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Conformational Plasticity Of Amino Acids: A computational Review Of Small Molecule Interactions

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Abstract: The basic building blocks of proteins, amino acids, have dynamic conformational flexibility that has a big impact on biological structure and function with small molecules can modulate these conformations, leading to altered biochemical behavior with implications in drug design, enzymatic regulation, and molecular recognition. This review presents a comprehensive computational investigation into the conformational changes of amino acids induced by small molecule interactions. Utilizing molecular dynamics (MD) simulations, quantum mechanical (QM) calculations, and hybrid QM/MM approaches, we explore how non-covalent interactions—such as hydrogen bonding, π-π stacking, and van der Waals forces—affect the torsional angles and side-chain orientations of amino acids in isolated and solvated environments. Emphasis is placed on the role of solvent effects, energy landscapes, and potential energy surface (PES) mapping in elucidating these conformational shifts. Case studies involving biologically relevant ligands demonstrate the diverse effects of small molecules on the structural plasticity of amino acids. By integrating data from recent computational studies, this review highlights emerging trends, methodological advancements, and key challenges in the field. The findings provide critical insights for rational drug design, peptide engineering, and understanding protein-ligand interactions at the molecular level.

Index Terms - Amino Acid Conformational Changes, Small Molecule Interaction Computational Chemistry, Molecular Dynamics Simulations, Quantum Mechanical Studies, Protein-Ligand Interactions, Conformational Flexibility, Non-Covalent Interactions, QM/MM Methods, Drug Design Insights, Structural Biology, Energy Landscape Analysis, Bioinformatics, Molecular Modeling, Theoretical Chemistry

I. INTRODUCTION

IMPORTANCE AND ROLE OF AMINO ACIDS:

Amino acids are the key building blocks of proteins, and their sequence and chemical properties are critical in shaping the structure and activity of proteins.[1,2] Proteins are essential macromolecules in living organisms, serving various functions such as enzymatic catalysis, cell signalling, structural support, and more. The sequence of amino acids in a protein chain dictates its folding pattern, which in turn influences its three-dimensional structure. This structure is crucial for the protein's proper functioning. Even small changes in the amino acid sequence can lead to misfolding and dysfunction. The diversity of amino acids arises from their side chains, often denoted as "R" groups, shown in Fig-1.1. Each amino acid has a unique side chain that confers specific chemical properties, such as hydrophobicity, hydrophilicity, charge, and reactivity. These properties play a crucial role in how proteins interact with their environment and with other molecules, enabling them to carry out their functions effectively by virtue of respective conformations.

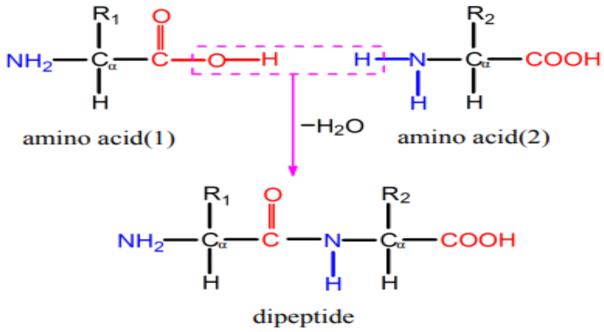


Fig-1.1 The formation of a dipeptide by two α-amino acids with different side chain R1 and R2.

The hydrogen bonds and zwitterionic forms highlight the intricate nature of amino acid interactions. Hydrogen bonds, which can form between the hydrogen atom of the amino group and an electronegative atom (usually oxygen or nitrogen) in the side chain or backbone of another amino acid, contribute to protein stability and shape. The presence of zwitterionic forms (where an amino acid has both a positively charged and a negatively charged group) adds complexity to the interactions within and between proteins.[3] Indeed, the unique properties of certain amino acids and peptides can provide valuable insights into the behavior of more complex biological systems. For examples, arginine and the dipeptide arginylglycine[4,5] demonstrate the structures and properties of small molecules, which can contribute to a deeper understanding of larger biological systems. Furthermore, small molecules like individual amino acids and dipeptides allow researchers to study the basic principles of molecular interactions, including hydrogen bonding, charge distribution, and conformational preferences. Knowledge about these molecules can have practical applications in drug design, materials science, and biotechnology, where the behavior of biomolecules is crucial. Also amino acids have great biological relevance: these amino acids and peptides are fundamental components of proteins, which are central to biological processes. Insights gained from studying small molecules can lead to a better understanding of how proteins function in various contexts, including enzymatic reactions, signaling pathways, and structural stability. Researchers have also been investigating the complex history of chemical processes in the Solar System, which could have led to the synthesis of the basic building blocks of life from the materials present in the interstellar medium. On the other hand, soluble organic compounds found in meteorites, including amino acids, are generally believed to have formed shortly after the Solar System's formation. This is thought to have occurred through the action of aqueous fluids on the asteroids that eventually led to the creation of meteorites. In this context, the carbon, nitrogen, and hydrogen needed to form the amino acids in meteorites like the well-studied Murchison meteorite likely came from reactive precursors present in the interstellar medium. However, the amino acids themselves are thought to have formed on the parent body of the meteorite.

STUDY OF AMINO ACIDS IN GAS PHASE:

Studying gaseous amino acids and their derivatives provides a unique perspective on their intrinsic properties, biochemical processes, and interactions. While both experimental and theoretical approaches have their challenges, the combination of advancements in theory and experimental techniques has propelled progress in this field, contributing to a deeper understanding of molecular behavior and conformational changes. Amino acids are interesting to computational chemists, as they have diverse internal interactions, are flexible in shape, and are suitable for advanced calculations. These studies aid in identifying amino acids through their microwave or IR spectra. While various groups have undertaken research on amino acids, most have examined only a subset of potential shapes. Glycine has been extensively studied, while other amino acids like alanine, serine, and cysteine have been studied at lower levels of theory, focusing on favorable interactions like hydrogen bonding. The author has studied to comprehensively understand the conformations of these amino acids, considering all possible shapes. They have used a multi-level approach involving semiempirical and ab initio calculations to explore the potential energy surfaces and identify stable conformations.[6]

Their reports are based on conformations which were analyzed for their IR intensities, rotational constants and dipole moments. The objective was to provide a comprehensive overview of the conformational landscape of the selected amino acids[7]**.** Different conformers of glycine, represented as distinct arrangements of its atoms, have been identified based on experimental data[8,9,10,11] and theoretical calculations.[12] These calculations predict the electronic energies and structural parameters of different conformers. The identification of conformers relies on the agreement between theoretically predicted rotational constants and those obtained from experimental measurements. This comparison allows researchers to match observed species with theoretically predicted energy minima. Again, the conformational aspects and relative energies of different conformers of glycine, the simplest alpha-amino acid, have been studied by Salvatore *et.al*[13]**.** They have highlighted the role of electron correlation energy in refining energy predictions. Their findings have implications for predicting conformer populations and behavior in different phases and environments. The conformational flexibility of neutral amino acids, specifically focusing on glycine and alanine highlighted the interplay between experimental and theoretical approaches in understanding molecular structures. Early discrepancies between theoretical predictions and experimental data for glycine's lowest-energy form demonstrated the importance of accurate theoretical calculations.[14] Frey *et al.'s* study emphasized the impact of electron correlation energy on conformational analyses, revealing inaccuracies in HF conformational energy maps and the limitations of MP2 energies. High-level theoretical calculations are considered essential for accurate structural insights, especially for complex systems like peptides. Different calculated conformers of glycine and alanine have been reported in details.[15] The relative energies and total energies of selected glycine and alanine conformers, along with important geometry parameters and theoretical/experimental rotational constants and dipole moments concluded that both alanine and glycine exhibit similar conformational behaviour, supported by theoretical results and the MMW spectroscopy measurements on alanine. Glycine's importance in peptides and proteins has led to intense experimental and computational investigations into its different stable conformers, denoted as I_p and II_{in}.[16] Early confusion over their energy ordering was resolved by theoretical calculations, confirming Gly-Ip as the global energy minimum. The non-planar structure of Gly-II remained debated, but recent computational methods have provided more accurate equilibrium structures for both conformers. This research have emphasized the importance of understanding glycine's molecular configurations and the role of computational techniques in resolving structural uncertainties.[17]

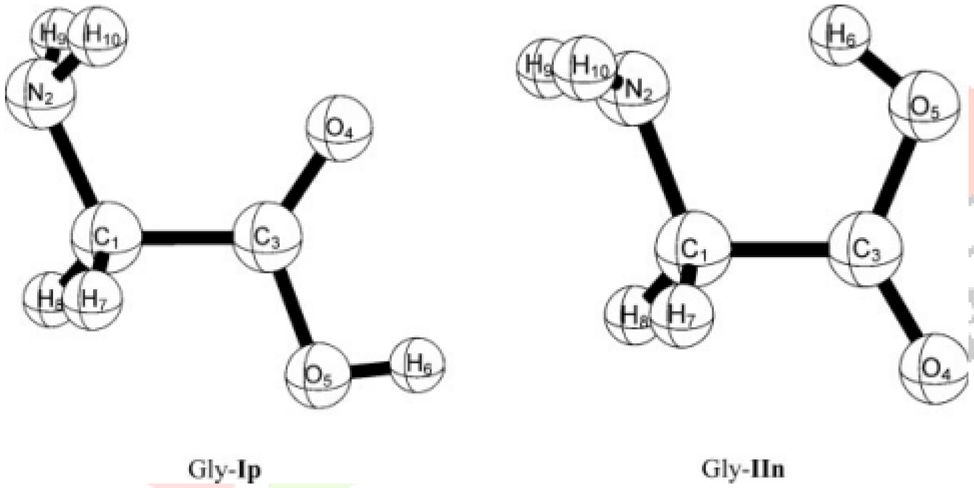


Fig-1.2 Structure of the two lowest-energy conformers of neutral glycine.

The evolution of *ab initio* self-consistent field calculation in chemistry, particularly their application to larger molecules, has enabled the study of biologically important molecules like amino acids. Glycine, the smallest amino acid, has been extensively studied using these methods. Researchers have computed its conformations, energy differences and SCF energies using a specific Gaussian basis set. *Ab initio* SCF calculations have also been performed on a range of neutral amino acids and their zwitterionic forms, these calculations were utilized to explore interactions with water. Additionally, the non-empirical PRDDO method was employed for understanding electronic structure and bonding in various amino acids like glycine, alanine, serine, cysteine and threonine. [18] They provided details such as SCF energies, dipole moments, ionization potentials, proton affinities, and estimated energy changes during transitions between solid and gaseous states, as well as solvation energies for zwitterions. Experimental data for larger amino acids are limited, with glycine being a primary subject of research. However, due to limited reliable experimental data and the influence of rotational barriers and basis sets, making direct comparisons between experimental and calculated dipole moments is difficult. For instance, the gas phase dipole moment of the glycine might be influenced by multiple conformations. The highly basis set-dependent nature of dipole moments makes comparing different computational methods challenging. The challenges and complexities associated with predicting energy differences and conformations in computational chemistry studies of amino acids. It highlights the difficulty in accurately determining dipole moments and energy differences due to factors such as experimental limitations, rotational barriers, and basis set dependence. Different computational methods yield varied results, making comparisons problematic. The accuracy of predicting small energy differences is acknowledged to be a significant challenge. Several authors mentioned studies on glycine's rotational energy surface using various methods, demonstrating inconsistencies in results. Correlated level calculations with extended basis sets are deemed necessary for converging accurate predictions. Glycine, known to exist as a zwitterion in crystals and solutions, is addressed in its neutral form in the gas phase due to experimental support. The study focuses on neutral glycine conformers. Despite the simplicity of its structure, glycine has been subject to numerous experimental structural studies, including investigations into its rotational constants and molecular structure in the gas phase. X-ray and neutron diffraction studies of glycine crystals are also noted. Overall, several reports have emphasized the complexities of accurately predicting amino acid conformations and energies and the necessity of advanced computational methods.[19]

The theoretical vibrational frequencies and infrared intensities of different glycine conformers could help to interpret the gas-phase vibrational spectrum of glycine in future experimental investigations. In a recent study, Levy's research group in Chicago accomplished a significant feat by recording the first-ever gas-phase electronic spectrum of aromatic amino acids—phenylalanine and tyrosine. They employed laser-induced fluorescence (LIF) to excite the molecules, which were isolated within a helium-free jet expansion setup. Despite the amino acids' challenging characteristics, such as being non-volatile and thermally unstable, the researchers successfully obtained vibrationally resolved LIF spectra. This allowed identification of five conformers for phenylalanine and ten for tyrosine, all stable at low temperatures. However, the precise structures of these conformers remained undetermined.[20]

R-amino acids (NH_2-CH(R)-COOH) play a crucial role in protein structure due to their flexible conformations. These conformations are determined by intricate interactions, including hydrogen bonding. In condensed phases like crystals or solutions, amino acids take charge-separated forms (NH_3+-CH(R)-COO-) through hydrogen bonds. In the gas phase, isolated neutral forms (NH_2-CH(R)-COOH) reveal intrinsic preferences. Supersonic jet expansion is used to study these conformers, while rotational spectroscopy provides precise structural details. Gas-phase studies were challenging due to amino acids solid nature, but advancements are revealing the

conformational landscape of these critical biomolecules. Isoleucine is an essential aliphatic R-amino acid with a (2S,3S) sec-butyl side chain (R)-CH(CH_3) CH_2CH_3) and a melting point of 295-300 °C. It's not synthesized by mammalian tissues and is often found inside proteins and enzymes, influencing their tertiary structure. Being an essential aliphatic amino acid with a specific side chain, it plays important role in protein structure. However, its gas-phase structure and behavior haven't been studied before. Similar to smaller amino acids, isoleucine's conformational behavior is likely influenced by hydrogen bonding within its backbone.[21] Different stable configurations arise from various intramolecular interactions. Its larger side chain compared to other amino acids complicates its conformational landscape. Experimental observations of isoleucine using a specialized technique will provide valuable insights into its individual conformers and shed light on how intramolecular forces impact amino acids' behavior in the gas phase. Such study has determined the stable conformers of isoleucine and calculates relevant molecular properties for analyzing its rotational spectrum.

In the gas phase, amino acids are neutral, but in liquid or solid phases, they adopt a zwitterionic structure with positive and negative charges. This structure allows for the formation of hydrogen bonds, which stabilize the molecule. Alanine is a hydrophobic amino acid with a methyl group side chain. It exists in two chiral forms; L-alanine, which is naturally occurring, and D-alanine found in bacterial cell walls. At the isoelectric point, the amine group of alanine becomes protonated and the carboxyl group becomes deprotonated, resulting in a zwitterion with both positive and negative charges.[22] Researchers studied the vibrational spectra of L, D, and Z-alanine in the gas phase to understand their activities and interactions. The accuracy of computational methos used in such study was elevated by comparing the calculated frequencies with experimental observations.[23]

A comprehensive exploration of the conformational space of the peptides containing lysine and homologs was done using a semiempirical quantum chemical level of theory by Yuntao Zhang *et al*·[22] The methodology involved selecting protonated peptide conformations that match experimental IRMPD spectra, and then breaking down their vibrational modes into internal coordinates using Vib Analysis. By assigning normal modes, identifying primary modes, and calculating relaxed force constants, the researchers gain insights into the structural and vibrational characteristics of the peptides, helping to explain their IR features observed in the experimental spectra. By accurately characterizing the selected amino acids and comparing the computed results to experimental data, a reliable methodology and reference benchmarks for studying these essential molecules have been developed. A detailed analysis of the conformations, stability, and molecular interactions of α-amino acids with polar side (serine, cysteine, and aspartic acid and asparagine) chains using advanced quantum chemical calculations and their comparison with experimental observations has been reported by Barone *et.al.*[23] They have discussed how natural amino acids with polar side chains have a complex conformational landscape due to interactions between intra-backbone (within the backbone) and backbone (side chain) hydrogen bonds.[24] This interaction creates a rich variety of possible conformations.

Studying biomolecules in the gas phase is essential for understanding their inherent properties without the influence of their surrounding environment.[25, 26] To investigate these properties, various experimental methods have been used, such as proton affinity (PA) gas phase basicity (GB)[27-34]**.** Additionally, computational approaches have gained prominence due to advancements in quantum chemistry methods and computer hardware.[35-39] R. Pang *et al.* have explored the relative electronic energies and conformational stability of different neutral, protonated and deprotonated glutamine conformers in gas phase using different methods including DFT and CCSD which offer better agreement with experimental data.[40]

STUDY OF AMINO ACIDS IN SOLVENT PHASE:

Amino acids are integral to life as we know it, serving as the foundation for biological macromolecules and contributing to the diverse functions that sustain living organisms. They play a crucial role in biochemistry and serve as the fundamental constituents of proteins and other biologically significant molecules. They are essential for various biological processes, including protein synthesis, cell signaling, and enzyme catalysis. The presence of both the amino (-NH2) and carboxylic acid (-COOH) functional groups in amino acids provides them their distinctive name and chemical structure. This dual functionality allows amino acids to participate in chemical reactions that are pivotal for forming peptide bonds and creating the complex three-dimensional structures of proteins. Amino acids can indeed be classified based on the solubility of their R groups in water, which in turn affects the overall solubility of the amino acid itself.[41] This classification is a fundamental aspect of understanding the properties and behaviors of amino acids within biological systems; (i) Hydrophilic Amino Acids (Water-soluble): Amino acids with hydrophilic (water-loving) R groups tend to be soluble in water. The R groups of these amino acids are often polar[42] and have the ability to form hydrogen bonds with water molecules. Examples of hydrophilic amino acids include serine (Ser), threonine (Thr), asparagine (Asn), and glutamine (Gln). (ii) Hydrophobic Amino Acids (Water-insoluble): Amino acids with hydrophobic (water-repelling) R groups are less soluble in water. These amino acids have nonpolar R groups that do not readily interact with water molecules.[43] Instead, they tend to cluster together in hydrophobic environments. Examples of hydrophobic amino acids include alanine (Ala), valine (Val), leucine (Leu), and phenylalanine (Phe).

The solubility of amino acids was studied by Needham *et.al*[44] in different solvent systems, particularly in pure solvent systems and mixed solvent systems, under various pH conditions. The solubility was found to be higher in water (an aqueous solvent) than alcohols. The solubility of amino acids was inversely related to the length of the nonpolar portion of the molecule, which suggests that amino acids with shorter nonpolar portions have higher solubility in water. A bridge between theoretical and experimental approaches was investigated by Nohad Gresh and his co-worker.[45] They have explored the calculations of interaction energies, consideration of solvent effects (dehydration energies), and comparison with experimental data to gain insights into the molecular recognition and binding preferences between amino acids (lysine, arginine, glutamine, and glutamic acid and nucleic acids) and nucleic acids.[45]

Glycine (GLY) is the smallest amino acid, and its interactions with its surroundings, especially water, are biologically significant. High-level *ab initio* molecular orbital techniques have been used to investigate the possible range of conformers for the GLYZW: H_2O complexes and the potential energy surface of the 1: 1 complex between the glycine zwitterion (GLYZW) and water (H_2O).[46] The computed vibrational frequencies and normal mode, forms of the minimum energy complex resemble experimental assignments for the glycine zwitterion in bulk water based on Raman spectroscopy. Amino acids are the basic structural units of proteins, and their side chains contribute to protein structure and function and their side chains vary in size, shape, charge, hydrogen-bonding capacity, hydrophobicity, and chemical reactivity. Theoretical and computer simulation studies are important for understanding how different amino acid residues interact with each other, solvent, and ions. Understanding amino acid contributions to electrostatic fields and energetics is useful for enzyme design and predicting protein conformational stability.[47-55] Electrostatic contributions to the solvation energies of zwitterions for all 20 amino acids were calculated.[56] Various sets of charges and radii from different force fields (AMBER, CHARMM, CVFF, GROMOS, OPLS, PARSE) were used, along with an *ab initio*-derived charge set. The obtained results were found to align with the predictions based on a basic analytical theory formulated by Onsager. The investigation also developed into the electrostatic interactions that cause shifts in the pKa values of the carboxyl groups in all 20 amino acid zwitterions. Amino acids are fundamental in chemistry. Their amphoteric nature leads to a tautomeric equilibrium between neutral and zwitterionic forms. While the neutral form is energetically favored in the gas phase, the ionic form is more stable in condensed phases like polar solvent solutions and crystals. Hydrogen bonding interactions involving these functional groups are crucial for interactions in solvents and crystals, detectable through techniques like

IR, Raman spectroscopy, and NMR. Moreover, most amino acids are chiral molecules, existing in enantiomerically pure forms. The stability of the zwitterionic forms of the amino acids alanine and glycine in aqueous solutions has been predicted by using the Polarizable Continuum Model (PCM) which shows good agreement with experimental data, particularly for the stability of the zwitterionic forms of alanine and glycine in water solution and for properties like vibrational frequencies and VCD spectra, the agreement with experimental data is generally satisfactory.[57] Spectroscopic and theoretical studies on the behavior of glycine (GN) and its zwitterionic form (GZ) in various contexts reveal that in the gas phase, GN is the primary form, while in solutions or crystals, GZ prevails. The continuum model used for solvent effects is based on representing the solute as a charge distribution within a cavity surrounded by a solvent medium. The method involves a charging process to simulate solute-solvent interactions and calculate thermodynamic quantities.[58-65] The solvent effect on the proton transfer surfaces of both unhydrated and trihydrated systems is considered using a continuum model.[66] In the presence of water, the zwitterionic cis conformation of glycine is stabilized compared to the neutral cis form. The calculated free energy stabilization of GZ (cis) relative to GN (cis) is approximately 5.4 kcal/mol for the solvated tri-hydrated complex, which aligns well with an experimental value of 7 kcal/mol. More over the three water molecules in the GN (neutral form), TS (transition state), and GZ (zwitterionic form) structures are taken in to consideration for conformational studies, The most stable configuration involves an open geometric arrangement of the water trimer. In this configuration, each of the outermost water molecules serves as both a proton donor to the carbonyl oxygen and an acceptor, binding to the water proton. Meanwhile, the central water molecule plays a dual role as a donor, participating in two hydrogen bonds with neighboring water molecules.

The determination of the most stable configurations of macromolecules like peptides and proteins in solution, as well as the structural organization of the solvent around them is very important topic in computational chemistry. Continuum models have gained popularity for studying solvent effects on chemical systems. The interaction between the solvent and the solute significantly impacts the structural properties of the solute. [67,68,69] The conformational stability of glycine and its interaction with the solvent are crucial for understanding its behavior in solution. Comparison of the relative stability of different glycine conformers in both polar (water) and non-polar (cyclohexane, acetone) solvents has been studied by Selvarengan et.al. by using ab initio and density functional theory (DFT) methods.[70] Their findings suggest that the stability of the system in a liquid phase is influenced not only by a significant dipole moment but also by factors like hydrogen bonding interactions and interactions with the solvents. Water's role in stabilizing the zwitterion, the impact of solvent on glycine's functional groups, and the effects of partial solvation was studied theoretically. The study has modelled gradual solvation by adding water molecules step by step and compares results with continuum calculations.[71] Solvent microstructures and interactions impact zwitterion stability and tautomerization energetics were studied. Water molecules tend to form hydrogen bonds with each other and glycine, affecting stabilization. Specific bond lengths, dihedral angles, and hydrogen bond distances hold good with the experimental values. Amino acids' interactions with water significantly impact protein structure and function. The density functional theory (DFT) method was used to investigate glycine-(water)3 complexes, in which three water molecules interact with glycine's amino group through many-body interactions, considering basis set superposition errors (BSSE).[72,73,74]

Generally, how many solvent molecules are needed to solvate an amino acid, particularly in terms of transitioning the amino acid from its gas-phase neutral form to a zwitterionic solvated structure has been studied by various researchers. Both experimental and theoretical approaches, utilizing density functional theory (DFT) with the B3LYP/6-31+G** basis set, were employed to investigate this phenomenon using tryptophan-water$_n$ complexes (n=1-6) and tryptophan-methanol$_n$ complexes (n=1-9).[75] Interestingly, the behavior of micro-solvation by both methanol and water has been found to be similar for small solvent complexes (n=1-4). Through a comprehensive analysis of both experimental and theoretical spectra, the study not only identifies preferred solvent binding sites on the amino acid but also sheds light on the evolving conformational structures of tryptophan as the number of attached solvent molecules increases. Solvation is vital in forming protein tertiary and quaternary structures and impacts protein dynamics. Water molecules interact with proteins on different scales, influencing their overall behavior.[76-81] Studying biomolecule-solvent interactions experimentally is challenging due to the complexities involved. However, understanding hydration mechanisms around simple biomolecules, such as amino acids, can shed light on more complex interactions.[82] The characterization of different conformations of the glycine-water heterodimer, as well as the effects of water addition on the potential energy surface and conformational preferences of glycine were studied by using theoretical methods: *ab initio* (MP2) and density functional theory (DFT) methods and experimental methods like Raman spectra by Roman M. Balabin.[83] The study has confirmed that the interaction between water and glycine is dominated by the acidic character of the carboxylic acid group in glycine. The addition of a water molecule significantly alters the potential energy surface and conformational preferences of glycine. Water stabilizes conformations that allow the formation of closed-ring, hydrogen-bonded structures.[84] Glycine's tautomerization process, which involves its transformation between the neutral (NE) and zwitterionic (ZW) forms in aqueous solution, was conducted using the conductor-like polarizable continuum model (CPCM) at the B3LYP, MP2, and CCSD levels with the 6-311+G(d,p) basis set. Interestingly, when evaluating the Gibbs free energies of activation (ΔG) for tautomerization from the ZW to NE, the study found that these energies were consistent with experimental observations. [85] The impact of different polar solvents, including Water, Methanol, and Ethanol, on the thermodynamic functions of Alanine, Valine, Arginine and Lysine were also theoretically investigated. 86 The results indicated that polar solvents have a stabilizing effect on these amino acids.[87,88]

AMINO ACIDS IN INERSTELLAR MEDIUM:

Astrochemistry is an inherently interdisciplinary subject, with researchers in the area coming from the astronomy, chemistry and physics communities. Astrochemical research itself spans observations, modelling, and laboratory based investigations (both theoretical and experimental).[89] The field of astrochemical research on the molecular composition of space has developed in the area of exploration of organic molecules and their complexes as pre-biotic species, which are essential to study the origin of life.[90] A wide range of conditions and reaction mechanisms can generate the spectrum of compounds observed in meteorites and dust particles. Soluble organic compounds like amino acids in these meteorites, generally thought to have been produced soon after the formation of the Solar System, by the action of aqueous fluids on the asteroids which gave rise to the meteorites.[91] In this scenario, the carbon, nitrogen and hydrogen that combined to form the amino acids found in the well-studied Murchison meteorite.[92,93] The experimental synthesis of amino acid in which the ice mixture was used, were thought to be representative of the interstellar medium. In this regard Bernstein et al. report the synthesis of three amino acids (glycine, serine and alanine) in a mixture of water, methanol, ammonia and hydrogen cyanide, where the ratio of the components was 20:2:1:1, respectively.[94] Such amino acids would naturally have a deuterium excess similar to that seen in interstellar molecular clouds, and the formation process could also result in enantiomeric excesses if the incident radiation is circularly polarized. These results suggest that at least some meteoritic amino acids are the result of interstellar photochemistry, rather than formation in liquid water on an early Solar System body. Similarly, the spontaneous generation of amino acids in the interstellar medium is possible and that prebiotic molecules could have been delivered to the early Earth by cometary dust, meteorites or interplanetary dust particles, was demonstrated by Muñoz Caro et al.[95] They have reported the synthesis of 16 amino acids and several other compounds in their 2:1:1:1:1 mixture of water, methanol, ammonia, carbon monoxide and carbon dioxide.

A wide range of conditions and reaction mechanisms can generate the spectrum of compounds observed in meteorites and dust particles. Isotopic evidence (especially enrichments in 15N and deuterium) supports the idea that at least half of the insoluble organic matter in carbonaceous meteorites originated from sources that existed before the Solar System formed[96,97]. In contrast, soluble organic compounds in these meteorites, including amino acids, are generally thought to have been produced soon after the formation of the Solar System, by the action of aqueous fluids on the asteroids that gave rise to the meteorites [98] In this scenario, the carbon, nitrogen and hydrogen that went into forming the amino acids found in the well-studied Murchison meteorite would have been carried by reactive precursors from the interstellar medium, but the amino acids themselves would have formed on meteorite's parent body. So, it is possible that the amino acids found in meteorites originated in the interstellar medium, they were synthesized on the asteroid parent bodies of the meteorites by the action of aqueous fluids. Results from the Tagish Lake meteorite [99] which fell to Earth in 2000, make the picture more complicated till date. Although it contains evidence of aqueous alteration, and although the bulk abundance of organic carbon is similar to that of the Murchison meteorite, concentrations of amino acids in the Tagish Lake meteorite are around a thousand times lower than those in Murchison.

Recent improvements of radio astronomy techniques have increased the ability to identify interstellar organic molecules. The possibility of prebiotic molecules such as amino acids, which are the building blocks of living organisms, may provide important information about the history of the Solar System and the origins of life on Earth.[100] Kuanet al.[101] searched for glycine (NH2CH2COOH), the simplest proteinaceous amino acid, through hot molecular cores associated with the star-forming regions Sgr B2(NLMH), Orion KL, and W51 e1/e2. However, more than 70 compounds (including glycine) have been identified in meteorites, as in the case of the Murchison meteorite[102] (Cronin, J.R. and Pizzarello, S. (1983) Amino acids in meteorites. Adv Space Res 3:5–18). In addition, Sandford et al. (2006) analyzed cometary samples returned to Earth by NASA’s Stardust spacecraft and found several amines and possibly the glycine amino acid.[103] Subsequently, the stable carbon isotopic ratios of glycine identified in Stardust-returned foil samples measured by gas chromatography–mass spectrometry coupled with isotope ratio mass spectrometry was presented by Elsila et al. The δ13C value for glycine of +29±6% strongly suggests an extraterrestrial origin because it represents the first detection of a cometary amino acid.[104] Again the formation of amino acids from simple compounds such as CO, CO2, CH4, NH3, H2O and H2 (and others) have been performed for at least 60 years in an attempt to simulate primitive Earth conditions or interstellar/protoplanetary grain mantles. In most of those experiments, the gas mixtures (or the frozen gas mixtures) were submitted to ionizing radiation sources (electrons, photons, ions), which trigger the chemistry that allows complex molecules to be formed. The detection of the amino acids in organic residues after vacuum UV irradiation of several astrophysical ice mixtures containing H2O, CO, CO2, CH3OH, CH4, and NH3 at low temperatures (10–80 K) was performed by Nuevo et al. (2008).[108] A detailed study of the amino acids produced from the vacuum UV irradiation of interstellar ice analogs. Pilling et al. suggested the presence of zwitterionic glycine (NH3 + CH2COO-) among the organic inventory produced by the radiolysis of ammonia-containing ices by employing heavy cosmic ray analogues.[109,110,11,112,113] However the formation of glycine was also the subject of several theoretical studies involving different reactions set in the gas phase and in interstellar grain analogues. Investigation of the thermo-chemistry of several glycine formation routes involving formic acid, carboxylic acid, and carboxyl radical, as well as their ionic species, with nitrogen-rich compounds that have been detected (or may occur) in space, such as NHx, NH2OH, NH2CHx, and NH2CH2OH, as well as their ionic species have been reported by Pilling et al.[114] Suggested scenarios for glycine formation via carboxylic acids inside star-forming regions illuminated by UV and soft X-rays has been shown in fig-X.

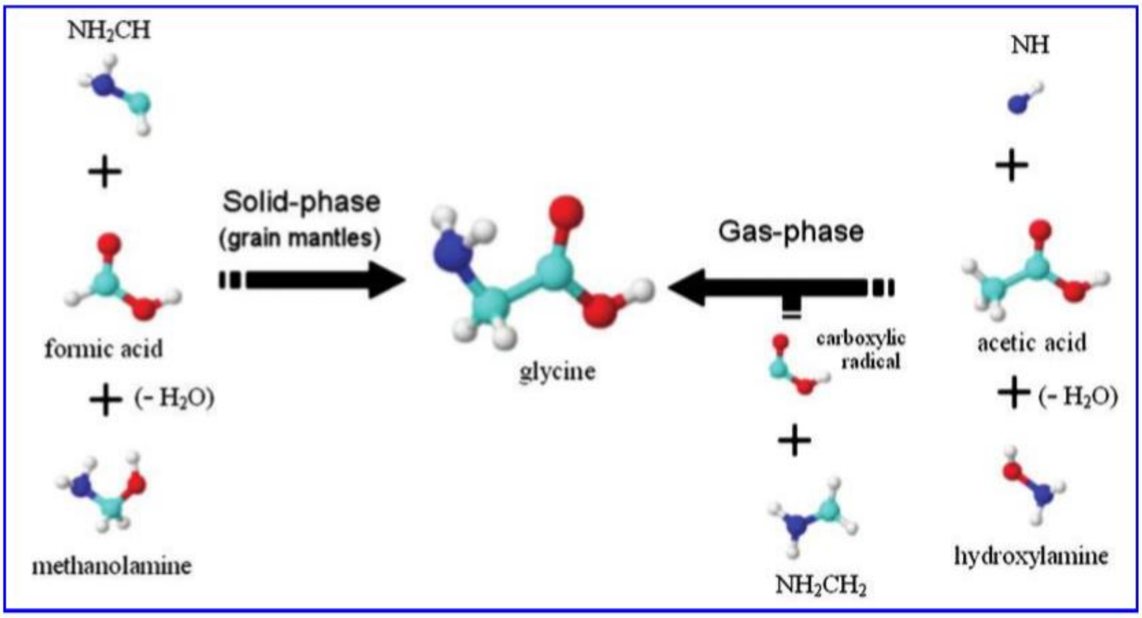
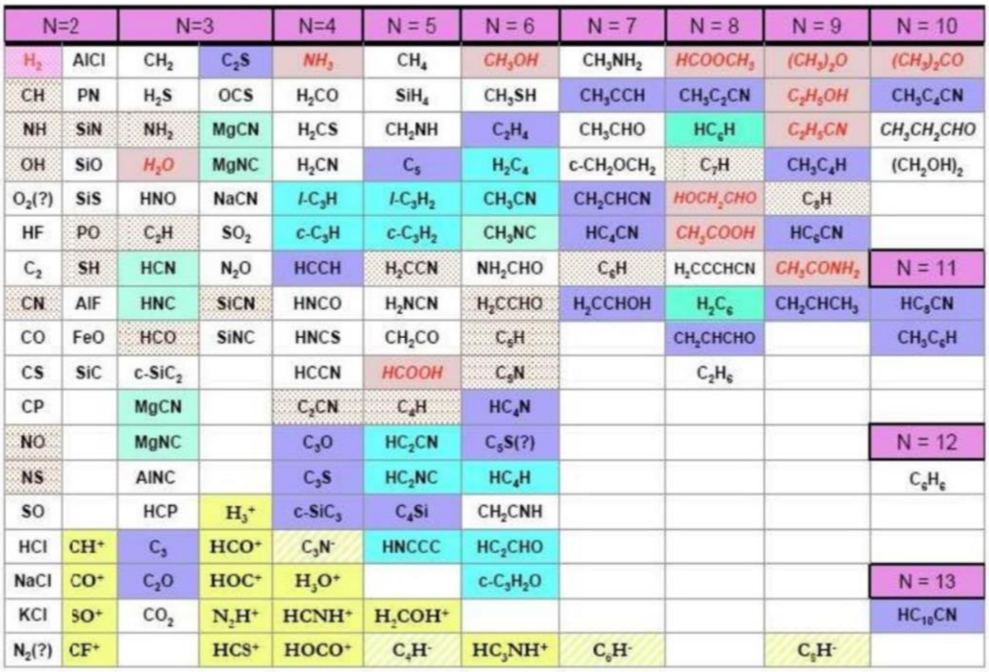


Fig-1.3 Glycine formation via carboxylic acids inside star-forming regions illuminated by UV and soft X-rays.

Besides glycine, some other amino acids have been detected in the interstellar medium, as such serine, a hydroxy amino acid, which is a polar and non-essential amino acid with the molecular formula HO2CCH(NH2) CH2OH, has been detected in abundance in CR2 meteorites (GRA 95229 and LAP 02342). Eight of the meteorite amino acids are also found in proteins (glycine, alanine, proline, valine, leucine, isoleucine, aspartic acid, and glutamic acid) and numerous other compounds are encountered in terrestrial metabolisms. In the gas phase, where these intermolecular interactions have no effect, they exist as non-ionized. The study of the conformational behavior of non-ionized amino acids is important for understanding the dynamics of the peptide and protein backbones.

A significant topic in astrobiology and prebiotic chemistry is the search for amino acids and their precursors in the ISM. The exploration of serine formation from simpler interstellar molecules using quantum-chemical methods has been done by Shivani et.al [115] Despite some reactions having high potential barriers, the study suggests that serine formation is feasible in the interstellar medium (ISM), especially at low temperatures. Reactions may occur when molecules adhere to cosmic dust grains, providing sufficient time for reaction, and potential barriers within the range observed in the ISM conditions. Overall, the findings indicate that serine formation is possible in both gas-phase and icy grain environments within the ISM. The exploration of complex organic molecule formation in the interstellar medium (ISM), which contains a wide range of molecular materials has been studied by various researcher using quantum chemical techniques, particularly density functional theory (DFT), the study has investigated gas-phase reactions involving detected interstellar molecules like CH3CN and HCOOH in the ISM.[116]

After careful consideration of literature review, it has been summarized that astronomical organic molecules are of enormous interest for last several years. On following the footsteps of the laboratory spectroscopists, since the beginning of microwave spectroscopy by Cleeton & Williams in the early 1930s to till date more than 150 number of astronomical molecules[117] (Fig 1.4) have already been reported. Stable organic molecules continue to be an important component, but there are an even larger number of exotic molecules, some of which are so reactive and elusive in the laboratory that they were quite unknown until identified in space.



N=2		N=3		N=4	N = 5	N = 6	N = 7	N = 8	N = 9	N = 10
H_2	AlCl	CH_2	C_2S	NH_3	CH_4	CH_3OH	CH_3NH_2	$HCOOCH_3$	$(CH_3)_2O$	$(CH_3)_2CO$
CH	PN	H_2S	OCS	H_2CO	SiH_4	CH_3SH	CH_3CCH	CH_3C_2CN	C_2H_5OH	CH_3C_4CN
NH	SiN	NH_2	MgCN	H_2CS	CH_2NH	C_2H_4	CH_3CHO	HC_6H	C_2H_5CN	CH_3CH_2CHO
OH	SiO	H_2O	MgNC	H_2CN	C_5	H_2C_4	c-CH_2OCH_2	C_7H	CH_3C_4H	$(CH_2OH)_2$
O_2(?)	SiS	HNO	NaCN	l-C_3H	l-C_3H_2	CH_3CN	CH_2CHCN	$HOCH_2CHO$	C_8H	
HF	PO	C_2H	SO_2	c-C_3H	c-C_3H_2	CH_3NC	HC_4CN	CH_3COOH	HC_6CN	
C_2	SH	HCN	N_2O	HCCH	H_2CCN	NH_2CHO	C_6H	$H_2CCCHCN$	CH_3CONH_2	N = 11
CN	AlF	HNC	SiCN	HNCO	H_2NCN	H_2CCHO	H_2CCHOH	H_2C_6	CH_2CHCH_3	HC_8CN
CO	FeO	HCO	SiNC	HNCS	CH_2CO	C_5H		CH_2CHCHO		CH_3C_6H
CS	SiC	c-SiC_2		HCCN	HCOOH	C_5N		C_2H_6		
CP		MgCN		C_2CN	C_4H	HC_4N				
NO		MgNC		C_3O	HC_2CN	C_5S(?)				N = 12
NS		AlNC		C_3S	HC_2NC	HC_4H				C_6H_6
SO		HCP	H_3^+	c-SiC_3	C_4Si	CH_2CNH				
HCl	CH^+	C_3	HCO^+	C_3N^-	HNCCC	HC_2CHO				
NaCl	CO^+	C_2O	HOC^+	H_3O^+		c-C_3H_2O				N = 13
KCl	SO^+	CO_2	N_2H^+	$HCNH^+$	H_2COH^+					$HC_{10}CN$
N_2(?)	CF^+		HCS^+	$HOCO^+$	C_4H^-	HC_3NH^+	C_6H^-		C_8H^-	

Fig-1.4 Small molecules other than Glycine found in the Interstellar medium.

The astronomical molecules are mainly composed of the cosmically abundant biogenic elements H, C, N, O and S, but 11 molecules contain Si, and there is at least one molecule with F, Mg, Cl, Na, K, Al or P. A large number of molecular isotopic species have also been reported. The number of new molecules are still increasing by ~3 per year.

It is worth emphasizing the remarkably high quality of nearly all the astronomical identifications. Since interstellar molecular gas is typically cold, radio lines are often extremely sharp, even by laboratory standards, and in favorable cases it is possible to match astronomical lines to laboratory frequencies to a few parts in 107. At this accuracy, it does not take many lines to achieve a conclusive identification; a number of molecules in figure 1.4 have dozens of precisely measured astronomical lines, and as a result can be assigned with a confidence approaching certainty. When it is claimed, for example, that formaldehyde or methanol or a number of others among the many identified in space exist in a particular interstellar cloud, there is essentially no dissent from astronomers, chemists or physicists who examine the data. There is probably no area of astrophysics where the qualitative analysis is more secure. The quantitative analysis also can be very good. The intensity of the molecular radio emission lines in space depends mainly on two factors, both of which can be well determined: the molecular electric dipole moment and the rotational partition function, which depends on the populations of the various levels. For stable molecules, the dipole moment can be measured from the Stark effect to about 1%, and even for some reactive molecules where the measurement is difficult, it can often be measured to almost the same value. In addition, for many reactive astronomical molecules, dipole moments can now be calculated with quantum numerical codes to a few per cent. Calculation of the partition function requires knowledge of the rotational excitation and the effective rotational temperature, but this can often be done in the order of 10%. Weakly bound molecular complexes can be considered to be a bridge between individual isolated molecules and the bulk phase, a bridge along which proper- ties of matter change dramatically. Intermolecular interactions in molecular complexes affect optical properties and reaction dynamics of molecular systems and, thus, are of a general importance. Molecular complexes have been considered to play a large role in the chemistry of the ISM, in particular in dense and cold molecular clouds, and also at the higher density and higher temperatures found in planetary atmospheres, where they can contribute to the atmospheric chemistry and climate.[118] Molecular dimers have been proposed to be a major constituent of cometary matter[119] and to be contained in interstellar grain mantles [120]. One more work, which can be mentioned in this context, is the first laboratory observation of a rotationally resolved millimetre-wave spectrum of the water dimer recorded under atmospheric conditions.[121] A huge number of weakly bound complexes have been probed spectroscopically in the gas phase.[122,123,124] But in spite of this "huge number" a large amount of necessary information for many important species is not available.

CONCLUSION:

Despite the extensive body of research on molecular interactions, a significant gap remains in the available structural and spectroscopic data for many astro-chemically relevant species. This review emphasizes the importance of computational investigations in bridging this knowledge gap, particularly focusing on the conformational changes of amino acids like glycine and its derivative, amino acetonitrile, upon interaction with small molecules. By examining weakly bound complexes stabilized through hydrogen bonding and van der Waals forces, valuable insights into their structural, energetic, and spectral properties can be obtained—insights that are often inaccessible through experimental means alone.

The inclusion of small astrochemical molecules in such studies is especially crucial, as it enhances our understanding of the molecular diversity and interaction mechanisms occurring in interstellar environments. These computational explorations not only support the identification and characterization of such complexes in space but also highlight critical deficiencies in current laboratory and theoretical datasets. By identifying these gaps, this work sets the stage for future research efforts aimed at expanding molecular databases and refining spectral parameters necessary for astronomical detection. Ultimately, this study contributes to the broader goal of elucidating the molecular foundations of astrochemistry through a deeper understanding of amino acid conformational behavior in the presence of small molecular partners.

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