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INVESTIGATION OF SOLVATION DYNAMICS AND HYDRATION PATTERN OF SIALIC ACID BY AB INITIO AND DFT METHOD

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ABSTRACT: Sialic acid is the active site of neuraminidase virus and it proliferates the infection in the human body by cleaving it from the neuraminidase viral protein. The buried water molecule influences the binding between the ligand and the receptor. Hence, solvation dynamics and hydration pattern of sialic acid needs to be investigated to design the antiviral inhibitor. Cluster continuum solvation analysis reveals that the hydrated structures of sialate ion are progressive increases as a function of water molecules by explicit solvation method, and this pattern attests the presence of buried water molecules in the hexa hydrated structure. Thus, it confirms the presence of trapped water molecules near the functional site of sialic acid. Hence, it can be considered as a promising candidate for the design of a sialidase antiviral drug.

INTRODUCTION: Water molecule plays a central role in mediating the interaction between ligand and receptor. Hydration of bio-molecular species is of great importance in chemical and biological sciences at the molecular level. The importance of water molecules in protein-ligand interactions has been greatly recognized in the past few years¹. The water molecules stabilize the complex between the protein and ligand by hydrogen bonding, and thereby it attributes to the stability of the overall hydrated structures². The water molecule occupies less space than the polar side chains of protein, and also it forms multiple hydrogen bonds with the substrate to improve the binding affinity.

Since most of the biological process occurs in solution, the solvent effect must also be considered to unravel the hydration pattern and hydrogen bonding fashion of the biomolecules³. Sialic acid has received special attention in solvation dynamics and hydrogen bonding systems because it acts on the action of neuraminidase virus⁴. Hydration of sialic acid is one of the most ubiquitous processes in chemical as well as in biological systems. Hence, hydrogen bonding is most widely studied in a vast area of chemical systems, from simple intermolecular interaction to large bio-molecules⁵. Structure and dynamics study of recent literature of bio-molecules reveals that the presence of interlocked water molecules in the protein receptor interactions substantially increases the binding affinity of substrate⁶ and accounting for a new era in the inhibitor design.

Scientific reports have proved that the water molecule has a unique property, and thus it has a critical impact on the biological activity of DNA, protein, and enzyme catalysis⁷.

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In addition, the hydrogen bond formed by the interlocked water molecules affects the intramolecular proton transfer in a biological process. On account of this, the theoretical study of hydrogen bonding in a biological system is crucial for a deeper understanding of the protein interactions and enzyme activity; this eventually provides a rationalization of the protein structure and catalytic pathway of the enzymatic reaction⁸. In a nutshell, the solvation dynamics and microsolvation pattern provides better insight to develop and design of antiviral inhibitors. Computational chemistry provides a complementary tool to explore the ionic hydrogen bonds in enzymatic reactions and proteins⁹. Hence, explicit solvation analysis of proteins and key biological macromolecules will be useful in predicting the internal binding sites of the protein. The explicit solvation analysis is carried out by forming a hydration shell around the sialic acid by the explicit addition of water molecules.

Computational Methods: Solvation plays a cardinal role in a wide variety of the chemical process, especially in ionic systems. In ionic systems, solvent effects have a considerable influence on the rate and equilibrium of chemical reactions. Therefore, theoretical modeling of liquid-phase chemical reaction must include the solvent effect to predict the feasibility of the reactions. To attain this goal, it is inevitable to develop theoretical methods with the capability of predicting accurate values of solvation free energies. The continuum-based solvation models are very impressive, and its simplicity makes this model very fascinating and used extensively for solvation dynamics computation. Sialic acid structure is obtained from the X-Ray crystallographic database PDB¹⁰ code of MW21, and it is further refined by adding hydrogen atoms using the Gaussian suite of programs. The sialic acid, thus obtained, is used for the electronic structure calculations.

Sialic acid on solvation in the water medium becomes sialate anion due to its inherent ionization of acid group, and hence it referred to as sialate anion hereafter in this study. All the sialate anionic compounds are optimized using RHF/6-31G(d) level of theory and performed single point energy calculations using the B3LP/6-31G(d) level

of theory in the gas phase. The hydrated structures of sialate anionic compounds are formed by adding water molecules in the vicinity of key functional groups and likewise, monohydrated to hepta hydrated structures are formed by adding one water to seven water molecules. Conductor like polarized continuum model¹¹ (CPCM) is employed for solvent energy calculation in the solvent phase and water is employed as the solvent for the solvent phase. The solvation energy and gas-phase binding energy of the substrate and its hydrated structures can be calculated by using the following equation (1), (2), and (3).

$$\Delta E_{(\text{Bind})} = E_{\text{g(Substrate-Ligand Complex)}} - (E_{(\text{substrate})} + n E_{(\text{Ligand})_{\text{g}}}), \quad n=(1-7) \dots\dots(1)$$

$$\Delta G_{\text{solv}}^*(A^{\pm}) = \Delta G_{\text{clust}}^{\circ}(A^{\pm}(S)_n) + \Delta G_{\text{soln}}^*(A^{\pm}(S)_n) + n \Delta G_{\text{vap}}(S) \dots\dots(2)$$

$$\Delta E_{\text{gp}} = [E_{x-n\text{H}_2\text{O}} - E_x - E_{\text{H}_2\text{O}}] \quad n = (1-7) \dots\dots(3)$$

In the above relation, x is the sialate anion substrate selected for this study, and n is the number of addition of water molecules. The hydrated structures are formed by explicit solvation method¹², and the cluster continuum solvation model is employed for explicit solvation studies¹³. Ab initio and DFT calculation of all the hydrated structures have been carried out by using the Gaussian'03 suite of program¹⁴.

RESULTS AND DISCUSSION:

Analysis of Cluster Continuum Solvation Free Energy of Hydrated Structures: The explicit solvation analysis of sialate anion in the absence of hydration shell provides solvation energy of -76.7 kcal/mol with a charge density of 0.528 on C2 carbon and -0.771 on the O16 endocyclic oxygen atom. The structure of sialate anion is shown in **Fig. 1A**. The first water molecule is added in the vicinity of the C4 hydroxyl group of the sialate anion; the added water molecule forms a hydrogen bond with the C4 hydroxyl group and carbonyl oxygen at 2.324Å and 1.926Å. Hence, it acts as a bridge between the C4 hydroxyl group and thus stabilizes the monohydrated structure. Bridging of water molecules in the protein network increases the binding affinity between the substrate and receptor¹⁵. The monohydrated structure of sialate anion provides continuum solvation free energy of -73.5 kcal/mol, and its structure is shown in **Fig. 1**.

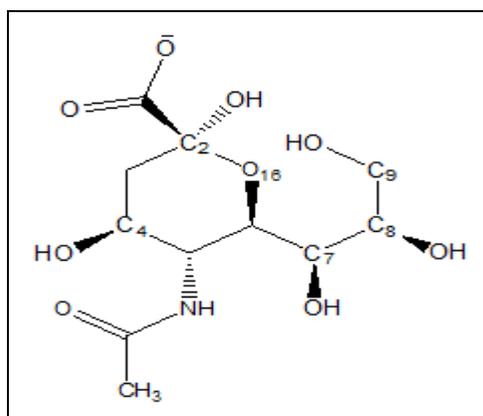


FIG. 1: SIALYATE ANION

The second water molecule is added in the vicinity of the C8 and C9 hydroxyl group of the glycerol side chain. The added water molecule forms two donor hydrogen bonds at 1.766Å and 1.937Å with the neighboring hydroxyl group. The dihydrated structure attains the solvation energy of -70.43 kcal/mol.

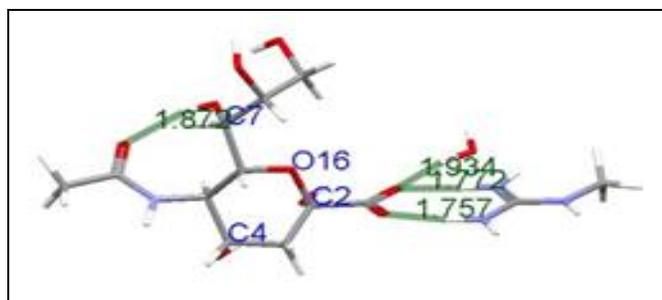


FIG. 1A: SIALYATE-METHYL GUANDINO COMPLEX

The fourth water molecule is added in between the C7 and C9 hydroxyl groups of the glycerol side chain of the sialate anion. The added water molecule forms a hydrogen bridge between two

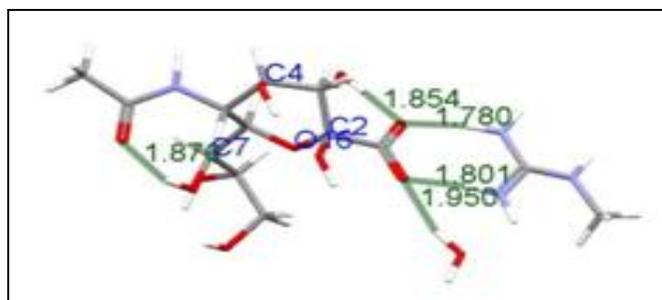


FIG. 1C: DIHYDRATED STRUCTURE

The tetra hydrated explicit structure of sialate anion yields solvation energy of -60.84 kcal/mol, and it clearly signifies that cluster continuum solvation free energy progressively increases as a function of the water molecule and invalidates the specific water molecule binding with the sialic acid. The

The hydration energy of a dihydrated structure is higher than the monohydrated structure, and thus, it signifies that the hydration energy increases with the explicit addition of water molecules¹⁶, and it is shown in **Fig. 1B**.

The third water molecule is added near the carbonyl oxygen of the amide linkage, and the added water molecule forms an acceptor hydrogen bond with oxygen at 1.875Å. **Fig. 1C** shows the hydration of the pattern of trihydrated structure. The trihydrated structure provides the cluster continuum solvation free energy of -63.65 kcal/mol, and it is higher than the continuum solvation free energy of dihydrated structure, and hence it nullifies the presence of water in the vicinity of carbonyl oxygen and favors the bulk interaction in solvation dynamics. Bulk interaction usually decreases the solvation energy due to multiple hydrogen-bonding interactions¹⁷.

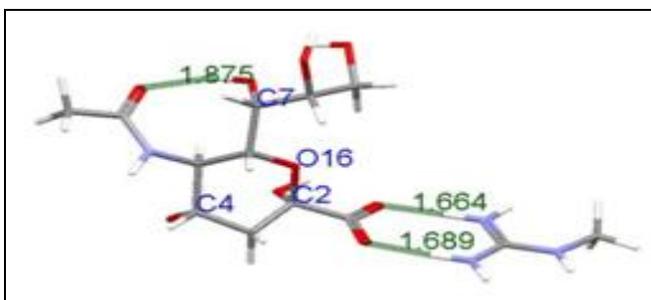


FIG. 1B: MONOHYDRATED STRUCTURE

hydroxyl groups by forming acceptor hydrogen bonds at 2.876Å and 2.046Å, and it is shown in **Fig. 1D**.

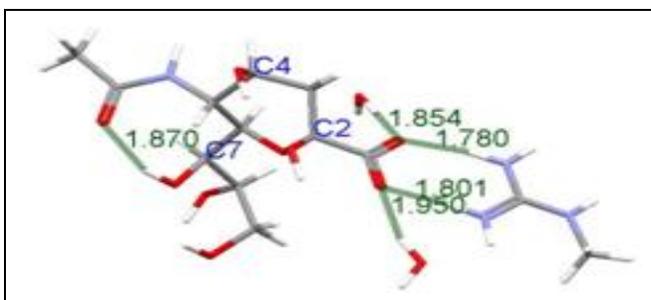


FIG. 1D: TRIHYDRATED STRUCTURE

fifth water molecule is added in the vicinity of carboxylate oxygen, and the added fifth water molecule forms an acceptor hydrogen bond with carboxylate oxygen and donor hydrogen bond with the C2 hydroxyl group, and it is shown in the **Fig. 1F**. The explicit Penta hydrated structure attains

continuum solvation free energy of -64.22 kcal/mol, which is higher than the previous tetra hydrated structure. Therefore, the presence of specific binding of water molecule is perhaps present in the vicinity of carboxylate oxygen on account of strong hydrogen bond and attributes

water-specific interaction¹⁸. Sixth water molecule is added in the vicinity of carboxylate oxygen, and its structure is shown in **Fig. 1G**, and it yields higher cluster continuum solvation energy of -61.46 kcal/mol.

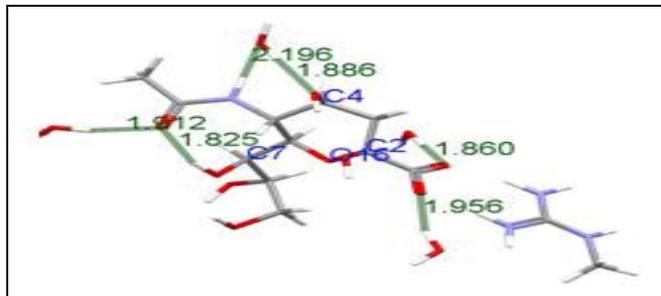


FIG. 1E: TETRA HYDRATED STRUCTURE

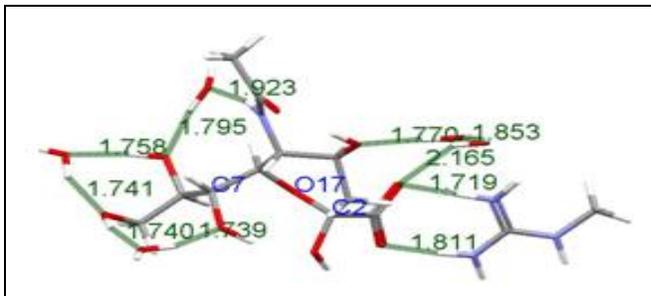


FIG. 1F: PENTA HYDRATED STRUCTURE

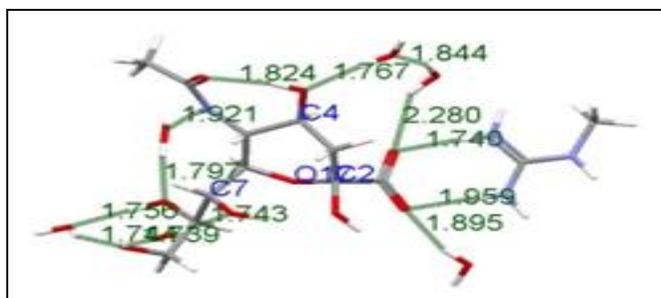


FIG. 1G: HEXA HYDRATED STRUCTURE

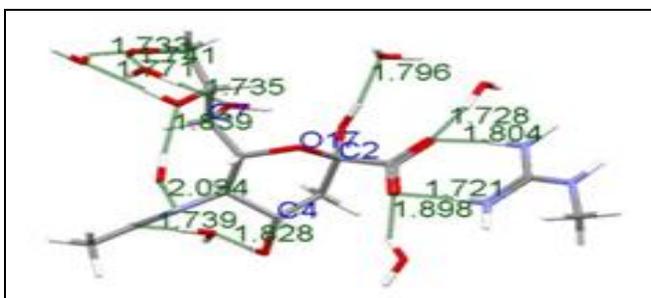


FIG. 1H: HEPTA HYDRATED STRUCTURE

The hexa hydrated structure reveals that the increase in the size of the hydration shell drastically increases the solvation energy. Moreover, the dynamics and bonding of water molecule in hexahydrated structure are strong, and so it attains higher continuum solvation energy, and this validates the presence of water molecule near the functional site of carboxylic acid¹⁹. The final and seventh water molecule is added in the bay space between the C4 hydroxyl group and carboxylate oxygen, and the added seventh water molecule forms hydrogen bridge between C4 hydroxyl and carboxylic group and stabilizes the structures; its structure has been shown in the **Fig. 1H**.

The bridging of water molecules plays a vital role in charge transfer and electrostatic attractions. The hepta hydrated structure provides a continuum solvation energy of -54.79 kcal/mol. It is clear from **Table 1** that the hexa and hepta hydrated structure attain the highest continuum solvation free energy on account of the larger hydration shell and it also due to the hydrogen bonding cooperative effects and electrostatic charge transfer between cooperative hydrated water molecules.

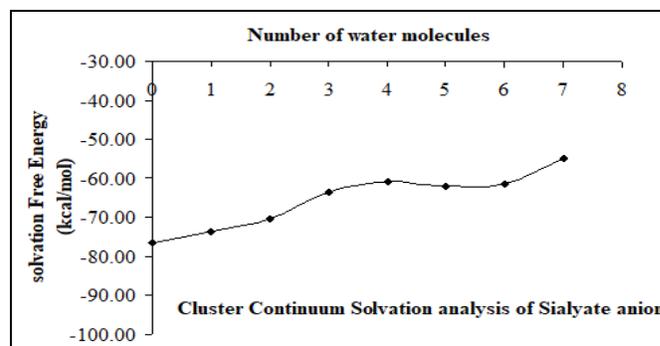


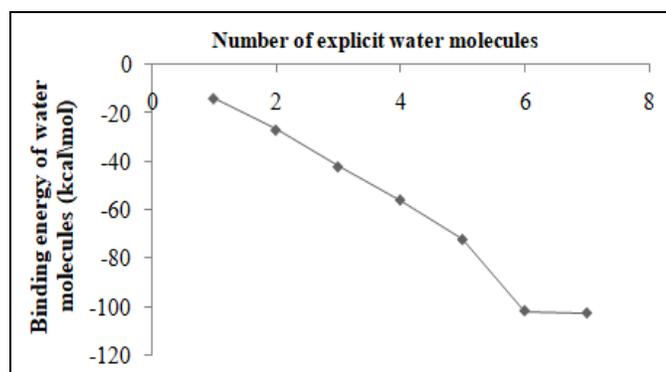
FIG. 2: CONTINUUM SOLVATION FREE ENERGY OF SIALYATE ANION

It further authenticates that the continuum solvation energy progressively increases as a function of explicit water molecules, and this analysis nullifies the presence of specific water molecules in the binding site, perhaps hexa and hepta hydrated structures have entrapped water molecules due to their higher continuum solvation energies and better charge transfer effects. Hence, it can be considered as the potential candidate for the further development of sialidase inhibitors. It is clear from **Fig. 2** that the continuum solvation free energy increases progressively with explicit solvation of water molecules.

TABLE 1: CLUSTER CONTINUUM SOLVAION FREE ENERGY OF SIALYATE ANION AND ITS HYDRATED STRUCTURES

Compounds	Solvation Free Energy HF/ 6-31(g) kcal/mol $\Delta G_{sol}(CC)$	Solvation free energy B3LYP/6-31G(d) (kcal/mol) $\Delta G_{sol}(CC)$	Charge density on O16 atom	Charge density on C12 atom	r(C2-O16) (Å)
N-NANA ⁻	-76.7	-64.13	-0.771	0.528	1.451
N-NANA:1H ₂ O	-73.50	-63.79	-0.770	0.526	1.444
N-NANA:2H ₂ O	-70.43	-62.71	-0.783	0.528	1.433
N-NANA:3H ₂ O	-63.65	-60.74	-0.771	0.525	1.424
N-NANA:4H ₂ O	-60.84	-60.78	-0.761	0.525	1.425
N-NANA:5H ₂ O	-64.22	-62.20	-0.768	0.515	1.442
N-NANA:6H ₂ O	-61.46	-62.65	-0.781	0.553	1.419
N-NANA:7H ₂ O	-54.79	-60.31	-0.771	0.516	1.438

Analysis of Gas-Phase Hydration Energy: The analysis of water-binding energy of hydrated structures is carried to explore the frozen water molecule in the protein network. The monohydrated structure obtains gas-phase water binding energy of -13.98 kcal/mol. It appears that monohydrated structures attain low binding energy. The sialate anion dihydrated structure provides binding energy of -26.97 kcal/mol. It seems that binding energy decreases as a function of water molecules. The trihydrate sialate anion attains binding energy of 42.2 kcal/mol. Invariably all the hydrated structures losses the binding affinity with water molecule on account of the hydrogen bonding cooperative effects. The tetra hydrated structure attains gas-phase water binding energy of -55.88 kcal/mol and attains insignificant affinity due to the poor orientation of water molecules in the hydration shell. Next, the Penta hydrated structure obtains the gas-phase water binding energy of -72.24 kcal/mol and thus lowers binding energy of Penta hydrated structure and which leads to the conclusion that the increase cluster size decreases the binding energy. The hexa hydrated and hepta hydrated structure of sialate anion attains binding energy of -101.7 and 102.64 kcal/mol.

**FIG. 3: BINDING ENERGY AS A FUNCTION OF EXPLICIT WATER MOLECULES**

There is a marginal difference is observed between hexa and hepta hydrated structure, and it implies that the explicit addition of water molecules attains limiting value in gas phase binding energy and it is validated in **Fig. 3**, which clearly depicts that the addition of seventh water molecule has no effect on the binding affinity with sialate anion. Hence, the addition of water molecules beyond hepta hydrated structure is insignificant.

Analysis of Solvation Free Energy of Hydrated Structures of Sialate Anion: The sialate anion provides solvation free energy of -76.7 kcal/mol without hydration sphere. The monohydrated structure of sialate anion provides free solvation energy of -75.72 kcal/mol and it reveals the hydration favors the solvation of sialate anion. The dihydrated structure of sialate anion provides solvation free energy of -75.56 kcal/mol, it appears that the monohydrated and dihydrated structure have the identical solvation free energies due to their stereo orientation effect of water molecule. The trihydrated structure attains solvation free energy of -71.14 kcal/mol. The solvation energy of trihydrated structure is higher than the dihydrated structure, and thereby, it favors the presence of water molecules in the trihydrate functional site. The tetra hydrated structure of sialate anion yields a solvation energy of -69.93 kcal/mol.

So, it clearly conveys the information that increases in addition of explicit water molecule increases the solvation energy. It is due to the hydrogen cooperative effects caused by the multiple hydrogen bonds formed by the water molecules. The Penta hydrated structure yields solvation free energy of -63.71 kcal/mol. The addition of a fifth water molecule increases solvation free energy and thus promotes the solvation dynamics of sialate anion with its hydration shell.

It is clearly shown in **Fig. 4** that the increase in hydration size increases the solvation free energy due to the effective charge transfer between sialate ion functional site and the explicit water molecules and thereby facilitates the biological interaction. The hexa and hepta hydrated structures attains solvation free energy of -49.98 kcal/mol and -54.79 kcal/mol, this data clearly signifies that solvation progressively increases as a function of water molecules.

Especially, hexa hydrated structure attains high solvation energy. The solvation dynamics of hexa hydrated structure has a better orientation to favor the intermolecular interaction and charge transfer between the ligand substrate complexes.

The effective charge transfer between the ligand and substrate complex paved the way for the efficient design of antiviral sialidase inhibitors.

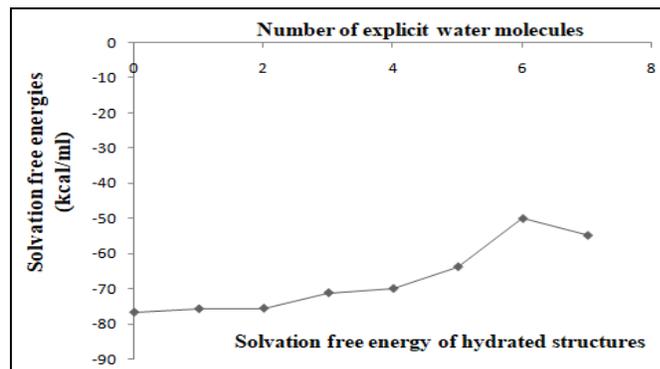


FIG. 4: SOLVATION FREE ENERGY OF HYDRATED STRUCTURES OF SIALYATE ANION

TABLE 2: SOLVATION FREE ENERGY AND GAS PHASE BINDING ENERGY OF SIALYATE ANION HYDRATED STRUCTURES

Compounds	Solvation free energy (kcal/mol) HF/6-31(g) ΔG_{sol}	Solvation free energy B3LYP(6-31G(d) (kcal/mol) ΔG_{sol}	Gas-phase water binding energy (kcal/mol) HF/6-31(g)	Gas-phase water binding energy (kcal/mol) B3LYP(6-31G(d)
N-NANA ⁻	-76.7	-64.13	0	0
N-NANA:1H ₂ O	-75.72	-62.4	-13.49	-13.98
N-NANA:2H ₂ O	-75.56	-61.61	-25.73	-26.97
N-NANA:3H ₂ O	-71.14	-57.29	-38.74	-42.20
N-NANA:4H ₂ O	-69.93	-56.48	-52.46	-55.88
N-NANA:5H ₂ O	-63.71	-51.89	-74.92	-72.24
N-NANA:6H ₂ O	-49.98	-40.58	-106.7	-101.7
N-NANA:7H ₂ O	-54.79	-44.36	-104.14	-102.64

CONCLUSION: Ab initio and DFT investigation of solvation dynamics and hydration pattern of sialic acid reveals that the cluster continuum solvation energy progressively increases as a function of water molecules by explicit solvation method. It further reveals that the specific binding of water molecules might be present in the tri hydrated and tetra hydrated structures. Hence, the solvation dynamics should be further explored in trihydrated and tetra hydrated structures, and these compounds are recommended for the design of neuraminidase antiviral drugs. The analysis of gas-phase hydration of explicit water molecules reveals that the binding energy of water molecules in the gas phase drastically decreases as a function of water molecules. The hydrogen-bonded network in the gas phase is not strong to produce hydrogen cooperative effects, and as a result, the hydration decreases as a function of water molecules.

Finally, the analysis of solvation free energy of hydrated structures of sialate anion discloses that the solvation free energy of explicit hydrated

structure increases progressively as a function of water molecules. Hence, it reveals that the hydrogen bonding cooperative effects and ionic interactions are very strong in solvation phenomena. The solvation dynamics of hexa hydrated structure is very impressive because it provides higher solvation energy and thus, it indicates the presence of water molecules trapped inside the functional site of sialate anion. Hence, the microsolvation investigation concludes that the tetra hydrated, penta hydrated, and hexa hydrated structure can be considered for further analysis of design and development of sialidase antiviral drugs.

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CONFLICTS OF INTEREST: Nil

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