand binding calculations are defined by Lennard-Jones's potential approach [38]. Figure 1 indicates Van der Waals interaction. Thermodynamic parameters given in Table 2 are important parameters manipulated in protein design, bioengineering, and drug-vaccine studies. The molecular energy value is between the bonding atoms of the molecule, and it describes the energies required to bind related molecules in computational studies. Figure 1 shows the Coulomb interaction energy that allows proteins to approach the ligand or membrane surface.

The molecular mechanical energy values of the amino acids obtained in this study are presented in Table 2.It is concluded that the tertiary structures of proteins are affected by hydrophobic and Van der Waals interactions. Long-range Coulomb interactions, short-range Van der Waals interactions, and quantum mechanical repulsion between charged amino and carboxyl groups produce functional potential energy of proteins [35]. Protein folding will continue until the minimum energy level is reached [36], [37]. Moreover, the study of the time-dependent variation of these energy parameters is critical for determining the conformations of these molecules. It isdemonstrated that the molecular mechanical energy values of Alanine, Cysteine, Phenylalanine, and Lysine are compatible with the experimental results presented in Figure 1. It is exhibited that the molecular mechanical energies of ALA, CYS, LYS, and PHE fluctuate around the results given in Table 2 throughout the simulation. In addition, the Coulomb energy is quite low compared to the bond, angle, dihedral, and Van der Waals energies. Therefore, it is concluded that the remarkable negative energy in Coulomb energy is critical in preserving the natural structure of amino acids.

**Table 1.**Comparison of enthalpy as a result of MD simulations at 298 K temperature with experimental values [32].

| Amino Acid | MD Result (Kcal/mole) | Experimental (Kcal/mole) | Error (%) |
|---|---|---|---|
| Alanine | -128.88 | -134.45 | 4.14 |
| Arginine | **-167.89** | **-149.04** | **12.65** |
| Asparagine | -205.72 | -188.58 | 9.09 |
| Aspartate | -237.66 | -262.63 | 9.51 |
| Cysteine | -124.37 | -127.65 | 2.57 |
| Histidine | -92.90 | -105.60 | 12.03 |
| Isoleucine | -100.17 | -153.12 | 34.58 |
| Leucine | -124.45 | -154.60 | 19.50 |
| Lysine | -175.97 | -162.20 | 8.49 |
| Methionine | -112.08 | -138.0 | 18.78 |
| Phenylalanine | -103.03 | -110.09 | 6.41 |
| Proline | -62.62 | -121.30 | 48.38 |
| Serine | -126.40 | -175.13 | 27.83 |
| Threonine | -124.90 | -185.54 | 32.68 |
| Tryptophan | -76.51 | -97.18* | 21.27 |
| Tyrosine | -120.88 | -163.86 | 26.23 |
| Valine | -107.45 | -150.30 | 28.51 |

*for Tryptophan [14]

**Table 2.**Molecular mechanical average energy values (Kcal/mol) were obtained as a result of the simulation of amino acids at 298K temperature. $E_K$, kinetic energy, $E_P$, potential energy, H, enthalpy, $E_D$, dihedral energy, $E_A$, angular energy, $E_B$, bond energy, $E_{VDW}$, Van der Waals energy, $E_C$, Coulomb energy, $E_M$, molecular energy

| Amino Acid | $E_K$ | $E_P$ | H | $E_D$ | $E_A$ | $E_B$ | $E_{VDW}$ | $E_C$ | $E_M$ |
|---|---|---|---|---|---|---|---|---|---|
| Alanine | 10.65 | -139.19 | -128.88 | 2.66 | 23.83 | 4.89 | 7.97 | -116.52 | 31.80 |
| Arginine | 23.09 | -191.30 | -167.89 | 8.43 | 19.77 | 11.30 | 11.00 | -242.43 | 40.13 |
| Asparagine | 14.23 | -219.51 | -205.28 | 9.33 | 25.71 | 5.28 | 6.12 | -156.50 | 41.58 |
| Aspartate | 12.45 | -249.29 | -237.66 | 7.21 | 10.29 | 4.55 | 14.49 | -95.17 | 22.84 |
| Cysteine | 11.59 | -135.27 | -124.37 | 3.18 | 8.01 | 5.37 | 8.73 | -94.61 | 16.83 |
| Histidine | 16.89 | -110.14 | -92.90 | 12.03 | 20.67 | 7.37 | 5.18 | -155.68 | 40.36 |
| Isoleucine | 18.55 | -117.10 | -100.17 | 9.99 | 23.04 | 7.24 | 9.11 | -77.12 | 41.69 |
| Leucine | 18.65 | -142.39 | -124.45 | 10.63 | 24.66 | 7.26 | 4.59 | -99.78 | 43.81 |
| Lysine | 21.24 | -196.07 | -175.97 | 6.34 | 15.62 | 7.09 | 8.82 | -94.43 | 29.35 |
| Methionine | 16.91 | -128.26 | -112.08 | 4.83 | 15.28 | 7.03 | 5.71 | -74.93 | 28.11 |
| Phenylalanine | 19.53 | -122.27 | -103.03 | 12.42 | 21.85 | 9.11 | 17.04 | -96.19 | 44.27 |
| Proline | 14.26 | -76.73 | -62.62 | 7.50 | 11.63 | 4.82 | 1.12 | -31.79 | 24.31 |
| Serine | 11.57 | -138.67 | -126.40 | 2.94 | 10.05 | 5.86 | 13.22 | -54.50 | 19.13 |
| Threonine | 14.19 | -138.53 | -124.90 | 7.16 | 11.73 | 5.24 | 11.31 | -51.41 | 24.43 |
| Tryptophan | 23.07 | -99.04 | -76.51 | 6.19 | 16.70 | 10.89 | 15.22 | -29.55 | 34.06 |
| Tyrosine | 20.42 | -140.93 | -120.88 | 8.71 | 13.13 | 9.72 | 11.62 | -75.49 | 31.86 |
| Valine | 16.05 | -122.97 | -107.45 | 2.73 | 13.07 | 6.06 | 8.54 | -60.64 | 22.12 |

## 4. Conclusions and Suggestions

In this study, the enthalpy of solid formation for 17 amino acids and their molecular mechanical energies were calculated using the classical force-field approach. It has been observed that there is less than 10% error between the solid formation enthalpy calculated for ALA, ASN, ASP, CYS, LYS, and PHE and their corresponding experimental enthalpies. The improvement of models with a high error rate (referring to the experimental solid formation enthalpy) will be possible by improving the force field parameters.

These calculated enthalpy values will contribute to the determination of the thermodynamic stability of protein folding. Besides, it has been investigated that long-range interaction is more dominant than short-range interaction in amino acids. Since protein sequences are composed of amino acids, it is considered that long-range interaction is critical in the formation of these sequences and in preserving their natural structure. Furthermore, the obtained molecular mechanical energy values can be used in protein-lipid modification studies for electronic interaction, ligand binding to the cell surface, and accurate protein localization.

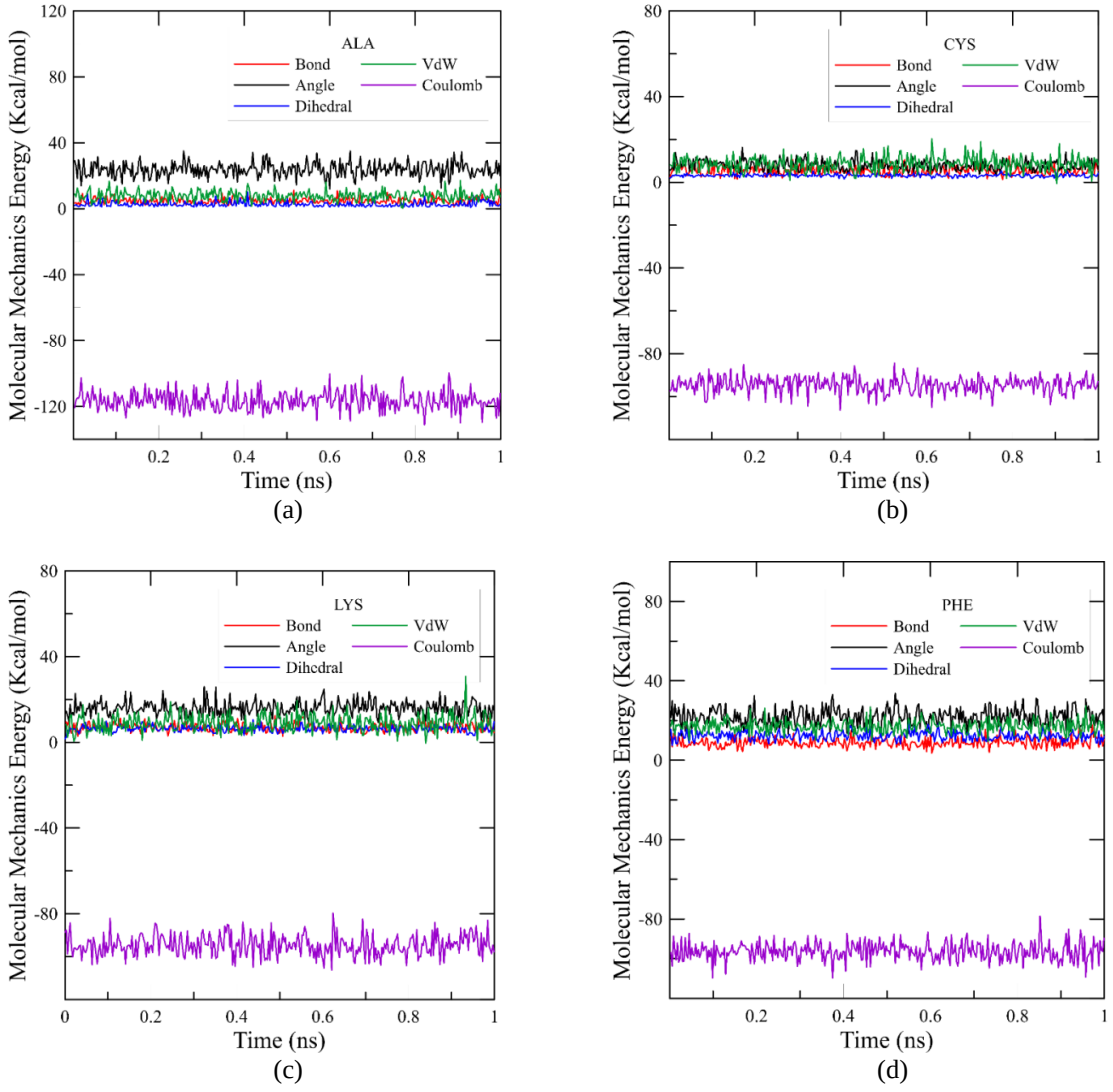


**Figure 1**. Molecular mechanical energy changes for amino acids (a) ALA, (b) CYS, (c) LYS, and (d) PHE, whose enthalpy values are close to the experimental measurements.

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**Contributions of the Authors**

Levent Songur performed the potential energy file generation process by applying the CHARMM topology (CHARMM36). Oguzhan Orhan carried out MD simulations with LAMMPS software. Levent Songur and Soner OZGEN commented on the results obtained from the study. All authors contributed to the writing of the article.

**Conflict of Interest Statement**

There is no conflict of interest between the authors.

**Statement of Research and Publication Ethics**

The study is complied with research and publication ethics

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