O‘ZBEKISTON MILLIY UNIVERSITETI XABARLARI, 2025, [3/1]
ISSN 2181-7324

FIZIKA
http://journals.nuu.uz
Natural sciences

UDC: 535.012

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EXPLORING MOLECULAR INTERACTIONS BETWEEN SERINE AND ACETIC ACID

Annotation

The intermolecular interactions between serine and acetic acid were investigated using Density Functional Theory (DFT) method. The study focused on solute–solvent interactions, hydrogen bonding, and noncovalent interactions using frontier molecular orbital (FMO), vibrational spectroscopy, atoms in molecules (AIM), and Noncovalent Interaction-Reduced Density Gradient (NCI-RDG) analyses. The results revealed the formation of O-H...O, N-H...O, and C-H...O hydrogen bonds between serine and acetic acid. AIM and NCI-RDG analyses confirmed the presence of noncovalent interactions, while vibrational spectra provided insight into the structural changes caused by these interactions. This work provides a comprehensive understanding of the molecular interactions between serine and acetic acid, which are related to biochemical processes and solvent effects in amino acids.

Key words: serine, acetic acid, DFT, hydrogen bonding.

ИЗУЧЕНИЕ МОЛЕКУЛЯРНЫХ ВЗАИМОДЕЙСТВИЙ МЕЖДУ СЕРИНОМ И УКСУСНОЙ КИСЛОТОЙ

Аннотация

Межмолекулярные взаимодействия между серином и уксусной кислотой были исследованы с использованием метода теории функционала плотности (ТФП). Исследование было сосредоточено на взаимодействиях растворенного вещества и растворителя, водородных связях и нековалентных взаимодействиях с использованием анализа пограничных молекулярных орбиталей (ПМО), колебательной спектроскопии, атомов в молекулах (AIM) и нековалентного взаимодействия с приведенным градиентом плотности (NCI-RDG). Результаты показали образование водородных связей O-H...O, N-H...O и C-H...O между серином и уксусной кислотой. Анализы AIM и NCI-RDG подтвердили наличие нековалентных взаимодействий, в то время как колебательные спектры дали представление о структурных изменениях, вызванных этими взаимодействиями. Это исследование дает всестороннее понимание молекулярных взаимодействий между серином и уксусной кислотой, которые связаны с биохимическими процессами и эффектами растворителя в аминокислотах.

Ключевые слова: серин, уксусная кислота, DFT, водородные связи.

SERIN VA SIRKA KISLOTASI O‘RTASIDAGI MOLEKULALARARO TA’SIRLARNI O‘RGANISH

Annotatsiya

Serin va sirka kislotasi o‘rtasidagi molekulalararo o‘zaro ta’sir Zichlik funksional nazariyasi (DFT) usuli yordamida tekshirildi. Tadqiqot chegaraviy molekulyar orbitallar (FMO), tebranish spektroskopiyasi, molekulalardagi atomlar (AIM) va nokovalent o‘zaro ta’sirlar – pasaytirilgan zichlik gradienti (NCI-RDG) tahlillari yordamida eruvchi va erituvchi o‘zaro tasiri, vodorod bog‘lanish va nokovalent o‘zaro ta’sirlarni o‘rganishga qaratilgan. Natijalar serin va sirka kislotasi o‘rtasida O-H...O, N-H...O va C-H...O kabi vodorod bog‘lanishlarning shakllanishini aniqladi. AIM va NCI-RDG tahlillari nokovalent ta’sirlarning mavjudligini tasdiqladi, tebranish spektrlari esa ushbu o‘zaro ta’sirlar natijasida yuzaga kelgan tarkibiy o‘zgarishlar haqida tushuncha berdi. Ushbu tadqiqot aminokislotalarda biokimyoviy jarayonlar va erituvchi ta’siri bilan bog‘liq bo‘lgan serin va sirka kislotasi o‘rtasidagi molekulyar o‘zaro ta’sirlarni har tomonlama tushunish imkonini beradi.

Kalit so‘zlar: serin, sirka kislotasi, DFT, vodorod bog‘lanish.

Introduction. Intermolecular interactions play a crucial role in determining the structure, stability, and function of biomolecules. Among these interactions, hydrogen bonding is particularly significant in biological systems, influencing protein folding, enzyme catalysis, and molecular recognition [1]. Serine, a polar amino acid, is known for its ability to form hydrogen bonds due to its hydroxyl (-OH) and amino ($-NH_2$) functional groups. Acetic acid, a simple carboxylic acid, is a common solvent and a model system for studying hydrogen bonding and solute-solvent interactions [2]. Understanding the interactions between serine and acetic acid is essential for elucidating the behavior of amino acids in acidic environments and their solvation dynamics.

Previous studies have extensively investigated hydrogen bonding in amino acids and carboxylic acids [3-6]. Density Functional Theory (DFT) calculations have been extensively employed to investigate the molecular interactions between amino

acids and solvent molecules, providing insights into structural properties, hydrogen bonding, and vibrational dynamics [7]. Gong et al. [8] conducted a comprehensive DFT study on 1:1 complexes of serine with water, exploring multiple geometries and hydrogen-bonding interactions. Their findings revealed that the polarity of the solvent significantly influences the structures and relative stabilities of different isomers. Ramírez et al. [9] performed a structural and vibrational analysis of serine in aqueous solution using Fourier transform spectroscopy combined with DFT calculations. They confirmed the zwitterionic structure of serine in solution and provided detailed assignments of vibrational bands, enhancing the understanding of solute-solvent interactions. Qun-yan Wu et al [10]. studied the hydrogen-bonded 1:1 complexes formed between formamide and serine molecules using DFT method at various levels. They reported a shift in the vibrational frequency.

Despite the extensive research on hydrogen bonding and solute-solvent interactions, the specific interactions between serine and acetic acid remain underexplored. This study aims to fill this gap by employing a combination of computational methods to analyze the intermolecular interactions between serine and acetic acid. The results will contribute to a deeper understanding of the molecular mechanisms underlying these interactions and their implications in biochemical processes.

Methods

All calculations were performed using Gaussian 09 software [11] at the B3LYP/6-311++G(d,p) level of theory. The molecular geometries of serine and acetic acid were optimized, and frequency calculations were conducted to ensure the absence of imaginary frequencies, confirming the stability of the structures. The topological parameters of the electron density distribution in the most stable structure were obtained using the Multiwfn [12] tool. The results of the NCI-RDG analysis were visualized using the tool VMD [13].

Results and Discussion

Structural and Energetic Properties

Figure 1 shows the optimal geometries of serine, acetic acid, and their 1:1 complexes determined using the B3LYP/6-311++G(d,p) functional set. The optimized geometry of the serine-acetic acid (SA) complex revealed strong hydrogen bonding interactions, primarily involving the hydroxyl, amino, and carboxyl groups. The results demonstrate that serine and acetic acid form strong hydrogen bonds, primarily through the hydroxyl and carboxyl groups. Table 1 presents the energetic parameters of the complexes, such as total energy (E_{tot}), relative energy (ΔE), bond energy (BE), Gibbs energy difference (ΔG), entropy (S), and enthalpy (H). The binding energies of the SA complexes range from 7 to 15.7 kcal/mol, in the following decreasing order: SA1>SA4>SA3>SA5>SA2. The results show that among the SA complexes, the SA1 complex has the highest binding energy. It was found that the Gibbs free energy difference of the SA1 complex is negative ($\Delta G<0$), while the remaining complexes (SA2, SA3, SA4, SA5) have a positive value ($\Delta G>0$). The negative value of the Gibbs free energy difference indicates thermodynamic stability. It was found by calculation that the SA1 complex is the most stable structurally and thermodynamically among the SA complexes.

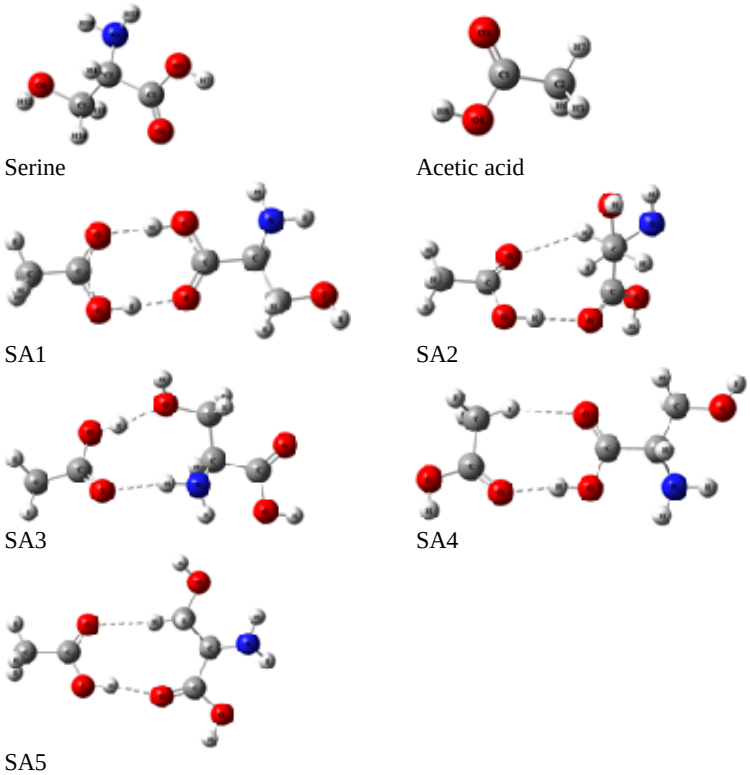


Figure 1. Optimal geometric structures of 1:1 complexes of serine and acetic acid molecules

Table 1. Energetic parameters of 1:1 complexes of serine and acetic acid molecules

Complex	E_{tot}, Hartree	ΔE, kcal/mol	BE, kcal/mol	ΔG, kcal/mol	S, kcal/mol*K	H, Hartree
SA1	-628,282061	0	-15,774	-3,398	119,279	0,190760
SA2	-628,267233	9,305	-6,470	3,823	126,475	0,190859
SA3	-628,270023	7,554	-8,220	2,601	125,028	0,191010
SA4	-628,270833	7,046	-8,729	1,781	125,901	0,190934

SA5	-628,268188	8,705	-7,069	3,319	126,358	0,190956

Frontier Molecular Orbitals (FMO) analysis

Frontier molecular orbitals (FMOs), also known as the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), play an important role in determining the chemical reactivity, biological activity, kinetic stability, electronic and optical properties of molecular complexes [14]. Table 2 lists the HOMO and LUMO energies of serine, acetic acid, and SA complexes, along with the parameters they describe, such as HOMO-LUMO gap (E_g), hardness (η), chemical potential (μ), global electrophilic index (ω), electron affinity (EA), and ionization energy (IE). The HOMO-LUMO gap values for serine and acetic acid molecules were found to be 6.291 and 7.580 eV, respectively. The FMO analysis showed a reduced HOMO-LUMO gap in the SA complexes compared to isolated molecules, suggesting increased stability and reactivity upon complex formation. The greater the HOMO-LUMO gap and hardness, the more stable and less reactive this molecular system is, and according to these values. It was found that the most stable complex is SA1, and the order is as follows: SA1>SA3>SA2>SA5>SA4.

Table 2. Parameters characterizing the reactivity of serine, acetic acid, and SA complexes.

Parameters	Serine	Acetic Acid	SA1	SA2	SA3	SA4	SA5
E_{HOMO} (eV)	-6,956	-8,003	-6,903	-6,904	-6,812	-6,652	-7,019
E_{LUMO} (eV)	-0,665	-0,422	-0,771	-0,815	-0,695	-0,837	-0,948
E_g=E_{HOMO}-E_{LUMO} (eV)	-6,291	-7,580	-6,132	-6,089	-6,117	-5,814	-6,071
η=(E_{HOMO}-E_{LUMO})/2 (eV)	-3,145	-3,790	-3,066	-3,04	-3,058	-2,907	-3,035
μ=-(E_{HOMO}+E_{LUMO})/2 (eV)	3,811	4,212	3,837	3,860	3,754	3,745	3,983
ω=μ^2/2η (eV)	-2,309	-2,341	-2,401	-2,447	-2,303	-2,412	-2,613
IP=-E_{HOMO} (eV)	6,956	8,003	6,903	6,904	6,812	6,652	7,019
EA=-E_{LUMO} (eV)	0,665	0,422	0,771	0,815	0,695	0,837	0,948

Vibrational analysis

Table 3 presents the C=O, O-H and N-H stretching frequencies of serine, acetic acid and SA complexes. The C=O stretching frequencies of serine and acetic acid were found to be 1814 and 1818 cm^{-1}, respectively. The N-H symmetric and asymmetric stretching frequencies of serine were 3514 and 3597 cm^{-1}, respectively. The O-H stretching frequencies of serine and acetic acid were 3759 and 3858 cm^{-1}, respectively. Vibrational analysis revealed red shifts in the stretching frequencies of carbonyl (C=O), hydroxyl (O-H) and amino groups (NH_2), consistent with hydrogen bond formation (Table 3). These spectral shifts provide experimental validation of the computational predictions regarding interaction sites. The vibrational spectra provide evidence of structural changes induced by hydrogen bonding, consistent with previous studies on amino acid-solvent interactions [3].

Table 3. Selected vibrational modes and frequencies of serine, acetic acid, and SA complexes (without scale factor)

Vibrational modes/frequencies (cm^{-1})	Serine	Acetic acid	SA1	SA2	SA3	SA4	SA5
ν(C=O)	1814	1818	1708 1758	1759 1789	1781 1809	1763 1789	1775 1793
ν(O-H)	3759 3858	3759	3858 3235 3121	3856 3750 3500	3860 3760 3441	3859 3751 3428	3858 3752 3559
ν(N-H)	3514 3597	-	3517 3600	3517 3597	3486 3575	3515 3598	3514 3596

AIM and NCI-RDG analyses

Atoms in Molecules (AIM) theory is a useful tool for studying the nature of weak interactions, especially hydrogen bonding, in various molecular systems. According to this theory, the existence of critical bonding points (BCPs) is the key to describing any chemical bond, including hydrogen bonding. The topological parameters of the electron density in the BCPs, such as the density of all electrons ρ(r), the Lagrangian kinetic energy G(r), the Potential energy density V(r), the Energy density H(r), the Laplacian of electron density $\nabla^2\rho(r)$ and the Hydrogen bond energy E_{HB}, characterize the nature and strength of the bond. Table 4 lists some topological parameters of the hydrogen-bonding BCPs of SA complexes. It was found that the electron density and the electron density Laplacian in SA complexes are in the range of hydrogen bonding [15]. A negative value of the energy density (H(r)<0) means that the hydrogen bond is covalent in nature, and a positive value (H(r)>0) means that it is electrostatic in nature. The hydrogen bond energy was calculated using the formula E_{HB}=-V(r)/2. AIM analysis showed that the SA complexes are formed by O-H…O, N-H…O and C-H…O hydrogen bonds. The O-H…O bond energy varies in the range of 6.714-14.150 kcal/mol, with the SA1 complex having the highest binding energy.

Table 4. Topological parameters in BCPs of SA complexes

H-bonds	*r, Å*	*ρ(r)*, a.u.	*G(r)*, a.u.	*V(r)*, a.u.	*H(r)*, a.u.	$\nabla^2\rho(r)$, a.u.	E_{HB}, kcal/mol
SA1							
O18-H22…O6	1.690	0.0448	0.0374	-0.0414	-0.0040	0.1337	12.989
O5-H7…O17	1.666	0.0477	0.0397	-0.0451	-0.0054	0.1370	14.150
SA2							
O18-H22…O6	1.817	0.0304	0.0266	-0.0250	0.0016	0.1125	7.844
C2-H4…O17	2.539	0.0085	0.0057	-0.0049	0.0008	0.0260	1.537
SA3							
O18-H22…O8	1.780	0.0343	0.0302	-0.0298	0.0003	0.1220	9.350
N9-H10…O17	2.168	0.0156	0.0118	-0.0098	0.0019	0.550	3.075
SA4							
O5-H7…O17	1.797	0.0340	0.0294	-0.0290	0.0004	0.1194	9.099
C16-H20…O6	2.903	0.0116	0.0079	-0.0066	0.0013	0.0370	2.071
SA5							
O18-H22…O6	1.851	0.0266	0.0242	-0.0214	0.0028	0.1080	6.714
C1-H14…O17	2.366	0.0115	0.077	-0.0066	0.0011	0.0356	2.071

NCI-RDG is a method used to visualize and estimate the strength of non-covalent interactions based on electron density and its derivatives. This analysis helps to distinguish between hydrogen bonds, van der Waals interactions, and repulsive forces. Figure 5 shows the results of NCI-RDG analyses of SA complexes. Blue areas (sign(λ_2)ρ<0) in the diagrams represent mutual attraction forces (hydrogen bonds, halogen bonds, etc.), green areas (sign(λ_2)ρ≈0) represent van der Waals forces, and red areas (sign(λ_2)ρ>0) represent repulsive forces. The results of NCI-RDG analyses show that hydrogen bonds are dominant in SA complexes.

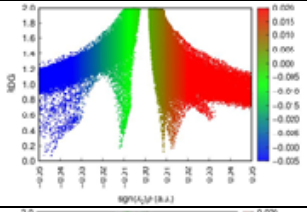
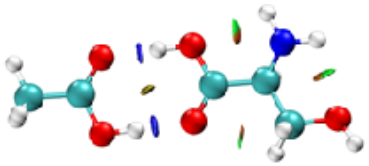
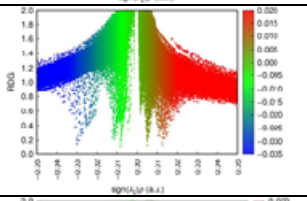
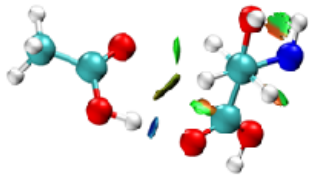
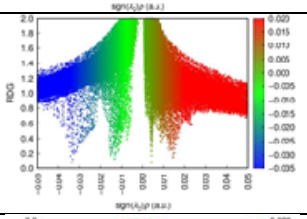
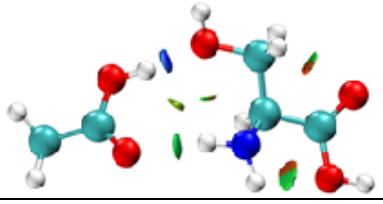
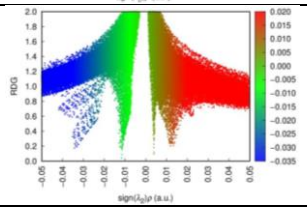
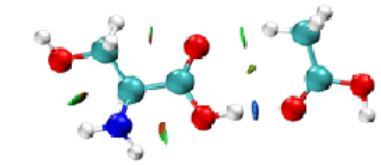
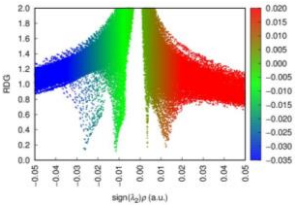
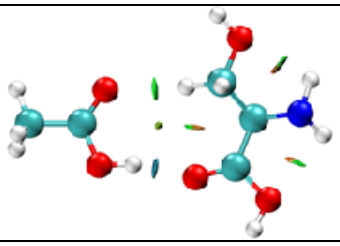
	RDG scatter map	NCI isosurface
SA1		
SA2		
SA3		
SA4		
SA5		

Figure 5. RDG scatter maps and NCI isosurfaces for SA complexes

Conclusion. This study provides a detailed computational analysis of the intermolecular interactions between serine and acetic acid. Using DFT calculations at the B3LYP/6-311++G(d,p) level, key hydrogen bonding and electronic properties were elucidated through MEP, FMO, vibrational, AIM, and NCI-RDG analyses. The results demonstrate significant stabilization effects due to hydrogen bonding, contributing to the broader understanding of solute-solvent interactions in biochemical and pharmaceutical contexts. Future studies may explore these interactions in larger biomolecular systems to further investigate solvation dynamics and their role in biological processes.

REFERENCES

1. Jeffrey, G. A. (1997). An Introduction to Hydrogen Bonding. Oxford University Press.
2. Khushvaktov, K., Jumabaev, A., Pogorelov, V., et al. (2018). *J. Phys. Appl.* 6(6), 169-174.
3. Jumabaev, A., Holikulov, U., Hushvaktov, H., et al. (2023). *J. Mol. Liq.* 377, 121552.
4. Jumabaev, A., Holikulov, U., Hushvaktov, H., et al. (2022). *Ukr. J. Phys*, 67(8), 602.
5. Buemi, G. (2009). *J. Phys. Org. Chem.* 22(10), 933-947.
6. Takei, K. I., Takahashi, R., Noguchi, T. (2008). *J. Phys. Chem. B.*, 112(21), 6725-6731.
7. Becke, A. D. (1993). *J. Chem. Phys.* 98(7), 5648–5652.
8. Gong, X., Zhou, Z., Du, D., Dong, X., Liu, S. (2005). *Int. J. Quantum Chem.* 103(1), 105-112.
9. Ramírez, F. J., Tuñón, I., Silla, E. (2004). *Chem. Phys.* 303(1-2), 85-96.
10. Wu, Q. Y., Zhang, H., Zhou, Z. Y., Lu, J. F., Zhao, G. (2005). *J. Mol. Struct. THEOCHEM 757*(1-3), 9-18.
11. Frisch, M.J., et al. Gaussian 09 (Gaussian, Inc., Wallingford CT, 2009).
12. Lu, T., Chen, F. (2012). J. Comp. Chem. 33(5), 580-592.
13. Humphrey, W., Dalke, A., Schulten, K. (1996) *J. Mol. Graph.* 14, 33-38.
14. Holikulov, U., Kazachenko, A. S., Issaoui, N., et al. (2024). *Spectrochimica acta. Part A* 124600.
15. Tang, T.-H., Deretey, E., Knak Jensen, S.J., Csizmadia I.G. (2006). *Eur. Phys. J. D* 37, 217-222.