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Structural and Electronic Properties of Hyaluronic Acid

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Abstract

The study of hyaluronic acid is of paramount importance due to its widespread applications in biomedical and cosmetic fields. Analyzing its structural and electronic properties through Density Functional Theory (DFT) holds significant implications for understanding its behavior at the molecular level. Across the DFT application, we can delve into the intricate details of hyaluronic acid's structure and electronic configuration and potential applications. In this work, the structural and electronic properties of hyaluronic acid are studied, and partial density of states analysis guides the design of biomaterials with tailored mechanical, chemical, and biological properties, suitable for applications in regenerative medicine and biotechnology.

Keywords: Hyaluronic; Structural; Electronic; Molecular Orbital; Nanometric scale

Abbreviations: DFT: Density Functional Theory; HA: Hyaluronic Acid; SAXSA: Small-Angle X-ray Scattering; RDF: Radial Distribution Function; HOMO: Highest Occupied Molecular Orbital; LUMO: Lowest Unoccupied Molecular Orbital; PDOS: Partial Density of States

Introduction

The study of hyaluronic acid (HA) in nanotechnology is emerging as a highly relevant area due to its remarkable properties. Understanding the nature of this material is fundamental to knowing its structure and intrinsic properties, thus expanding the horizon of possibilities for scientific and technological innovation. HA is a substance of great biomedical interest, a curiosity that began in 1934 when scientists Karl Meyer and John Palmer discovered it during the analysis of bovine vitreous humor [1]. Initially, it was isolated from this ocular tissue and named "hyaluronic acid" due to its origin in the hyaloid (vitreous humor) and uronic acid. Later, in 1986, the term "hyaluronan" was introduced to conform to polysaccharide nomenclature [2].

In this context, it was in the biochemistry laboratory at Columbia University that researchers Karl Meyer and John Palmer conducted the experiment involving the extraction of a high molecular weight polysaccharide acid from the vitreous humor of 100 bovine eyes transported directly from the slaughterhouse on ice. They described that HA was obtained from the acetone precipitate of fresh vitreous and was characterized by its high molecular weight and composition, including uronic acid, an amino sugar, and possibly a pentose, as reported by the authors and their associates [3]. The researchers went on to discuss the chemical properties and possible relationship of this acid to the pathogenesis of glaucoma, emphasizing its uniqueness and relevance to future ophthalmic research. It was clear from the beginning that this polysaccharide had a wide range of potential applications. However, the therapeutic application of HA began with veterinary treatments for traumatic arthritis in racehorses, demonstrating its efficacy in alleviating joint pain [2]. Years later, as predicted by the scientists who discovered HA, the material proved to be a valuable resource in the treatment of various ocular conditions, such as in dry eye solutions, vitreous substitutes, and viscoelastics during ophthalmic surgery.

Ophthalmic studies have shown that HA plays a critical role in protecting the corneal endothelium and maintaining the intraocular space, allowing for necessary surgical maneuvers such

as intraocular lens implantation. Comparative studies have shown that HA, especially at specific concentrations such as 2.3%, is superior in maintaining intraocular pressure and preserving the endothelium after surgery. Since then, the material has been used as a component in visco-anesthetic solutions to reduce patient discomfort during phacoemulsification, a surgical technique used in ophthalmology for cataract removal in which the cloudy lens of the eye is fragmented into small pieces by ultrasound waves [4].

Another example is its use in dry eye syndrome, a common ocular condition related to age, gender, disease, environment, diet, surgery, or as a side effect of medications. Adding HA to artificial tears can improve and prolong moisture retention. In eye drops, high levels of HA stabilize the tear film and increase conjunctival goblet cells. HA can be formulated in different ways in eye drops and can be used in combination with other compounds to increase tear film thickness [5].

In addition to its traditional applications, hyaluronic acid has also been studied in nanotechnology, where it is converted into nanoparticles for various biomedical applications. HA has been an essential component in nanoparticle formulations for precise drug delivery in disease treatment. Its application as a contrast agent in medical diagnostics has been explored to accurately localize affected areas, such as in cancer cases. Its remarkable biocompatibility and ability to selectively interact with target cells make it a promising tool for targeted treatments and more precise diagnostics.

At the forefront of nanoscience, hyaluronic acid can therefore be a central element in various applications. With a molecular structure that allows for modification and functionalization at the nanoscale, the polysaccharide under study offers a wide range of possibilities. Structurally, the material has a linear polymer chain composed of disaccharide units, which allows manipulations to achieve different sizes and molecular weights [6]. Furthermore, this malleability is extremely relevant in nanotechnology, where manipulation at the nanometric scale is essential.

Nanoscience

Nanoscience, by exploring materials and processes at the nanometric scale, reveals a fascinating universe of unique properties, arousing curiosity and forging links between diverse disciplines such as chemistry, physics, engineering, biology, and biochemistry. In physics and electrical engineering, it is characterized by the study of the quantum behavior of electrons and photons in nanometric structures [7]. Nanoscience reveals properties that often challenge our understanding. Nanometric structures, such as carbon nanotubes and semiconductor quantum dots, exhibit unique electronic and optical properties, providing opportunities for the development of highly efficient and sensitive devices [8].

In medicine, nanoscience is emerging as a revolutionary promise for diagnostics and therapeutics. Controlled drug delivery systems based on nanostructures offer the prospect of more precise and personalized treatments. The meticulous study of minute structures not only reveals diverse scientific phenomena, but also promises extraordinary discoveries and advances. Moreover, nanotechnology, as a natural extension of nanoscience, goes beyond mere exploration by applying this knowledge to create practical solutions with the potential to transform various scientific fields.

Hyaluronic Acid

This natural glycosaminoglycan is naturally present in various tissues and fluids of the human body, such as skin, cartilage, bone, and synovial fluid, and has hydrating and lubricating properties, as well as anti-inflammatory and antioxidant properties [9].

In the human body, HA helps cells heal by recognizing specific signals and facilitating the deposition of collagen and the growth of new blood vessels. It also stimulates the activity of certain skin cells, such as keratinocytes, during various stages of healing, lubricates joints and absorbs shock. In the skin, it is rapidly degraded in less than a day, either by enzymes or by reactive oxygen species [10] (BICUDO, 2011). From an electronic point of view, hyaluronic acid (HA) is a negatively charged polymer, a property that can be exploited in its application as a contrast agent in imaging techniques such as nuclear magnetic resonance. In addition, its interactions with organic and inorganic molecules can be modulated by chemical modifications, such as the introduction of specific functional groups.

Relationship with Water

As mentioned above, one of the most remarkable properties of hyaluronic acid (HA) is its ability to retain water, giving it a gelatinous consistency, high viscoelasticity and a high degree of hydration. Unlike other glycosaminoglycans, HA is not covalently linked to a protein core, but can form aggregates with proteoglycans. In a neutral aqueous solution, hyaluronic acid forms hydrogen bonds with water molecules as well as carboxyl and N-acetyl groups.

The hydrogen bonds formed by hyaluronic acid not only stabilize the macromolecule in solution, but also impart rigidity to the polymeric system, thereby influencing the properties of hyaluronic acid solutions. These bonds can occur both within a macromolecule and between adjacent molecules, resulting in complex secondary and tertiary structures [11]. The retention capacity contributes to its stability, as observed in studies where formulations with higher water content were more stable due to the hygroscopic properties of the material [12].

Although hyaluronic acid can retain water between its molecules, this does not prevent it from dissolving in water. This ability is attributed to the molecular structure of HA, which allows the formation of hydrogen bonds with water molecules.

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However, the water solubility of hyaluronic acid is facilitated by specific functional groups in its structure. Hydroxyl groups (-OH) and the salt group ($-COO^{-}Na^{+}$) facilitate the interaction with water molecules, allowing the natural dispersion of the HA polymer in an aqueous medium. The retention property discussed helps in the treatment of dermatological diseases, which has enormous potential for the cosmetic industry [13].

We observe that HA has a wide range of applications, but despite continuous advances in theoretical understanding, there is a notable lack of studies integrating the physical and/or chemical aspects of this material. Among the existing possibilities, Density Functional Theory (DFT) emerges as an option to fill this gap. In this work, the structural and electronic properties of hyaluronic acid are studied and possible applications are highlighted.

Computational Methodology

The electronic calculations were performed using the CASTEP software [14]. During execution, the progress of the calculations was monitored to ensure successful completion and to verify the convergence of the results. The input files required for the DFT calculations were prepared based on the crystalline structure of the material of interest. Essential parameters such as the k-point settings (3x3x3) and the cutoff energy (750 eV) were defined to ensure the accuracy of the calculations. With this configuration, the physical properties of the material can be calculated, allowing us to obtain accurate and reliable data about the material under study, such as its structural and electronic properties.

In the next step, a quantitative analysis of the results was carried out using a graphing software (ORIGIN), where statistical methods were used to interpret and quantify the information collected. This process allows the identification of trends and relationships between the variables studied, providing a solid basis for analysis. Additional information on the methodology can be found in the reference [8].

Structural Properties

Understanding the properties of the material in its primitive form requires establishing an ideal stability among the atomic components. The application of predetermined parameters to optimize their geometry is part of this process, with the goal of minimizing energy. More detailed information will be provided in the following sections, where we will discuss the geometric properties of HA, the parameters established for optimization, the arrangement of atoms, and other relevant issues.

The Hyaluronic Acid Molecule

Figure 1 shows a molecular structure of hyaluronic acid with the chemical composition C42H48N3O41.50Na3. Analysis of the molecule revealed the presence of 139 atoms. It is important to note that the structure has trigonal symmetry as shown in Figure 1(a). In Figure 1(b) we present a visualization of the molecular system from another angle.

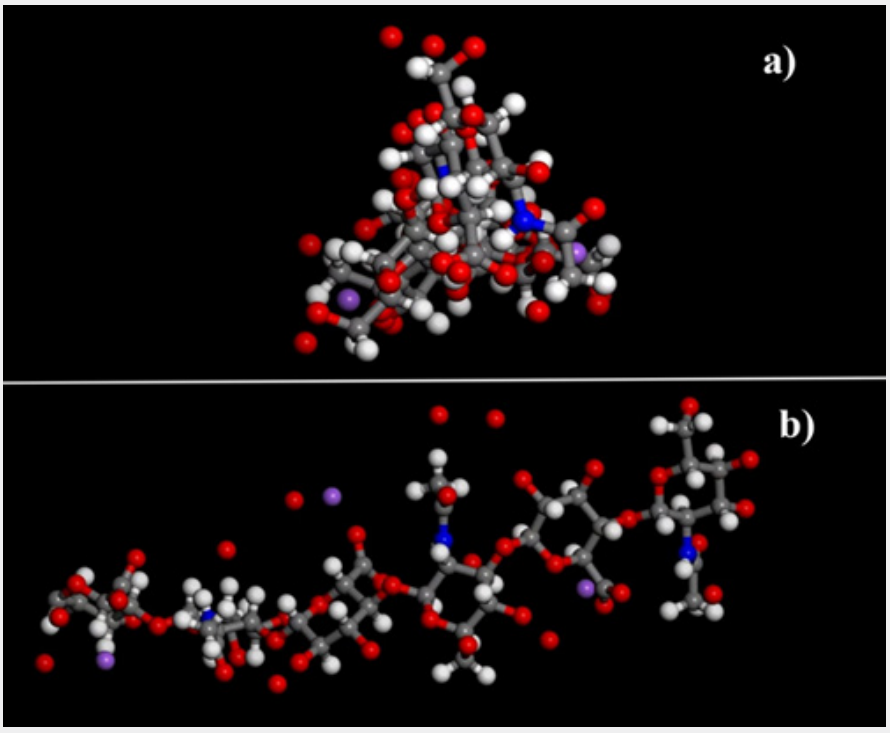

Figure 1: Molecular structure of Hyaluronic Acid.

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The lattice parameters, which represent the dimensions and angles between the defining vectors of the unit cell, have been determined and can be seen in Table 1. The column 'cal' indicates the type of calculation performed. In this column, the results obtained by DFTB+ calculations and the experimental values are presented.

Table 1: Lattice parameters (a, b, c, α, β, and γ) and volumes (V) obtained in DFTB+.

a (Å)	b (Å)	c (Å)	α (°)	β (°)	γ (°)	V(Å)	CAL
11.698	11.698	11.698	120	120	120	3371.32	DFTB+
11.7	11.7	11.7	120	120	120	3378.68	Exp.

Geometry Optimization

The molecular geometry optimization of HA was performed using the DFT formalism. The DFTB+ (Density Functional Tight Binding Plus) module of the Materials Project software was used for this analysis. DFTB+ is an atom-based implementation of DFT and provides a competent approach to perform electronic structure and molecular property calculations with adequate accuracy. Geometric optimization was performed using the 3ob Slater-Koster library. The default eigenvalue solver was used and dispersion correction was enabled. Spin was restricted and thermal smearing was used with a parameter of 0.005 Ha (with the Methfessel-Paxton function). It's important to note that DFTB+ does not use "functionals" in the same sense as traditional DFT theory. Instead, DFTB+ implements a semi-empirical method that combines DFT principles with experimentally adjusted parameters.

Small-Angle X-ray Scattering (SAXS) for Hyaluronic Acid Molecule

In Figure 2, we present the results of the SAXS technique obtained through calculations performed in the FORCITE software. SAXS is an experimental technique that allows the analysis of the structural behavior of a sample in terms of its electron density, using the Fourier transform to process X-ray diffraction data. However, interpreting these results with respect to our specific molecule requires a deeper understanding. We observe that the graph shows a gradual decay pattern as we move along the scattering vector axis.

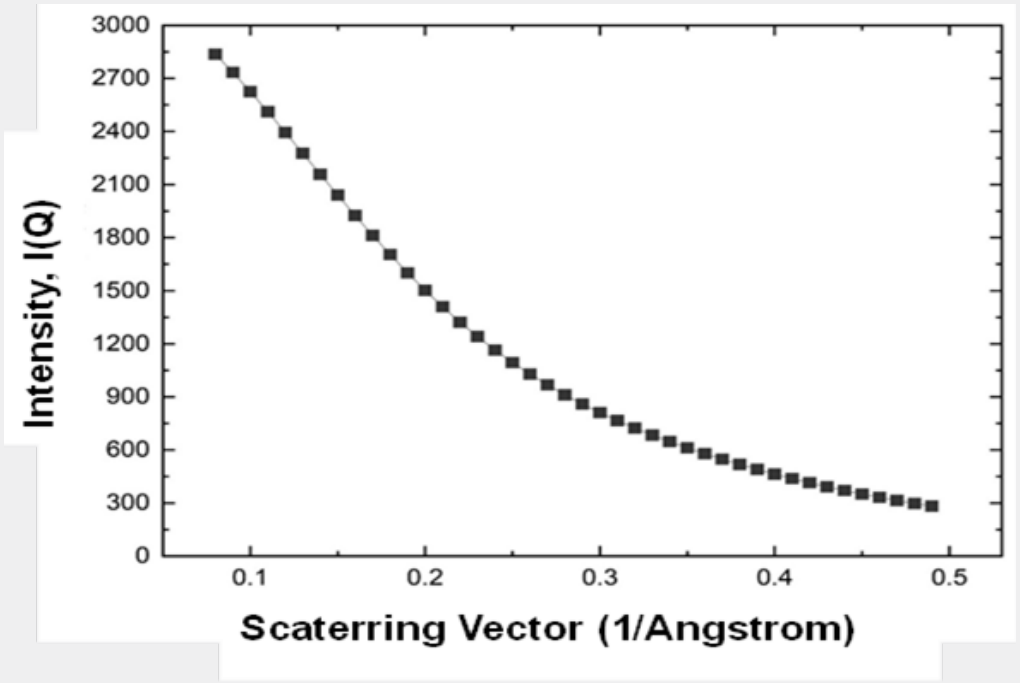

Figure 2: X-ray diffraction intensity versus scattering vector for Hyaluronic Acid

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As we can see in Figure 2, this indicates how the scattering intensity varies with the increase of the scattering vector (Q). Hyaluronic acid is a large and highly polymeric molecule. The gradual decay pattern reflects the spatial distribution of the repetitive units in the molecule and their degree of organization, indicating a well-distributed molecular structure without significant irregularities.

Radial Distribution Function (RDF) in Hyaluronic Acid

Figure 3 shows the radial distribution function (RDF) obtained with DFTB+. The RDF provides us with information about the spatial distribution of atoms in hyaluronic acid. The horizontal axis of the plot, represented by "r" in Angstroms (Å), shows the radius from a reference atom, indicating the distance between this atom and another atom in the molecule. The vertical axis, represented by "g(r)", expresses the RDF itself. This axis gives the probability of finding an atom at a given radial distance from another atom in the molecule. Therefore, the values of "g(r)" indicate the frequency or probability of finding atoms at different radial distances.

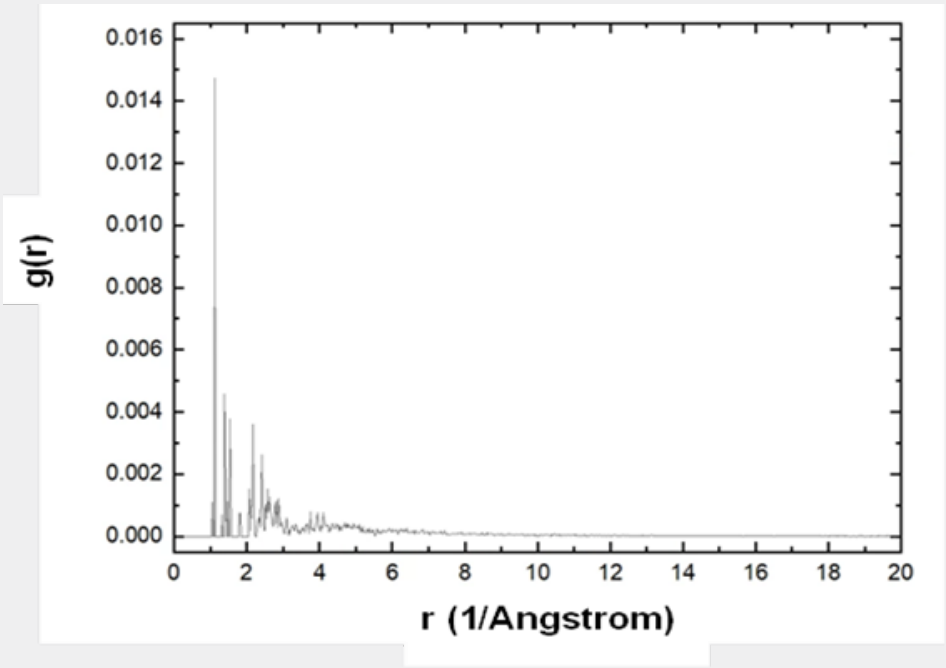

Figure 3: Analysis of Radial Distribution Function (RDF) in the Molecular Structure of Hyaluronic Acid.

The prominent peaks in the RDF indicate preferred distances between atoms in the molecule, often reflecting typical bond distances or ordered structural arrangements. On the other hand, the valleys in the RDF indicate distances where the probability of finding atoms is lower, which may indicate regions of disorder in the molecular structure. We note that it reaches its maximum point when the value on the horizontal axis is 1, and reaches a value of 0.014 on the vertical axis, meaning that the probability of finding an atom at a radial distance of 1 angstrom from another atom in the molecule is 0.014.

Electronic Properties

By studying the electronic properties of hyaluronic acid, we enter a fascinating world of molecular interactions. Analysis of the Homo-Lumo reveals subtle nuances in its electronic structure that affect its transport and reactivity properties. Understanding the density of states gives us a deep insight into the distribution of available energy, while analyzing the calculated energies allows us to better understand its behavior. The Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) orbitals reveal the highest and lowest occupied energy levels, respectively. The difference between these orbitals, known as the LUMO-HOMO gap, was calculated by subtracting the HOMO energy from the LUMO energy.

i. HOMO energy: 6.5299675 eV.

ii. LUMO energy: 3.4913388 eV.

iii. The LUMO-HOMO gap is therefore 3.0386287 eV.

It is well known that the energy gap between orbitals provides information about the properties of the material being studied. A smaller gap indicates that less energy is required to excite an

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electron, suggesting a conductor or semiconductor material. Conversely, a larger gap indicates an insulating material. In addition, the size of the energy gap between orbitals also provides information about the stability of the material, which can be further explored.

Density of States

For a more comprehensive understanding of the electronic properties of hyaluronic acid, we investigated the partial density of states (PDOS), plotted as a function of energy. We analyzed the contribution of the s and p orbitals to the total DOS, covering the energy range from -21 eV to 40 eV, as shown in Figure 4. We emphasize that the blue region corresponds to the d orbital (characteristic of materials with magnetic properties, which does not apply to HA).

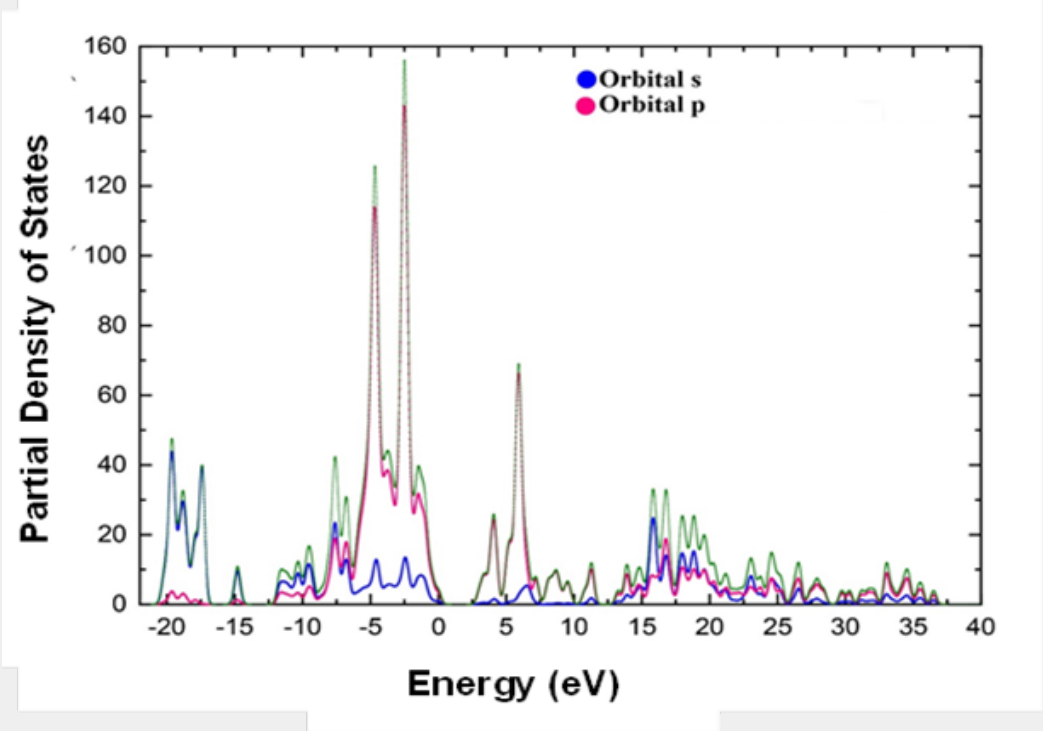

Figure 4: Partial Density of States (PDOS) of Hyaluronic Acid.

We started our analysis with the s orbital, which is characterized by the absence of an orbital magnetic moment. We observed that its partial density of states has a significant peak in the -19.65 eV region. This result is interesting because it helps us understand the distribution of electronic states associated with the s orbital and its influence on the electronic properties of the material. Next, we studied the p orbital, which plays an important role in the formation of the valence bands of the material. As a result, we can observe two significant peaks in the energy region of -2.5 eV and -4.7 eV. These peaks indicate a significant concentration of electronic states associated with the p orbital in this energy range. By summing the contributions of the s and p orbitals, we obtained the total DOS of the material, represented by the green color.

In hyaluronic acid, the predominance of s and p orbitals in the partial density of states occurs due to the nature of the atoms that make up the molecule and their chemical bonds. Additionally, the predominance of s and p orbitals in the partial density of states reflects the participation of these orbitals in the covalent bonds and molecular geometries that define the structure of hyaluronic acid.

Analysis of Calculated Energies of Hyaluronic Acid Molecule

Table 2 summarizes the calculated energies in kcal/mol for the molecule under study, providing an analysis of various relevant energy aspects. These energies were obtained through computational simulations performed in FORCITE and provide valuable information about the molecule. The total potential energy, with a value of 601.87579498, represents the total energy associated with the molecular configuration. Among the highlighted energy components, the binding energy, with a value of 15.90655756, indicates the energy required to break the chemical bonds present in the molecule.

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Table 2: Multifaceted analysis of molecular energies in kcal/mol.

Total potential energy	601.875795
Binding energy	15.90655756
Angular energy	517.0500373
Torsional energy	3.90592722
Van der Walls energy	65.01327293
Total valence energy	536.8625221
Non-bonded energy	65.01327293

In addition, the table shows the angular and torsional energies, which reflect the energy contributions associated with the angles and torsions between the atoms of the molecule, respectively. The Van der Waals energy (65.01327293) represents the energy resulting from the attractive interactions between adjacent atoms. The total valence energy includes the energy associated with the interactions between atoms in the molecule, while the unbonded energy is the difference between the total potential energy and the total valence energy.

Conclusions

The comprehensive study of hyaluronic acid is very important due to its extensive use in both biomedical and cosmetic fields. The use of DFT to study its structural and electronic properties provides profound insights into its molecular behavior. Through DFT analysis, we gain a nuanced understanding of the intricate structure and electronic configuration of hyaluronic acid, paving the way for potential applications in various fields.

Our study of the structural and electronic properties of hyaluronic acid, coupled with partial density of states analysis, plays a key role in the creation of biomaterials with tailored functionalities. These materials, characterized by specific mechanical, chemical, and biological properties, are poised to make impactful contributions in regenerative medicine and biotechnology. As such, this study underscores the immense potential of hyaluronic acid research in advancing innovative solutions to diverse biomedical and cosmetic challenges.

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