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Prebiotic Chemistry and Sepiolite: A Density Functional Theory Approach

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Abstract
Sepiolite, a natural clay mineral, offers a large surface area due to its fibrous structure, allowing it to exhibit adsorption properties. In this study, the molecular interactions of sepiolite, a biocompatible clay mineral known as a biomaterial, and purine and pyrimidine molecules forming the bases of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) molecules were modeled by Density Functional Theory. In addition to geometry optimization, calculations of interaction energy, bond critical points, and electrostatic potential revealed that essential molecules for our source of life interact with basal surface of the clay. For example, the best interaction energies between bases/sepiolite were found to be -127.47 kJ/mol for guanine and -121.35 kJ/mol for cytosine, respectively. Looking at the modeling results, one of the most important factors affecting the interaction energies is hydrogen bonding. To reveal this, bond critical point analysis was performed, and it was computed that a large amount of intermolecular interaction energies came from hydrogen bonds. For example, it was calculated that approximately 70% of the total energy in the guanine/TOT (two tetrahedra and one octahedron) model comes from hydrogen bonds. Furthermore, this value for the cytosine/TOT model was found to be around 72%. The most effective indices in these two models are 145 and 135, with the H-bond energies recorded as -22.41 and -31.41 kJ/mol, respectively. Considering all analyses, it can be concluded that basal surfaces of sepiolite serve as suitable hosts for nitrogenous bases, which are the basic components of life. The aim of this study is to show that sepiolite offers an important surface feature to protect and stabilize DNA and RNA nucleic acid bases, which are necessary for the existence of living organisms, and to reveal the existence of a robust adsorption interaction between sepiolite and bases, thanks to the surface and chemical properties of sepiolite.

1. Introduction

Sepiolite is a clay mineral belonging to the serpentinite family, which is abundant and produced in the Eskişehir region of Turkey. There are two different types of minerals belonging to the clay mineral family: serpentinite and smectite. The main difference between serpentinite and smectite minerals is that serpentinites are fibrous and contain both crystalline water and zeolitic water. Another important feature of serpentinites is that they consist of channels and tunnels resulting from their fibrous structure. This makes them suitable surface areas for molecules of certain sizes, such as drugs, DNA, and RNA bases. Considering these unique structural and textural features, sepiolite mineral consists of magnesium hydrosilicate, and its general formula is $Mg_4Si_6O_{15}(OH)_2 \bullet 6(H_2O)$. When examining the literature, it is evident that sepiolite is extensively utilized in the healthcare sector. For instance, Hermosin et al. demonstrated the potential utility of sepiolite as a pharmaceutical excipient for drugs

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susceptible to oxidative degradation through hydrogen bonds (H-bond) [1, 2]. In another study, it was revealed that drug molecules can be adsorbed onto sepiolite due to the presence of silanol groups, and the clay is instrumental in the controlled release of the drug [3, 4]. It was generalized in another study that sepiolite is also a good drug carrier in the presence of biocompatible and biodegradable polymers [5]. In addition, it was emphasized that biohybrid nanomaterials containing sonicated sepiolite in the presence of various polyvalent cations could serve as an alternative carrier for DNA transfer [6]. Smirnov et al., demonstrated, that sepiolite can be a DNA carrier mediator through their experimental study and stated that sepiolite can facilitate the delivery of bound molecules such as DNA to cells, especially through clathrin-mediated endocytosis and macropinocytosis [7]. Due to the physical and mechanical properties of sepiolite, it has been proven to interact by breaking the double strands of DNA in incubated *Escherichia coli* bacteria. As a result, it has been demonstrated that the mutagenic effect of sepiolite fibers increases antibiotic resistance when combined with antibiotics. This increase stems from the friction generated by the peristalsis of farm animals' intestines, in addition to horizontal gene transfer. [8]. The aforementioned experimental studies also indicate that investigations into the interaction between sepiolite and DNA have been very popular in recent years. However, the important point is where the bases of the DNA really adsorb to the clay, this is a very curious situation. Computational studies on DNA-RNA/clay, especially with layered clays apart from sepiolite, have been discussed in recent years. For example, Robinson et al. and Mignon et al. explained in two different studies that due to the H-bond interactions nucleobases can be adsorbed on the surfaces of the clay minerals at the atomistic level with Density Functional Theory (DFT) [9, 10]. Since the representative clay surfaces selected in this study were chosen quite small, and thus the atoms were frozen, which may have changed the amount of adsorption and perhaps the type of interaction. Mignon et al. studied the adsorption of all nucleobases on sodium montmorillonite clay using periodic plane wave DFT [11]. The effect of atomic positions of bases in different configurations on adsorption was investigated in the presence of sodium cations [11]. In the presence of sodium cations, it was revealed that the contribution of intermolecular interaction driving force can vary for different configurations. For instance, while the dispersion contribution was higher for cation-pi interactions, the electrostatic interaction contribution was greater for cation-pi/displaced orientations [11, 12]. In another study by the same team, two different montmorillonite models, substituted in tetrahedral and octahedral sheets, were used to investigate the adsorption type and shape of DNA bases onto the external surfaces of clay [13]. In their DFT study, it was revealed that bases can adsorb parallel or perpendicular to the surfaces and octahedral substitution contributes to 10 kcal/mol more interaction than tetrahedral [13]. Michalkova et al. investigated the adsorption of uracil and thymine bases in the presence of sodium on frozen hydrated and non-hydrated tetrahedral and octahedral kaolin sheets [14]. The most important shortcoming of this study is that all clay atoms were frozen. In this non-periodic study, freezing of atoms prevented possible repulsive forces. If the atoms were unfrozen, distortions would be observed in representative clay models, and this would change the amount of the intermolecular interaction. Bhatt et al. conducted a study regarding cytosine adsorption onto montmorillonite in the absence and presence of the metal ions and concluded that adsorption can be enhanced due to the especially transition metals [15]. Pedreira-Segade et al. carried out experimental and theoretical studies with layered clays such as nontronite, lizardite, montmorillonite, chlorite and profilite under different pH, temperature, and salinity conditions. In these studies, adsorption of nucleotides on the lateral, basal and interlayer surfaces of the clay in different salt ratios and solvent compositions has been demonstrated. It has been reported that these mechanisms arise from physicochemical reactions and manifest in the form of ligand exchange and hydrogen bonds [16-18].

It is obvious that in all of these studies, adsorption of prebiotic building blocks on clay surfaces once again emphasizes the emergence of life. To support this, the adsorption of building blocks with sepiolite, a fibrous clay that has been little studied, was demonstrated in this study. The literature in question identifies the formation of hydrogen bonds as one of the most significant adsorption mechanisms. For the first time, an analysis of atoms in molecules (AIM) topology with electronic wave function was conducted to elucidate the contribution of hydrogen bonding to the binding energy.

2.Computational Setup

The process flow diagram of all DFT stages of this study, which was theoretically designed with the basic theories of computational chemistry, is presented in Figure 1.

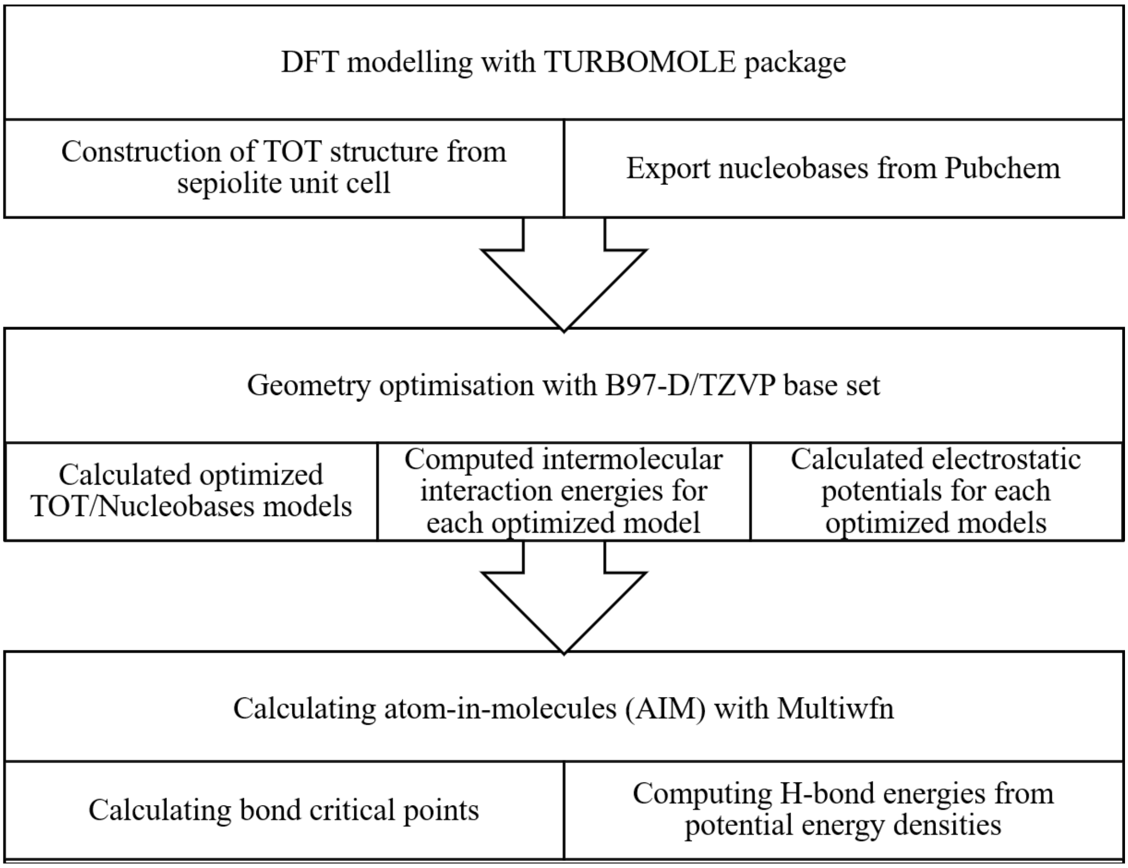


Figure 1. Process flow chart for each steps run

As mentioned in Figure 1, the representation of sepiolite clay was constructed using a published sepiolite crystal structure [19]. All dangling bonds in the model were saturated with hydrogen, as used in our previous studies [20-22]. The ball-and-stick representation of the structure consisting of 2 tetrahedra and 1 octahedron (TOT) was obtained from the sepiolite unit cell [19].

Input files were created by arbitrarily and randomly placing nitrogenous base molecules separately on the basal surface of the structure. After the creation of the input files, modeling was performed with the TURBOMOLE V6.1 package program [23]. Geometry optimization of each model was computed by using the B97-D functional to consider the dispersion contribution with the TZVP basis set. Binding energies of the optimized structures obtained as a result of geometry optimization were calculated with Equation 1 using Counter-Poise (CP) correction [24, 25]. Binding energies were corrected against the basis set superposition error (BSSE) with CP method. The negative interaction energies were obtained using the following formula:

$$E_{BE}^{CP} = E_{TOT+bases}^{(TOT+bases)} - (E_{TOT}^{(TOT+bases)} + E_{bases}^{(TOT+bases)}) \qquad (1)$$

where E_{BE}^{CP} is the CP corrected binding energy, $E_{TOT+bases}^{(TOT+bases)}, E_{TOT}^{(TOT+bases)}\ and\ E_{bases}^{(TOT+bases)}$ the total energies of the TOT+bases, TOT, and the bases of each molecules were calculated using the basis set of the complete system (TOT+bases).

After the geometry optimization, the electrostatic potentials of the optimized models were calculated. Electrostatic potentials (EPs) were visualized using TmoleX, a graphical user interface for Turbomole program [26].

In the final stage, topological analyses were also conducted to determine the types of interaction bonds and the energies of the hydrogen bonds. One of the topology bond critical points (BCP) was calculated using the Multiwfn program [27]. Multiwfn gives very fast and successful results in the calculation of cage and ring critical points in addition to the BCPs belonging to complex models; it has been used quite frequently in recent years [28, 29]. Therefore, detailed information about atoms in molecules (AIM) and the electron density topology can be obtained. In the case where two eigenvalues of the Hessian matrix of the function are negative, a BCP is formed. Electron density at the BCP can be reliably used to predict hydrogen bond binding energies [30]. H-bond [R-H----O (R=C, N, O)] energies, the relationship between bond energy E_{HB} and potential energy density $V(r)$ at the corresponding BCP (3,-1) can be approximately described as [31, 32]:

$$E_{HB} = V\ (r_{BCP})/2 \qquad (2)$$

where, E_{HB} is the H-bond energy and $V(r_{BCP})$ is the potential energy density at a certain BCP.

3. Results and Discussion

Electrostatic potential (EP) maps are highly productive in obtaining information about adsorption on mineral surfaces and revealing the regions of H-bond formation. Therefore, to understand the interactions of molecules with each other and therefore to follow the adsorption process, the electrostatic potentials of each structure used in the modeling were calculated with B97-D/TZVP base set and exhibited in Figure 2.

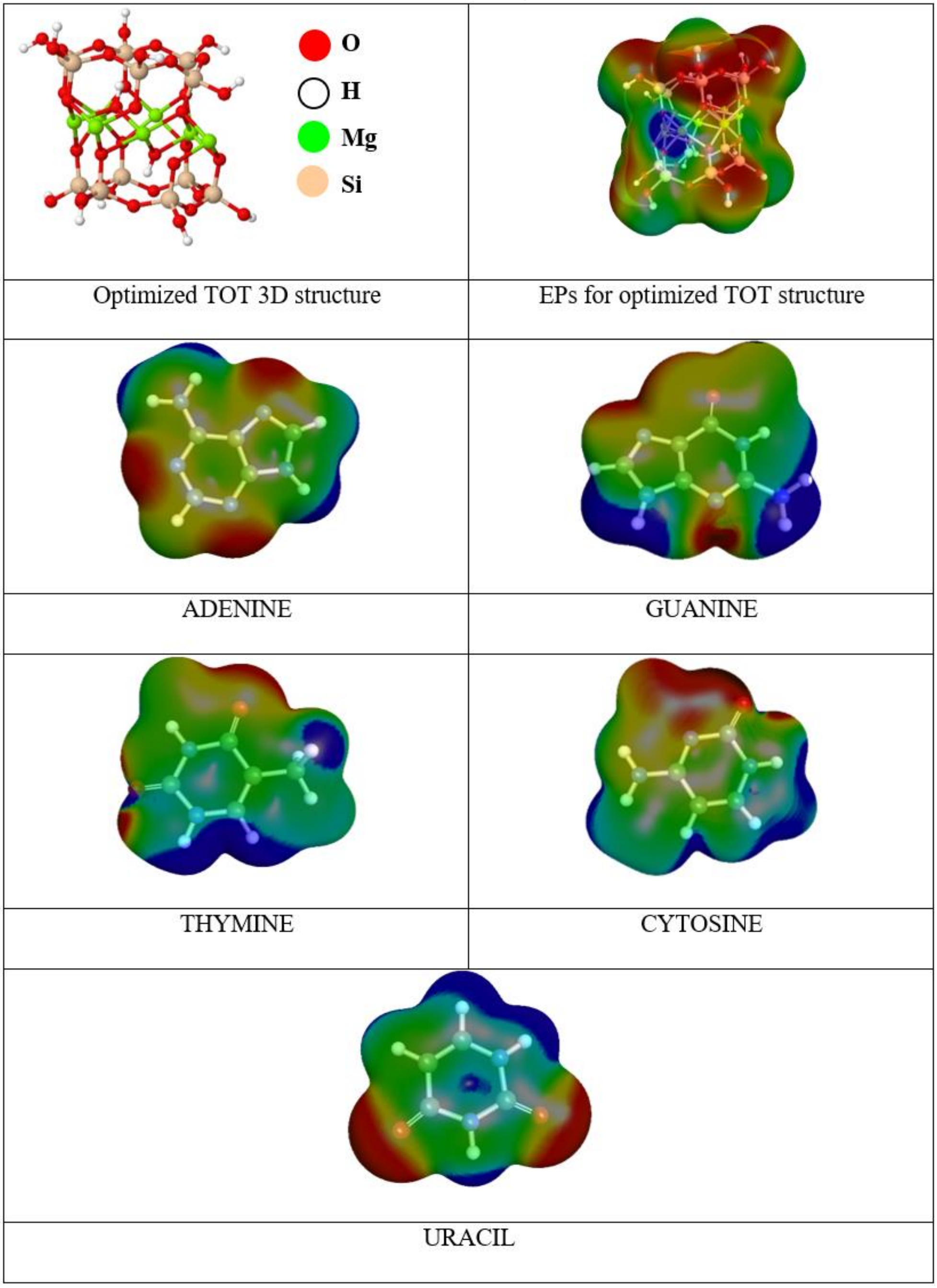
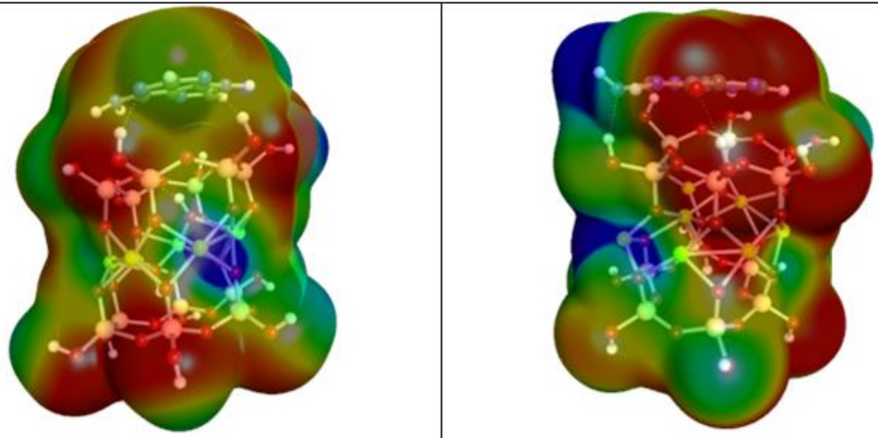


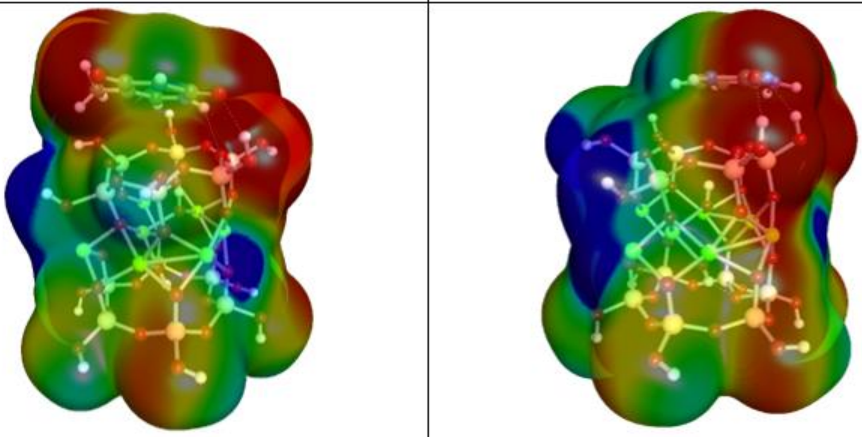
Figure 2. Maps of electrostatic potential of each structure. EPs are mapped onto electron density isosurfaces (0.007 e/au^3) at the B97-D/TZVP level

From the electrostatic potentials of the TOT model in Figure 2, it is seen that the electron accumulation increases in the groups belonging to the silanol groups (Si–O–H). In nitrogenous bases, on the other hand, it is understood that the regions with oxygen atoms become more negative due to the formation of red tones around them. The EP maps depicting the interactions of these adsorbate and adsorbent molecules are shown in Figure 3.



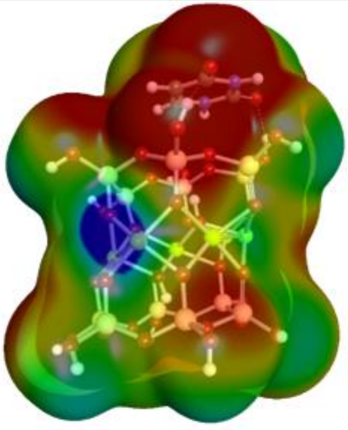
ADENINE/TOT

GUANINE/TOT



THYMINE/TOT

CYTOSINE/TOT



URACIL/TOT

Figure 3. Maps of electrostatic potential for each model

In Figure 3, it is observed that the interaction is concentrated in the tetrahedral region where the bases are located on the electrostatic surfaces visualized with Tmolex [26]. On the other hand, in the octahedral region, it is understood that the interaction decreases with the increase in blue color tones. The reason for this is that the relatively more negative oxygen atoms interact electrostatically with the neighboring cationic atoms [14, 33, 34]. The most important formations affecting adsorption is the H-bonds between oxygen, nitrogen and hydrogen atoms with partial negative and positive charges. These H-bond distances range from 2-3 Å. In terms of the formation sites of H-bond interactions, it is seen that guanine and cytosine are almost parallel and the others are placed on the surfaces as slightly tilted. These formations cause charge distribution and polarization in electrostatic potentials. The resulting H-bonds and charge polarization affect the amount of adsorption on the basal surface of the sepiolite as well as the formation of adsorption, and therefore, calculated energies as CP and non-CP for intermolecular interactions are shown in Table 1.

Table 1. CP and non-CP energies for nucleobases/TOT models in kJ/mol

NUCLEOBASES	MODEL	CP	non-CP
PURINES	ADENINE/TOT	-95.59	-107.86
	GUANINE/TOT	-127.47	-142.46
PYRIMIDINES	THYMINE/TOT	-81.79	-90.01
	CYTOSINE/TOT	-121.35	-133.20
	URACIL/TOT	-87.99	-97.57

The first thing that stands out from the results in Table 1 is that guanine interacts with TOT more than other purines and pyrimidines, which structurally contain very few atoms. As a matter of fact, while the interaction energy of guanine was -127.47 kJ/mol, the energy of the nearest base was calculated as -121.35 kJ/mol. Similarly, Mignon et al. reported that guanine and cytosine were more adsorbed onto the basal surfaces of montmorillonite [11]. On the other hand, the second striking result is that the interaction energy of adenine, structurally most similar to guanine, is very high and is calculated as -95.59 kJ/mol. The last interesting result is that uracil, the smallest and relatively planar structure, has lower in energy than thymine. Using the final coordinates obtained at the end of the geometry optimization, Bond Critical Points (BCPs) were calculated to reveal the H-bond contribution of interactions between molecules, and the images of the obtained points are shown in Figure 4.

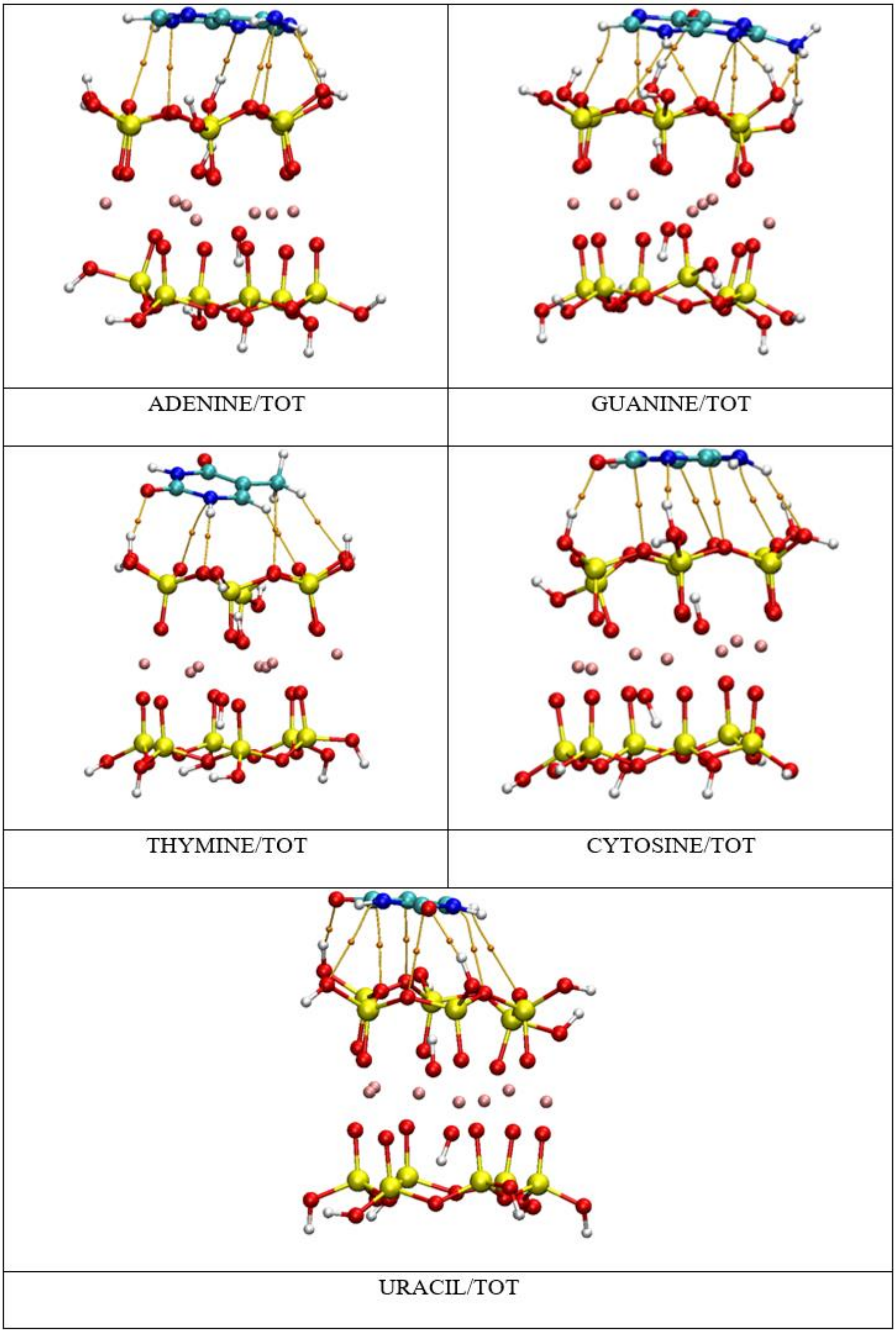


Figure 4. BCPs for nucleobases/TOT models. Yellow, red, blue, white, tile bergere, and aqua green colors are silicon (Si), oxygen (O), nitrogen (N), hydrogen (H), magnesium (Mg), and carbon (C), respectively

In Figure 4, BCPs of nucleobases/TOT models visualized using the VMD program are shown as yellow knotted threads. It is also observed that there is a tight relationship between the partially positive charged cation (–H$^+$) and the partial negative charged (–O$^-$ and –N$^-$) anions on the sepiolite basal surfaces. The number of BCPs for adenine and guanine is counted as 7 and 10, respectively, while it is 6, 7, and 8 for thymine, cytosine, and uracil, respectively. Compared to the results in Table 1, guanine, which exhibits the most binding, also stands out with the highest number of BCPs. Another striking result is the presence of 8 BCPs in the thymine/TOT model. It is understood that the H-bond contribution may be high in both models. To reveal this, the binding energies of each BCP index were calculated and presented in Table 2.

Table 2. Indices of BCPs and their H-bonds energies computed by potential energy densities

MODEL	indexes of BCPs	V(r)	BE, kJ/mol	MODEL	indexes of BCPs	V(r)	BE, kJ/mol
ADENINE/TOT	116	-1.65E-03	-2.16	THYMINE / TOT	102	-3.29E-03	-4.32
	137	-4.01E-03	-5.26		104	-2.31E-03	-3.04
	193	-1.12E-02	-14.72		162	-4.76E-03	-6.26
	217	-6.31E-03	-8.28		183	-5.83E-03	-7.65
	225	-3.77E-03	-4.95		218	-7.79E-03	-10.23
	255	-3.90E-03	-5.13		233	-2.29E-02	-30.03
	256	-2.16E-02	-28.34	CYTOSINE / TOT	128	-1.73E-03	-2.27
GUANINE/TOT	107	-4.37E-03	-5.74		135	-2.39E-02	-31.41
	111	-6.33E-03	-8.31		158	-5.52E-03	-7.24
	129	-4.21E-03	-5.53		189	-1.72E-03	-2.26
	141	-2.28E-03	-3.00		206	-2.31E-02	-30.38
	143	-6.83E-03	-8.97		209	-6.19E-03	-8.12
	145	-1.71E-02	-22.41		246	-4.07E-03	-5.34
	216	-4.91E-03	-6.45	URACIL / TOT	110	-9.31E-04	-1.22
	217	-4.68E-03	-6.14		137	-5.73E-03	-7.52
	233	-4.13E-03	-5.43		163	-3.84E-03	-5.04
	263	-1.35E-02	-17.73		178	-2.53E-03	-3.33
					199	-4.68E-03	-6.14
					208	-5.31E-03	-6.97
					238	-1.52E-02	-20.00
					246	-2.41E-03	-3.17

The index with the highest H-bond energy (-31.41 kJ/mol) in Table 2 belongs to the cytosine/TOT model, numbered 135. This is followed by the one with index number 206, which has -30.38 kJ/mol in the same model. The one that is slightly above these is the one with the index number 233 in the thymine/TOT model with an energy of -30.03 kJ/mol, while the other one belongs to the Adenine/TOT model with the index number 256, which is approximately 2 kJ/mol larger. On the other hand, in the Guanine/TOT model, the energies of 2 H-bonds were recorded as -22.41 and -17.73 kJ/mol for the index numbers 145 and 263, respectively, considerably lower than the others. In Uracil/TOT, it has the lowest energy index with the number 238 and an energy of -20.00 kJ/mol, as well.

4. Conclusion and Suggestions

In this study, the atomistic modeling of key molecules of life and sepiolite is investigated using DFT. It has been revealed that the basic building blocks of DNA and RNA, the indispensable molecules of life, are adsorbed on the basal surfaces of sepiolite. It has been revealed by both CP-corrected and BCP analyzes that the most important parameter playing a key role in this adsorption is H-bond. Considering the intermolecular interactions obtained as a result of the analyzes, it can be stated that the guanine/TOT model is the most stable model. As a result, the fibrous clay crystals such as sepiolite which possess abundant silanol groups, can be potential carriers in the transport of nucleotides. On the other hand, there are certain limitations within the scope of this study. Computational modeling methods such as DFT are utilized in the analysis of surface adsorption between sepiolite mineral and DNA bases. However, while theoretical calculations provide important insights, they oversimplify physical and chemical interactions. Consequently, there is a possibility of less accurate analysis of molecular properties by neglecting some obstacles that may occur in the reaction. Nonetheless, such theoretical studies still contribute to our understanding, complementing experimental studies. This study aimed to highlight the adsorption feature of purine and pyrimidine, the nucleic acid bases, on the surface of sepiolite mineral through DFT. The originality of this study lies in assessing the interaction capacity of the biocompatible clay mineral with DNA and RNA bases, fundamental molecules for life, and revealing the potential contributions of these interactions to biochemical processes. While there are numerous studies in the literature on the use of sepiolite in healthcare, this study explores the interaction of DNA and RNA bases with sepiolite mineral, investigating the contribution of sepiolite to prebiotic chemistry from the perspective of molecular modeling and computational chemistry.

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Statement of Research and Publication Ethics

The study is complied with research and publication ethics

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