

<https://doi.org/10.15407/ujpe71.11.867>

D.A. GAVRYUSHENKO,^{1,2} N.A. ATAMAS,^{1,3} A.N. GRIGORIEV,¹ O.K. MYRONENKO¹

¹ Taras Shevchenko National University of Kyiv

(60, Volodymyrska Str., Kyiv 01033, Ukraine;

e-mails: andgrigoriev@knu.ua, okmyronenko@gmail.com)

² Institute for Safety Problems of Nuclear Power Plants, Nat. Acad. of Sci. of Ukraine

(Lysohirska Str. 12, Kyiv 03028, Ukraine; e-mail: d.a.gavryushenko@knu.ua)

³ BOKU University

(Gregor Mendel Str. 33, Vienna 1180, Austria; e-mail: nataliia.atamas@boku.ac.at)

STRUCTURAL-DYNAMIC BEHAVIOR OF HISTAMINE IN SOLUTION: THE ROLE OF WATER MODELS

A highly dilute aqueous solution of histamine at $T = 300$ K was studied by molecular dynamics using the TIP3P and SPC/E water models. It was shown that the local structure of the solution around histamine is determined by local Coulomb interactions and hydrogen bonds and is practically independent of the choice of the water model. Dynamic analysis based on the mean square displacement functions revealed a significant dependence of the diffusion behavior of histamine on the water model. It was found that the TIP3P water model leads to overestimated values of the diffusion coefficients of water and histamine and a transition to diffusive motion. It was found that the SPC/E water model provides slower dynamics of the solution components, and the values of the diffusion coefficients are in better agreement with experimental data. It was shown that the dynamics of histamine is highly sensitive to the choice of the water model, and the SPC/E model is more suitable for the correct description of the dynamic properties of the “histamine-water” system under physiological conditions.

Keywords: imidazole ligand, SPC/E water model, TIP3P water model, local solution structure, diffusion, histamine.

1. Introduction

Imidazole ligands play a key role in coordination chemistry, biochemistry, and pharmacology due to their ability to participate in proton transfer, hydrogen bond (HB) formation and transition metal ion coordination. The central structural element of such compounds is the imidazole ring, a five-membered heterocycle with two nitrogen atoms, one of which exhibits pronounced σ -donor properties. Imidazole moieties are widely represented in the active centers of enzymes and metalloproteins, where they participate in catalytic processes, electron transfer, and stabilization of protein structures [1, 2]. The high sensitivity

of the imidazole ring to protonation makes such systems particularly dependent on the properties of the aqueous environment. A convenient model molecule for studying the behavior of imidazole ligands in water is histamine ($C_5H_9N_3$), which contains an imidazole ring and a primary amino group. The histamine molecule can exist in several protonated forms. Therefore, the dynamics and conformational equilibrium in solution are largely determined by the structure and dynamics of the hydration shell around histamine dissolved in water. Due to these properties, histamine is widely used to study solvation processes, hydrogen bond dynamics, and diffusion characteristics of small biologically active molecules [3]. At the same time, a correct description of the properties of water is a critically important condition for correct molecular dynamics (MD) modeling of ligand-water systems, since water is a complex associated fluid with a wide range of relaxation time scales. Therefore, even relatively small differences in the parameters of wa-

Citation: Gavryushenko D.A., Atamas N.A., Grigoriev A.N., Myronenko O.K. Structural-dynamic behavior of histamine in solution: the role of water models. *Ukr. J. Phys.* **71**, No. 11, 867 (2026). <https://doi.org/10.15407/ujpe71.11.867>.
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ISSN 2071-0194. *Ukr. J. Phys.* 2026. Vol. 71, No. 11

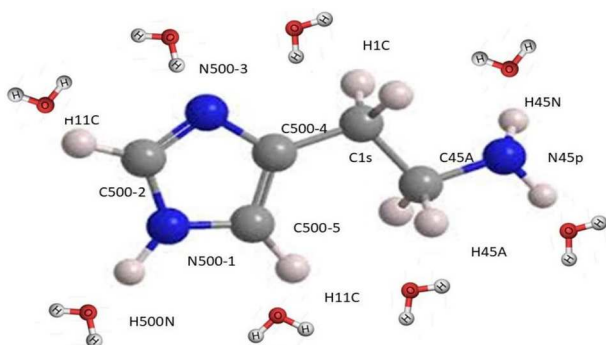


Fig. 1. Model representation of histamine ($C_5H_9N_3$)

ter models can lead to significant discrepancies in the reproduction of density, self-diffusion coefficients, dielectric constants, and HB lifetimes, which is directly reflected in the results obtained regarding the structural-dynamic behavior of the ligands dissolved in it. Among the classical rigid water models that are widely used in biomolecular MD calculations, a special place is occupied by the three-point models TIP3P and SPC/E [4]. Despite the formal structural similarity, these models differ significantly in their reproduction of the experimental thermodynamic and dynamic properties of water at the physiologically relevant temperature $T \approx 300$ K. Modern studies show that the choice of the water model directly affects the dynamic properties of ligands in solution [5]. The temperature $T = 300$ K is physiologically relevant and optimal for analyzing the differences between water models [6], since it is in this range that the most pronounced differences in the dynamics of the HB networks and the transport properties of the solvent are detected [7]. For histamine, which plays an important role in immune reactions, neurotransmission, and regulation of vascular tone, a correct description of the dynamics of hydration at this temperature is of great importance for understanding its functional activity. Despite the availability of data on the static hydration structure of histamine, the dynamic characteristics of the histamine-water system remain poorly understood, especially in the context of a systematic comparison of different water models. In this context, the study of a dilute histamine solution at $T = 300$ K using the TIP3P and SPC/E models allows us to isolate the influence of the microscopic properties of the solvent and assess how the choice of the water model affects the dynamics of the imidazole ligand.

2. Research Methodology

The molecular dynamics method for studying the structural and dynamic properties of water-histamine systems was implemented using the DL_POLY_4.06 [8] and DL_FIELD [9] software packages. The DL_FIELD package was used to generate the parameters and charges of the histamine molecule, which was described using OPLS force field parameters in this study (Fig. 1). Interactions between water molecules were modeled using the SPC/E or TIP3P potential. All calculations were performed with a time step of 2 fs for systems consisting of one histamine molecule and ~ 887 water molecules at a temperature of $T = 300$ K. The following molecular dynamics calculations were performed using the DL_POLY_4.06 software package in a cubic cell with periodic boundary conditions. The cell volume was calculated based on experimental data on the density of water at $T = 300$ K. The initial configuration of the studied water-histamine systems was equilibrated in the NVE ensemble for 1.5×10^6 steps, after which the final structure was used for further equilibration and calculations in the NVT ensemble with a Berendsen thermostat for 2.0×10^6 steps. Short-range Coulomb interactions were taken into account by assigning charges to each atom in the molecule, and long-range electrostatic interactions were taken into account by Ewald summation.

In the studied systems, intermolecular interactions in the system were described as the sum of Lennard-Jones and Coulomb interactions [10]:

$$U = U_{L-J} + U_{Coulomb} = \sum_{i,j} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \sum_{i,j} \frac{q_i q_j}{r_{ij}}, \quad (1)$$

where the parameters σ_{ij} and ϵ_{ij} correspond to the Lennard-Jones potential, which describes the interactions between atoms i and j in the molecule, r_{ij} is the distance between them, and q_i and q_j are the charges of the atoms, respectively. The interaction parameters between the atoms of the histamine molecule and water were calculated using the Lorentz-Berthelot rule.

3. Results and Discussion

3.1. Local structure of the water-histamine system

To understand intermolecular interactions in biologically significant systems, such as the water-histamine

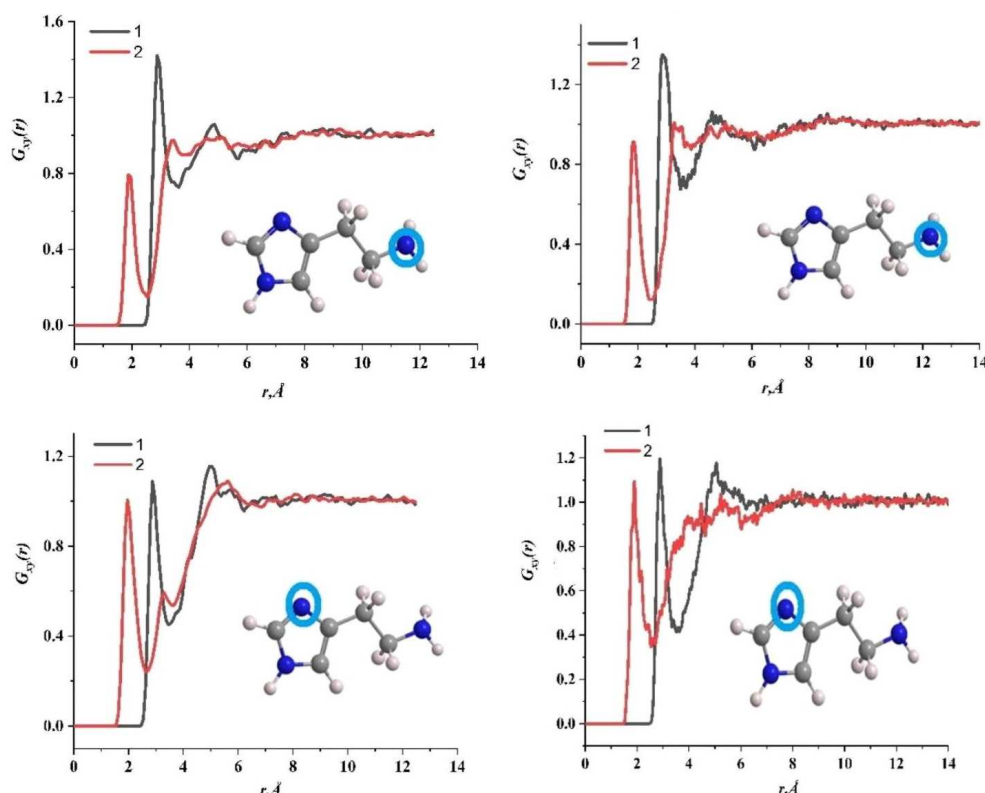


Fig. 2. $G_{XY}(r)$ RDFs for water-histamine systems at $T = 300$ K, in which water is represented by the TIP3P (left column) and SPC/E (right column) models: upper panel: N45p...O^W (1), N45p...H^W (2); lower panel: N500-3...O^W (1), N500-3...H^W (2)

system, it is important to assess not only the influence of the solute (histamine) on the formation of the local structure of the solution, but also the role of the chosen water model used in the simulation. For this purpose, the SPC/E and TIP3P water models were used to study the structural features of the water-histamine system at a temperature of $T = 300$ K. In addition, special attention was paid to determining the influence of the choice of the water model on the specificity of the interaction of water molecules with the atoms of the imidazole ring of histamine. Structural analysis of the solutions was carried out based on the analysis of radial distribution functions (RDFs), which allow quantitative determination of the structural parameters of solutions (distances between water molecules, distances between water and histamine molecules, the size of the free space between them, and the probability and characteristics of HBs between histamine and water). In general, the RDF $G_{XY}(r)$ gives the probability of finding particles of type y near particles of type x and can be calculated using the following

equation [10]:

$$G_{XY}(r) = \frac{\langle N_y(r, r + dr) \rangle}{4\pi\rho_y r^2 dr}.$$

In this equation, the numerator describes the average number of particles y in the spherical layer $(r, r + dr)$, and the denominator normalizes the distribution such that $G_{XY}(r) = 1$ when $N_y = \rho_y$, where ρ_y is the density of the system.

Fig. 2 shows the RDF for water-histamine systems, in which water is represented by TIP3P (left column) and SPC/E (right column) models. The RDF (Fig. 2) shows that water molecules can be located at a distance of ~ 3.0 Å from the N45p atom due to the Coulomb interaction between the N45p atom and the H^W hydrogen of the water molecule. In addition, due to the Coulomb interaction between the N45p nitrogen atom and the O^W oxygen atom of the water molecule, water molecules are also observed at a distance of ~ 2.8 Å in the vicinity of the NH₂ group, which leads to a change in the local structure of water in the NH₂ group region. According to the

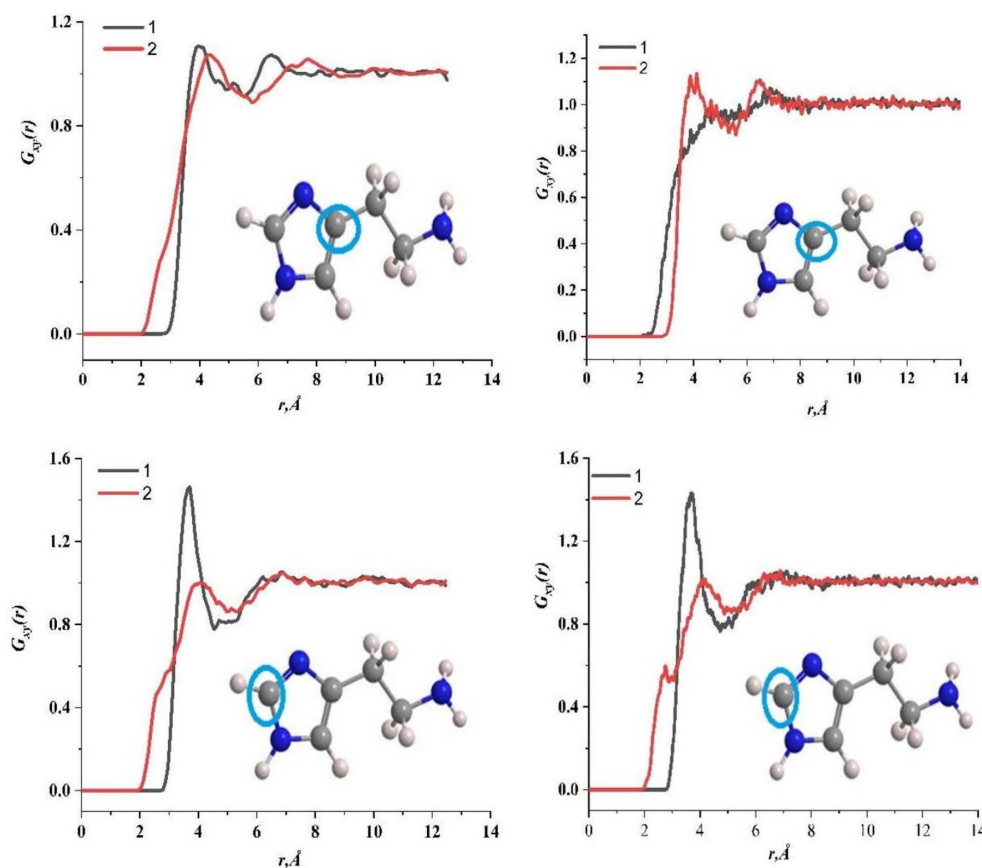


Fig. 3. $G_{XY}(r)$ RDFs for water-histamine systems at $T = 300$ K, in which water is represented by the TIP3P (left column) and SPC/E (right column) models: upper panel: C1s...O^W (1), C1s...H^W (2); lower panel: C500-2...O^W (1), C500-2...H^W (2)

RDFs (Fig. 2), the well-defined first RDF minimum for the N500-3...O^W and N500-3...H^W interactions indicates the formation of the first hydration shell with a size of up to ~ 2.7 Å. The size of the second hydration shell in the region of the N500-3 atom of the imidazole ring is ~ 4.5 Å. In addition, the RDF shows that in the region of the N500-1 atom of the imidazole ring, water molecules can be located at distance ranging from ~ 3.9 to ~ 4.8 Å. The RDF analysis allows us to establish that several hydration shells are formed in the vicinity of the N500-1 atom, and the radius of the first hydration sphere in the vicinity of this atom is ~ 5.7 Å.

The RDF analysis (Fig. 3) shows that due to the interactions between the C1s, C5002, C500-4, C500-5, and C45 atoms and the atoms of water molecules, water molecules can be located in the vicinity of the carbon atoms at a distance ranging from ~ 3.8 Å (in the case of the C500-2 atom) to ~ 4.0 Å (in the case of the C1s atom). Moreover, the first hydration shells

with a size of ~ 4.8 Å are formed around the C500-2 and C1s atoms of histamine. The second hydration shell around these atoms reaches ~ 8.0 Å.

It should be noted that the RDF (Fig. 3) shows that the choice of a model representation for describing the interactions between water and histamine molecules does not affect the size of the free space between histamine and water atoms, which is ~ 4.0 Å in the vicinity of the carbon atoms of the histamine molecule. The RDF (Fig. 4) shows that due to the interaction between the hydrogen atoms of the NH₂ group of histamine and the oxygen atoms of water molecules, HBs with lengths of ~ 2.0 Å and ~ 3.2 Å can be formed. In turn, interactions involving hydrogen atoms bound to the carbon atoms of the imidazole ring lead, with a relatively low probability (~ 0.8), to the formation of HBs without the formation of clearly defined hydration shells in their vicinity. Due to interactions involving the H45A atom, the CH₂ groups can form HBs with a relatively low probability (~ 0.8),

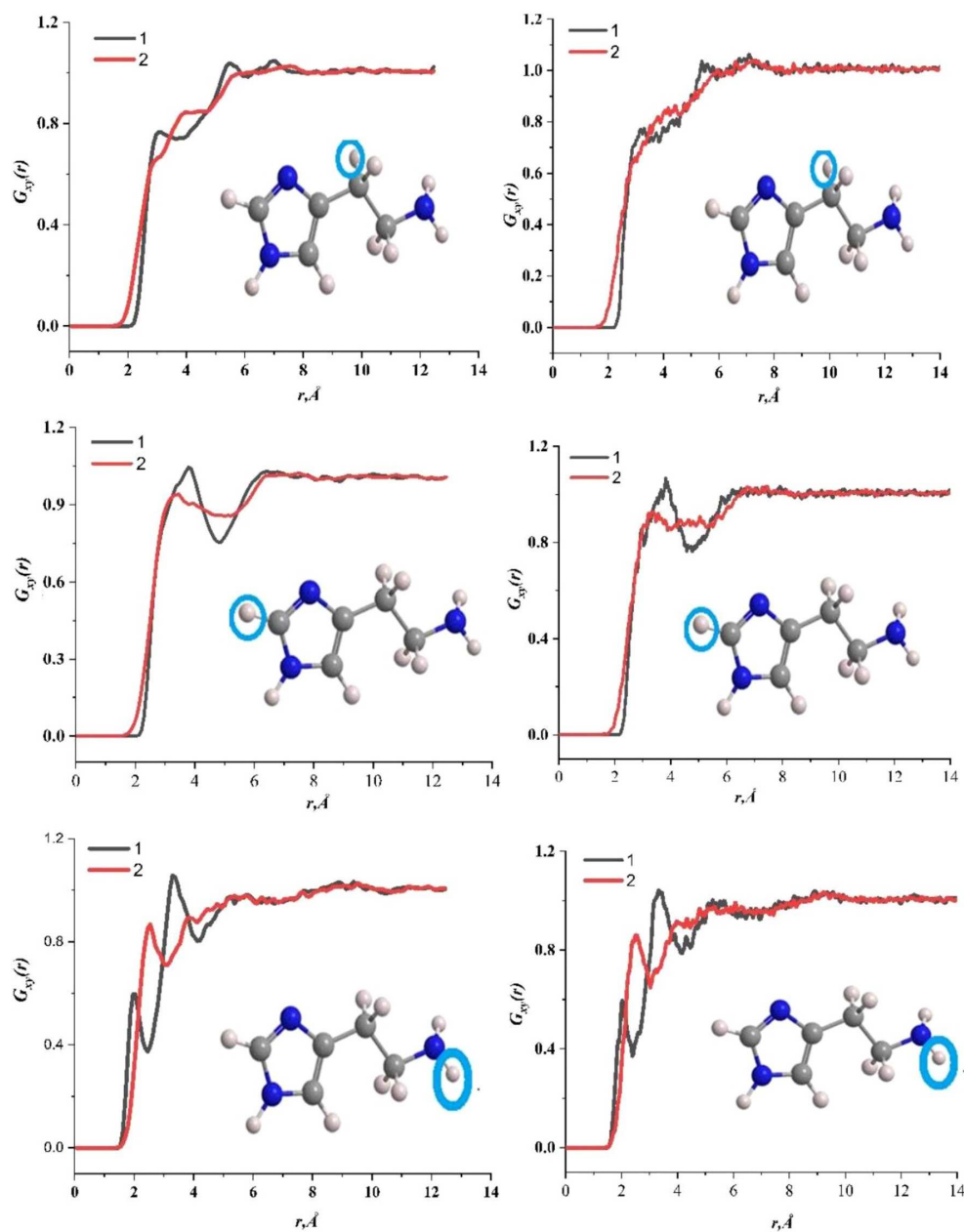


Fig. 4. $G_{XY}(r)$ RDFs for water-histamine systems at $T = 300$ K, in which water is represented by the TIP3P (left column) and SPC/E (right column) models: upper panel: H1C...O^W (1), H1C...H^W (2); middle panel: H11C...O^W (1), H11C...H^W (2); lower panel: H45N-2...O^W (1), H45N...H^W (2)

which also affects the processes underlying the formation of the local structure of the solution. In addition, the RDF (Fig. 4) indicates the possibility of the formation of an HB with a length of ~ 2.0 Å due to the interaction of a hydrogen atom bound to the nitrogen atom of the imidazole ring with the oxygen atom of the water molecule. Moreover, in the region of this hydrogen atom, a clearly defined first hydration shell

(with a size of ~ 2.8 Å) and a second hydration sphere (with a size of ~ 6.5 Å) are observed, which indicates a change in the local density of water.

The analysis of the RDF (Fig. 2, 3, 4) shows that the choice of model representation for describing the interactions between water and histamine molecules does not affect the positions of the maxima, probabilities and shape of the RDF [11]. This indicates

that the key structural characteristics of the first solvation shells remain stable regardless of the water model. Thus, in the molecular dynamics trajectories of water-histamine interactions, the first solvation shells, determined by the positions of the RDF maxima around the nitrogen atoms, are at comparable distances in both the TIP3P and SPC/E simulations. This is consistent with the general conclusion that different three-point water models under the same thermodynamic conditions reproduce similar positions of the first $G_{XY}(r)$ maxima, although the peak height and structuring outside the first shell may differ slightly due to the difference in the parameterization of the potentials, which is well illustrated by the example of pure water for TIP3P and SPC/E [4]. The RDF (Fig. 2) demonstrates that the distribution of water around the nitrogen atoms of histamine (e.g., N45p, N500-1, N500-3) forms clear first peaks at characteristic distances reflecting the first solvation shell, which correlates with the conclusions of the work [12]. That is, water molecules are located at close distances to the key functional groups of histamine, and the differences between the models are manifested by slight changes in the shape and RDF values for the first maxima, but not in their positions, which correlates with the conclusions of the work [13]. Such a stable nature of the RDF reflects the fundamental physicochemical principles of solvation: the local density of water around a dissolved organic molecule is determined primarily by its geometry and intermolecular distances in the liquid, and not by the subtleties of a specific parameterization of the three-point water model [14]. Taken together, the data obtained indicate that the choice of model representation (TIP3P or SPC/E) for describing water interactions with histamine has a negligible effect on the positions of the maxima, probabilities, and shape of the RDF, which is important when comparing the structural characteristics of different force fields in molecular dynamics.

3.2. Dynamics of the water-histamine system

It was previously established that the use of TIP3P in modeling the properties of solutions can lead to overestimated diffusion coefficients in the systems under study and underestimated lifetimes of solute-water hydrogen bonds [15]. The effect of the choice of water

model representation on the dynamics of the components of the histamine-water solution at infinite dilution at $T = 300$ K can be studied qualitatively by analyzing the mean square displacement (MSD) function. This function describes the displacement of the center of mass of the i -th molecule over the time interval from 0 to t and is determined by the following relation [4]:

$$\langle r^2(t) \rangle = \frac{1}{N} \left\langle \sum_{i=1}^N |\Delta r_i(t)|^2 \right\rangle.$$

The study of the values of the parameter α (Fig. 5) in the logarithmic dependence

$$\log \langle r^2(t) \rangle \sim a \log(t)$$

makes it possible to qualitatively distinguish time intervals in which the nature of the motion of the system components changes. Such changes are associated with the restructuring of the local structure of the solution and changes in diffusion mechanisms. In addition, given that the histamine-water system can be considered as a mixture of large (histamine) and small (water) particles with a mass ratio $\alpha = \frac{M_{\text{histamine}}}{M_{\text{water}}} > 1$, the structural rearrangement in the histamine-water solution, according to the conclusions of [16], is determined by the processes of short-term relaxation and diffusion at short times. Therefore, it is advisable to choose a short time scale ($t < 1000$ ps) for analysis when studying the dynamics of the solution components and the influence of the choice of the water model on the dynamics of the studied system.

Fig. 5 presents the functions $\langle r^2(t) \rangle$ for water (top panel) described by the SPC/E and TIP3P models. At times less than 200 ps, the values of $\langle r^2(t) \rangle$ for water in the different models coincide. At times greater than 200 ps, the values of the function $\langle r^2(t) \rangle$ for water described by the SPC/E model exceed the values of the function $\langle r^2(t) \rangle$ for water described by the TIP3P model. However, the behavior of the $\log \langle r^2(t) \rangle$ function for water in both the SPC/E and TIP3P models indicates that the water diffusion mechanisms coincide over the same time intervals.

Namely, at short times, water exhibits slow subdiffusive motion, which becomes nearly diffusive at relatively long times. In turn, the behavior of the function $\langle r^2(t) \rangle$ for a histamine molecule in water with different water models correlates with the behavior

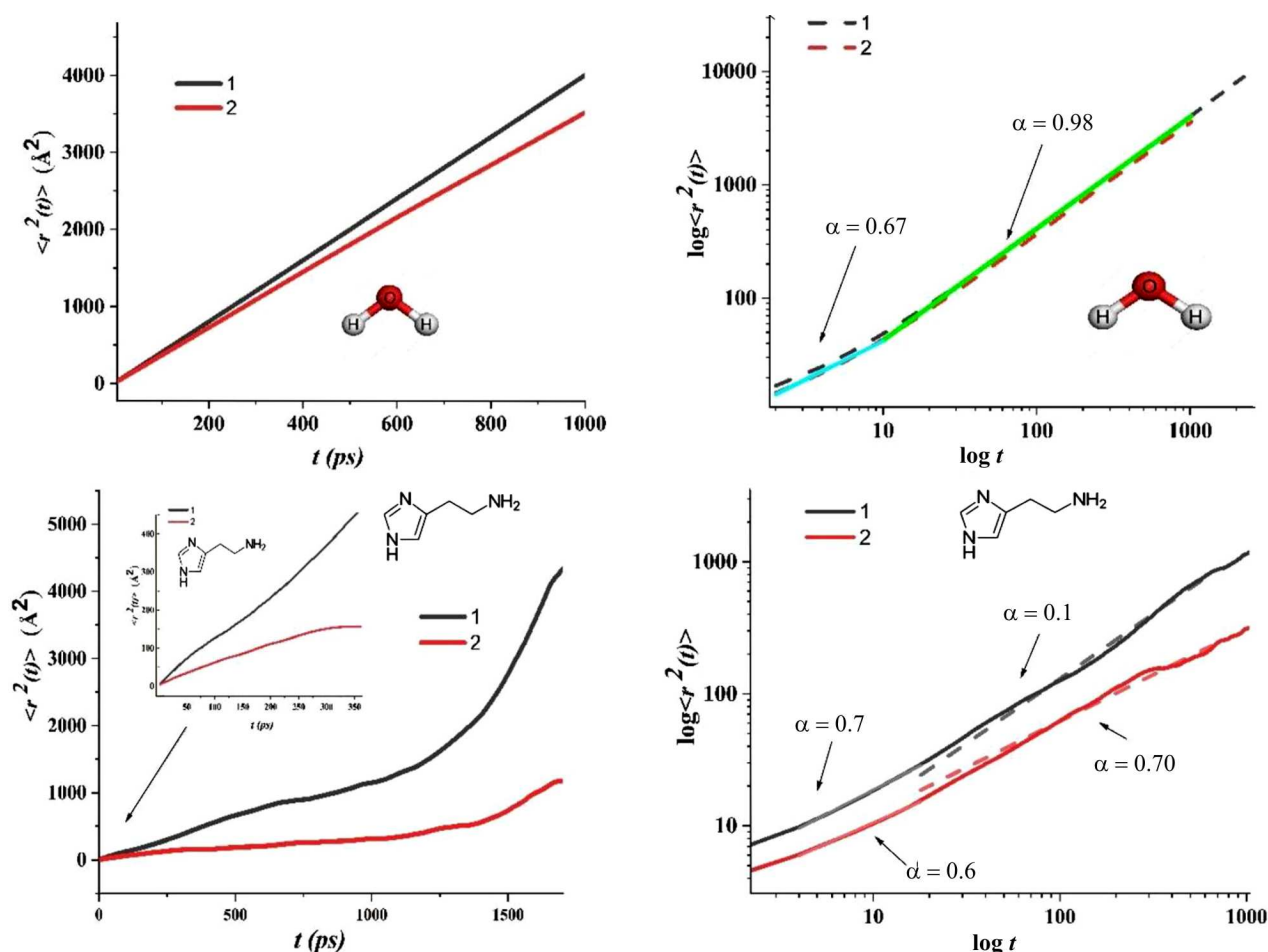


Fig. 5. Time dependence of the functions $\langle r^2(t) \rangle$ (a) and $\log \langle r^2(t) \rangle$ (b) for the centers of mass of a water molecule (upper panel) and a histamine molecule (lower panel) in the histamine-water system (water models: SPC/E (1), TIP3P (2)) at $T = 300$ K

of the corresponding $\langle r^2(t) \rangle$ functions for water. Namely, for a histamine molecule in water modeled using TIP3P, the function $\langle r^2(t) \rangle$ grows much faster than the corresponding function for histamine in water modeled using SPC/E. At time intervals of less than 200 ps, histamine motion in the studied systems can be described as slow and subdiffusive. At relatively long times in the histamine-water system modeled using TIP3P, histamine motion changes from a slow subdiffusive regime to a diffusive regime. No changes in the nature of histamine diffusion in the histamine-water system (SPC/E model) are observed. This result is consistent with the conclusions presented in [5, 16], which state that the use of the TIP3P model to describe water leads to larger values of the ligand diffusion coefficients in water, while the use of the

SPC/E model for water allows for a better description of the solvation processes.

This result is confirmed by the calculated self-diffusion coefficients of the components of the studied systems. These coefficients can be obtained using the Green-Kubo relation based on integration of the velocity autocorrelation function (VAF) [10]. The VAF is defined in terms of the velocity $\mathbf{V}(t) = \mathbf{p}/m$ of a tracked particle (a water or histamine molecule) moving through the liquid in the x direction:

$$Z(t) = \frac{1}{3} \langle \mathbf{V}(0) \mathbf{V}(t) \rangle = \langle V_x(0) V_x(t) \rangle,$$

where $\mathbf{V}(0)$ is the component of the particle velocity along its initial direction of motion, averaged over the initial conditions. The diffusion coefficients of the

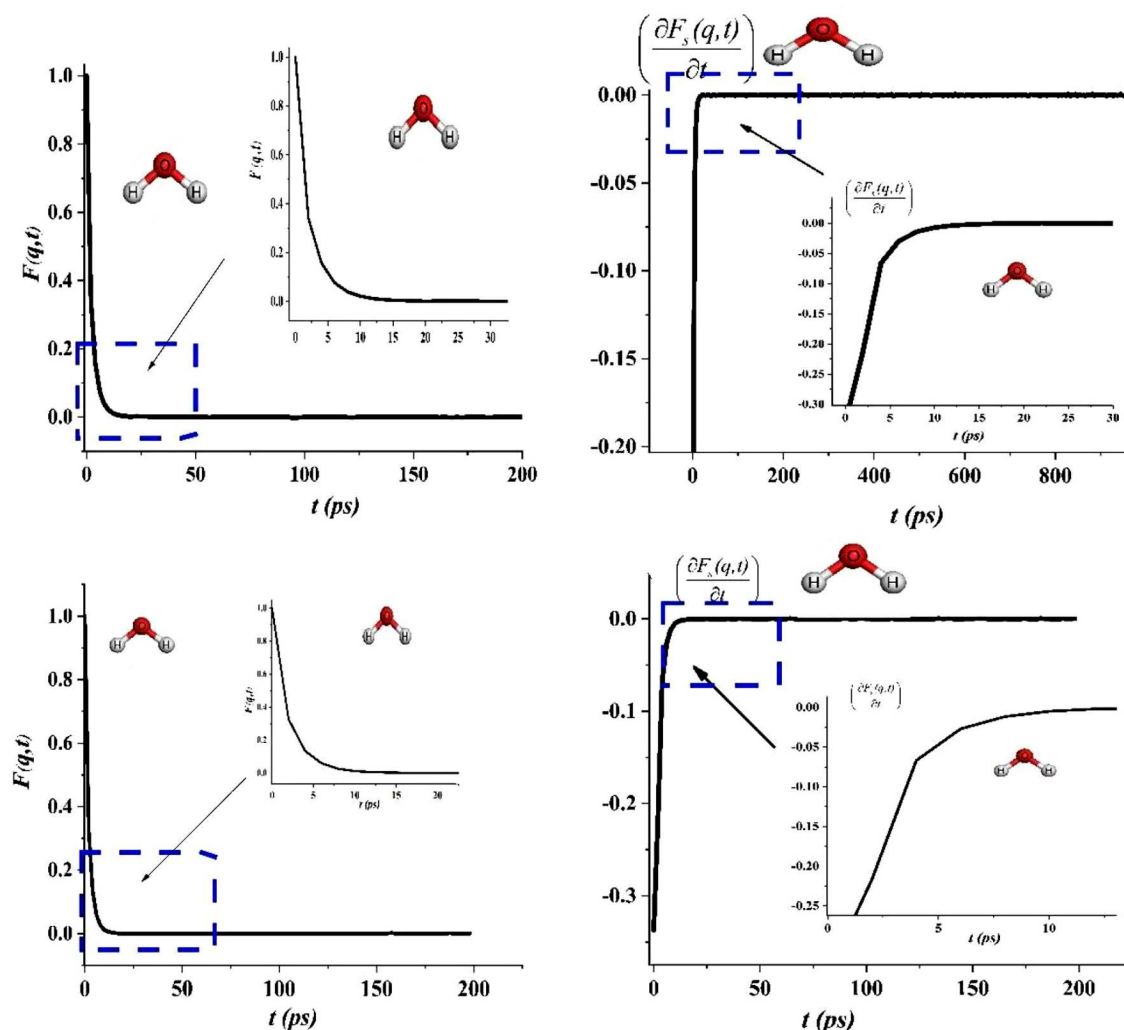


Fig. 6. Time dependence of the function $F_s(q, t)$ and its time derivative $\left(\frac{\partial F_s(q, t)}{\partial t}\right)$ for the center of mass of a water molecule in the histamine-water system with different water models at $T = 300$ K: TIP3P – upper panel; SPC/E – lower panel

components of the studied water-histamine systems were calculated according to the Green-Kubo relation:

$$D = \frac{1}{3} \int_0^{\infty} \langle V(t)V(0) \rangle dt.$$

The calculated value of the water diffusion coefficient in the histamine-water system (SPC/E model) is $2.85 \times 10^{-9} \text{ m}^2/\text{s}$, which is in relatively good agreement with the experimental value of the water diffusion coefficient [17]. The value of the histamine diffusion coefficient in the histamine-water system

(SPC/E model) is $0.38 \times 10^{-9} \text{ m}^2/\text{s}$. In turn, the value of the water diffusion coefficient in the histamine-water system (TIP3P model) is $5.94 \times 10^{-9} \text{ m}^2/\text{s}$, which significantly exceeds the experimental values of the water diffusion coefficient. The value of the histamine diffusion coefficient in this system is $4.61 \times 10^{-9} \text{ m}^2/\text{s}$. It should be noted that, when studying the dynamic behavior of the “water-histamine” system at $T = 300$ K, water at $T < 350$ K [18, 19] can be considered a nearly harmonic system with relatively rare “jumps” of water molecules from one equilibrium position to another [20]. At the same time,

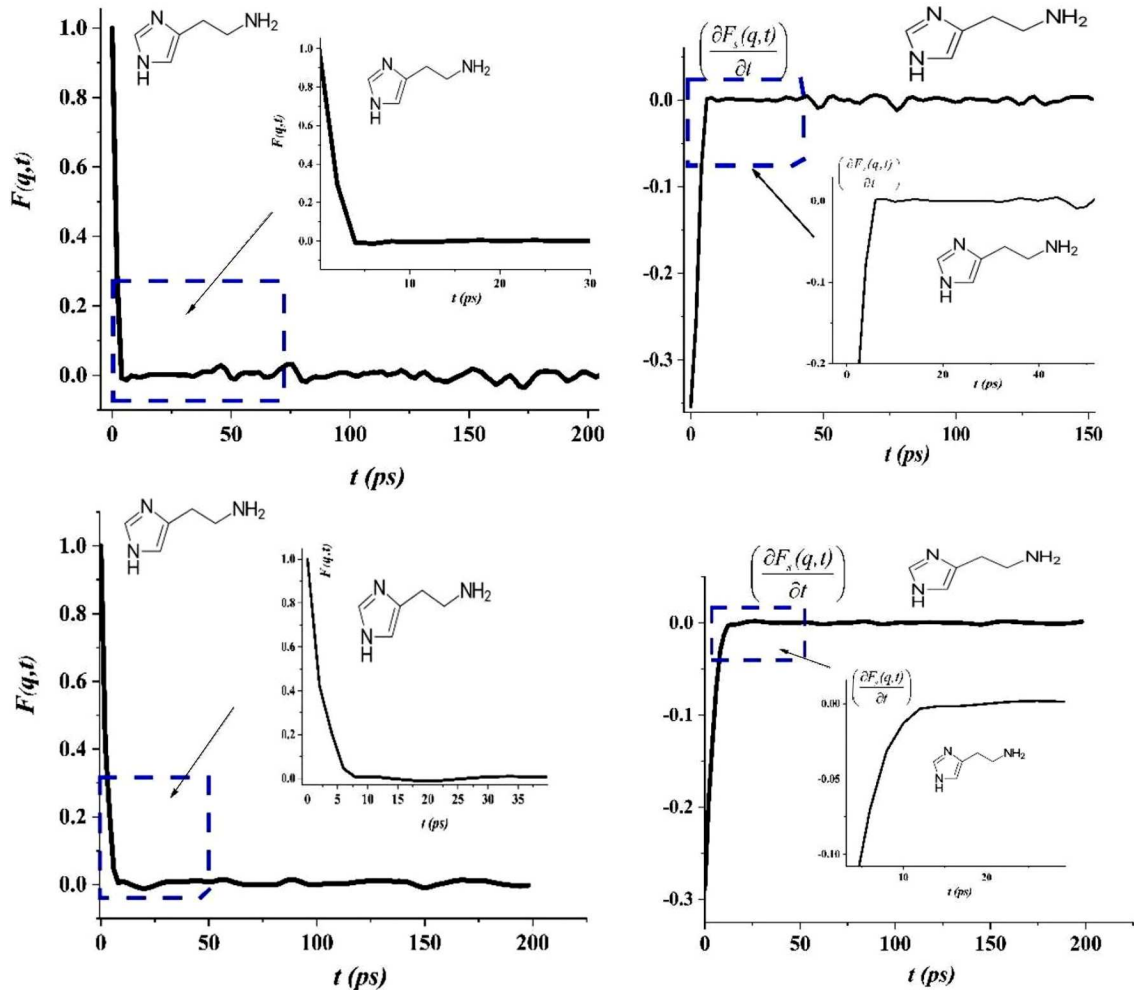


Fig. 7. Time dependence of the function $F_s(q, t)$ and its time derivative $\left(\frac{\partial F_s(q, t)}{\partial t}\right)$ for the center of mass of a histamine molecule in the histamine-water system at $T = 300$ K: TIP3P water model – upper panel; SPC/E water model – lower panel

according to Frenkel [21], the diffusion of components of highly dilute aqueous solutions can be described within the framework of the vibrational-jump diffusion model. Within this model, a particle in an equilibrium position can perform one or two oscillations. The complexity of the description lies in the lack of a clear criterion for separating the purely vibrational and vibrational-jump mechanisms of diffusion of a particle (water or solute) in the case when the particle makes only one or two oscillations between the jumps. This problem can be solved by analyzing the time dependence of the derivative of the correlation scattering function $F_s(q, t)$ [22, 23], which

allows us to determine the values of the corresponding times at which the diffusion mechanisms change in the system. The scattering function $F_s(q, t)$ can be represented as:

$$F_s(q, t) = \frac{1}{N} \sum_{j=1}^N \exp[i\mathbf{q} \times (\mathbf{r}_j(t) - \mathbf{r}_j(0))],$$

where $\mathbf{r}_j$ is the position vector of the j -th particle.

The first inflection point of the graph of $\left(\frac{\partial F_s(q, t)}{\partial t}\right)$ for water in both the TIP3P and SPC/E water models occurs at ~ 5 ps (Fig. 6). The second inflection

point of the function $\left(\frac{\partial F_s(q,t)}{\partial t}\right)$ is observed at ~ 8 ps for water. The first inflection point of the function $\left(\frac{\partial F_s(q,t)}{\partial t}\right)$ for histamine occurs at ~ 10 ps (Fig. 7). The second inflection point of the graph of $\left(\frac{\partial F_s(q,t)}{\partial t}\right)$ for histamine occurs at ~ 15 ps. At times less than ~ 3 ps, the functions $\left(\frac{\partial F_s(q,t)}{\partial t}\right)$ for water and histamine coincide. This indicates that at time intervals shorter than ~ 3 ps, the mechanisms of motion of histamine and water are the same. This result indicates that the time intervals over which the diffusion mechanisms change are independent of the choice of water model and are determined by the physical properties of the studied histamine-water system.

4. Conclusions

In this work, the structural characteristics of histamine hydration in a dilute aqueous solution at a temperature of $T = 300$ K were studied by molecular dynamics using two common three-point water models – TIP3P and SPC/E. Analysis of radial distribution functions allowed us to characterize in detail the spatial organization of water molecules around the key atoms of histamine, in particular the nitrogen atoms of the imidazole ring and the primary amino group, as well as the carbon atoms of the molecule. The work shows that histamine hydration has a well-defined shell structure. Stable first hydration shells with characteristic radii of ~ 2.7 – 3.0 Å are formed around the nitrogen atoms. The existence of a second and, in some cases, several hydration shells was established for the atoms of the imidazole ring, which indicates a complex solvation structure. Around the carbon atoms of histamine, the first hydration shells are more diffuse and localized at larger distances (~ 3.8 – 4.8 Å), which corresponds to a weaker specific interaction with water. The key result of the work is the finding that the choice of the water model (TIP3P or SPC/E) has practically no effect on the positions of the first RDF maxima, the corresponding shell radii, and the general topology of the first solvation shells of histamine. This indicates that the main structural characteristics of hydration are determined by the geometry and chemical nature of the histamine molecule, and not by the details of the parameterization of a specific three-point water model. The results obtained demonstrate the structural stability of the histamine hydration shell with

respect to the choice of the water model and confirm the validity of using both TIP3P and SPC/E to analyze the structural properties of systems containing an imidazole ligand and water. The dynamics of the system is described within the framework of the oscillatory-jump diffusion model: at short time intervals, the motions of water and histamine both exhibit subdiffusive oscillatory behavior. It is shown that the transition to nearly diffusive motion at relatively long times is observed only when the TIP3P water model is used, while in the system simulated using SPC/E, the motion of the components remains subdiffusive throughout the entire studied time range. Such a change in the nature of diffusion when the TIP3P water model is used may explain the overestimated diffusion coefficients obtained when modeling aqueous ligand solutions. The SPC/E model, on the contrary, provides stronger solvation and a physically correct description of diffusive mobility, consistent with experimental data.

N. Atamas acknowledges the support of the BOKU University (Vienna, Austria) financed through the MSCA4Ukraine project, funded by the European Union.

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Received 29.12.25

Д.А. Гаврюшенко, Н. Атамась,
А.М. Григор'єв, О.К. Мироненко

СТРУКТУРНО-ДИНАМІЧНА ПОВЕДІНКА ГІСТАМІНУ У РОЗЧИНІ: РІЛЬ МОДЕЛЕЙ ВОДИ

Методом молекулярної динаміки досліджено сильно розбавлений водний розчин гістаміну за температури $T = 300$ К із використанням моделей води TIP3P і SPC/E. Показано, що локальна структура розчину навколо гістаміну визначається локальною кулонівською взаємодією та водневими зв'язками й практично не залежить від вибору моделі води. Динамічний аналіз на основі функцій середньоквадратичного зміщення виявив істотну залежність дифузійної поведінки гістаміну від моделі води. Встановлено, що модель води TIP3P дає дещо завищені значення коефіцієнтів дифузії води й гістаміну, а також зумовлює перехід до дифузійного режиму руху. Виявлено, що в моделі води SPC/E отримуємо повільнішу динаміку компонентів розчину, а значення коефіцієнтів дифузії краще узгоджуються з експериментальними даними. Показано, що динаміка гістаміну є високочутливою до вибору моделі води, причому модель SPC/E коректніше описує динамічні властивості системи "гістамін-вода" за фізіологічних умов.

Ключові слова: імідазольний ліганд, SPC/E модель води, TIP3P модель води, локальна структура розчину, дифузія, гістамін.