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REVIEW

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Hydrogen Bond Interactions of Nucleobases: A Quick Review

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ABSTRACT. Hydrogen bond (HB) interactions in nucleobases; Adenine (A), Guanine (G), Cytosine (C), Thymine (T), and Uracil (U), were discussed quickly in this review work. The features of HB interactions were already investigated by the means of computer-based works and experiments. Formations of homo and hetero complexes of nucleobases through HB interactions could be characterizations using obtained parameters from X-ray, NMR and NQR techniques. Such spectroscopic properties could be evaluated by both of computations and experiments. Indeed, structural refinement could be also done by computations, in which more reliable results could be provided for further investigations. In addition to original nucleobases, their modified structures could also work their roles especially in medications. Due to such importance of the topic, the features of HB interactions in nucleobases were discussed in this quick review.

KEYWORDS. Hydrogen bond; Interaction; Nucleobase; DFT; DNA; RNA.

INTRODUCTION. After pioneering work of Watson on Crick on recognition of DNA structure, considerable efforts have been dedicated to characterize the features of these very much important building blocks of biological systems.[1] Indeed, the topic has become soon very much interesting for the researchers due to the importance in human related health science and technology.[2] Four nucleobases; adenine (A), guanine (G), cytosine (C), and thymine (T), are available in DNA, in which uracil (U) replaces T in RNA (Fig. 1). All the nucleobases play their own significant roles, in which their rational combinations could provide sequences with short and long lengths.[3] Homo and hetero structures of such oligomers have been seen to work as single standing structures in addition to their roles as DNA and RNA building blocks.[4] Because of biocompatibility, numbers of medicinal compounds have been synthesized from the original nucleobases.[5] Moreover, several attempts have been done to use such nucleobases as functional groups of other structures such as hydrophobic nanostructures for improving their properties and applications.[6] One of the dominant factors of nucleobases is their potential ability to contribute to intermolecular interactions in addition to covalent bonds of single-strand oligomer constructions.[7] This feature has made them as the topic of several works for recognition of such intermolecular interactions employing either experiments or computations.[8] Complicated environment of biochemical structures has led researchers to employ computational chemistry approach for the purpose of investigating intermolecular interactions at the atomic-scale using calculated parameters.[9] Additionally, some of the computer-based works have been done in combination with experimental measurements to characterize intermolecular interactions at higher accuracy.[10] It is worth to note that one of the important roles of computer-based works is their capability for interpreting experimental achievements.[11]

Various types of interacting forces have been seen for the nucleobases related complexes, in which the

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typical ones could be called as hydrogen bond (HB), van der Waals, London and pi-stacking.[12] Although each force has its own importance for the nucleobases, but HB interactions play indeed the most dominant role especially for stabilities of double-strand DNA or other geometrical configurations.[13] HB interactions are stronger than others and they could make somehow strong non-covalent complexes for homo or hetero combinations of nucleobases.[14] There are almost huge numbers of reported works in literature, in which they characterized various features for recognizing such HB interactions in the nucleobases and related complex systems.[15] It is noted that the story has not been yet finalized and the investigations on HB interactions in living systems will be still continued to future works and so on.[16] Due to such importance, a quick review on the HB interactions of nucleobases has been summarized in this work to show such importance for the potential readers. The next content of this work would be divided into two parts of computational and experimental approaches of recognition HB interactions in nucleobase.

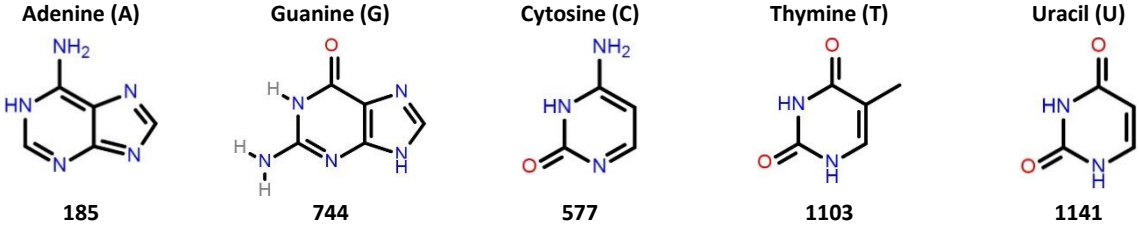

Fig. 1: Nucleobases. The ChemSpider IDs are indicated from ChemSpider.com.

COMPUTATIONAL APPROACH. When calling computational approach in this work, quantum chemical calculations are oriented to be focused for recognition of HB interactions of nucleobases at the atomic scale.[17] High-level quantum based computations could yield insightful information for the nucleobases complexes, in which improvements in density functional theory (DFT) have had a leading role for the purpose.[18] Evaluating properties for singular and interacting nucleobases and then comparing the results could show the effects of such HB interactions for the investigated systems.[19] It has been mentioned that chemical modifications of nucleobases are also important to be investigated, in which several new applications could be arisen for such modified structures.[20] In an earlier work, HB interactions were investigated in 9-methyladenine (9-MA) by DFT calculations (Fig. 2).[21] The point of this work was to employ original crystalline geometries for building an interacting cluster of 9-MA. Such parallel work was done for guanine (G) complexes to recognize properties of HB interactions in the molecular network.[22] In another work, the real crystalline structure was employed for C (cytosine) to make an interacting complex including/excluding water molecules to recognize the features of available HB interactions.[23] Such systematic work declared the importance of anhydrous and hydrated systems for investigating HB interactions in the C nucleobase. Moreover, HB interaction properties were investigated for 5-acetic acid functionalization of C (5-AAC), in which the computer-based optimization of hydrogen atoms positions of real crystalline system yielded a different interacting environment in comparison with the original interacting cluster.[24] The point is that the X-ray based crystallography methods could not locate the correct position of hydrogen atoms and the computer-based works could work for refinement of such crystalline structures, in which the mentioned work of 5-AAC focused on it. Thymine (T) and uracil (U) are the characteristic nucleobases of DNA and RNA respectively, in which the computer-based works were done for them to recognize HB interactions.[25, 26] It is worth to note that when defining HB interactions, the forces between nitrogen, oxygen and fluorine electronegative atoms through hydrogen atom bridging could be remembered. However, other types of HB interactions were recognized between non-electronegative atoms such as carbon, in which they have been called as non-classical HB interactions.[27] In a work focusing on such non-classical approach, C-H…O HB interactions were recognized in 1-methyluracil (1-MU) by the evaluated properties of DFT calculations.[28] This point was very much interesting because of the capability of computer-based works to recognize such types of HB interactions.

The parameters could be evaluated for both of atomic and molecular scales in the computational approach, in which spectroscopic properties have been seen very useful for the purpose. Nuclear magnetic resonance (NMR) and nuclear quadrupole resonance (NQR) are two very much useful spectroscopic techniques for this purpose of HB interactions recognition.[29] Fortunately, the experimentally measureable parameters of NMR and NQR could be very well reproduced by high-level quantum chemical computations as an advantage of employing computational approach for investigating matters at the lowest atomic scale.[30] For nucleobases, such properties were seen to be very much useful to recognize the features of singular structures and their related cluster systems.[31-35] Moreover, functionalization of nucleobases to nanostructures were carefully recognized by such useful spectroscopic parameters obtained by computations.[36-40] In such case, in addition to intermolecular distance and estimated values of interacting energies, their characteristic atomic-scale NMR and NQR properties could help for more accurate prediction of interpretation of HB interacting clusters of nucleobases.

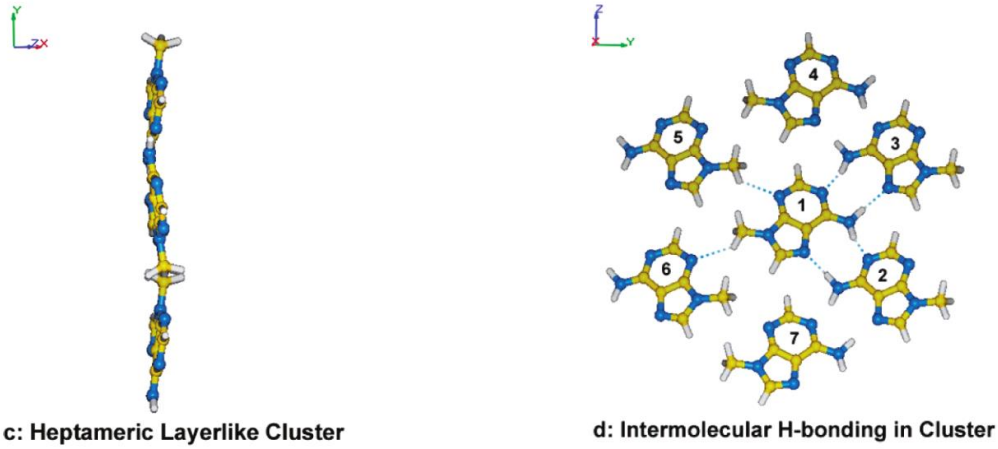

Fig. 2: Complex cluster of 9-methyladenine (9-MA).[21]

EXPERIMENTAL APPROACH. It is clearly known that the experimental approach is dominant for final recognition of real systems; however, there are always several limitations in both of knowledge and equipment to achieve the main purpose of investigation especially for those of complicated biological systems. Therefore, computer-based works could help to make more reliable experimental achievements by providing more information for better predictions and interpretations.[41] X-ray crystallography, NMR, and NQR are those typical experimental equipments which were used to recognize HB interactions in nucleobases cluster systems.[42] Although other equipment such as infrared (IR) spectroscopy are also important and useful for the purpose, but the achievements from those mentioned three equipments have been focused in this work. When talking about X-ray crystallography, positioning the atoms of molecular systems in the correct locals and determining other molecules of neighborhood is followed.[43] Afterwards, the HB interactions could be evaluated based on intermolecular distances and electronic properties for atoms. This technique is the most powerful one for positioning the correct structure, but commuter-based works could still help for structural refinements at higher accuracy.[44] In addition to such X-ray technique, both of NMR and NQR techniques could very well evaluate electronic properties for atoms and they could follow the shifts of chemical environment for atoms to recognize what happening inside the cluster structures in real system. For nucleobases, such works were done to evaluate NMR and NQR properties to recognize the features of HB interactions. In a typical work on U, the HB interactions were carefully recognized by both of NMR and NQR properties of oxygen atoms in the crystalline phase.[45] The parallel results were examined by the computed parameters and a strong discussion were made for the obtained achievements. Going through literature could show numerous experimental works on each of nucleobases to show the properties of HB interactions in their homo or hetero crystalline systems.[46-50] Since functionalized nucleobases could work as medicinal compounds, drug…target interactions were also reported by experimental measurements and also in combination with *in silico*

computer-based evaluation.[51] Molecular docking simulations could provide insightful information for the purpose.[52-57] Based on such recognition methodologies, the structures could be very well detected to investigate their functions for different purposes of biological related systems.

CONCLUSION. Discussing about HB interactions in nucleobases is almost a difficult task because of involving so many leading factors to define the interacting complex systems such as molecular configurations, interferers, environments, and so on. Indeed, the building blocks of life are constructed by HB interactions. Within this quick review, the topic was discussed quickly to may attract the interest of potential reader for considering such important problem in the biological systems. Computer-based methods in addition to experiments could help the problem to be partially solved by the evaluated parameters and features. Indeed, the type of nucleobase and its modifications are all very much important to recognize HB interactions. DFT calculations could provide optimized structures in addition to their ability for crystalline refinements and spectroscopic properties reproduction. X-ray, NMR and NQR are all among versatile techniques to investigate the purpose of describing HB interactions in nucleobases. This topic is dominant for achieving knowledge inside the biological systems. Hence, the results obtained by either experimental measurements or computer-based evaluations could all provide complementary information to recognize HB intermolecular interactions in both of homo and hetero complexes of nucleobases.

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