



Article Adsorption of Selected Molecules on (TiO₂)₂₀ Nano-Clusters: A Density-Functional-Theory Study

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Abstract: In this work, the adsorption energies and some of the main electronic properties of selected biological molecules adsorbed onto a (TiO₂)₂₀ cluster were studied. With this aim, Density-Functional Theory (DFT) calculations were performed using SIESTA code. The Perdew-Burke-Ernzerhof (PBE) functional within the Generalized Gradient Approximation (GGA) was used for the exchange and correlation potential. For this study, we chose molecules with very different characteristics and applications in everyday life, including antibiotics, anti-inflammatory drugs, vitamins, and so on. The TiO₂ substrate was considered due to its harmlessness and versatility of application in various industries. In particular, we studied the changes in some of the main electronic properties of the molecules after adsorption onto titanium dioxide. For all of the molecules studied here, we observed that this substrate can increase the stability of the adsorbed molecules, with values in the range of 12–150 meV/atom. The reliability of our calculations was verified through additional optimizations with other DFT codes, considering the hybrid functionals B3LYP and M06-L. Our results showed a reasonably good agreement among these three functionals, thereby revealing the possibility of adsorption of the selected biological molecules onto the vertex of the TiO₂ nanoclusters. Some of these molecules were considered as possible candidates for the delivery of drugs into the SARS-CoV-2 main protease, promoting the inhibition of this virus. We are not aware of any systematic study that has focused on the adsorption of the selected molecules on a $(TiO_2)_{20}$ substrate within the same framework, including the analysis of the differences in electronic properties through the use of different functionals.

Keywords: TiO₂-nanoparticle; drug delivery; SARS-CoV-2; DFT; nanocarrier

1. Introduction

Titanium oxide (TiO_2) is among the top-ten most-used materials wordwide in various industries, due to the variability of its applications and diversity of preparation techniques [1–8]. For instance, TiO_2 has been used in many industries, such as food [9], drugs [10], cosmetics [11], and construction [12]. It is also important to highlight its potential use in drug delivery [13,14] and in photocatalytic processes [5,8,10,13,14]. At present, this metal oxide is considered one of the most important materials, given its natural abundance (being the ninth most-common element on Earth) and large number of applications, which undoubtedly make it valuable in many ways [8].

Regarding the molecular structure and electronic properties of (TiO₂), state-of-the-art research has shown that titanium oxide can adopt several conformations, from clusters [15] to nanowires [16] and thin-films [17], as well as various existing bulk-phase conformations, such as anatase, rutile, brookite, and even an amorphous version [18]. In particular, many efforts have been made to improve the photochemical activity of TiO₂ bulk phases [19–23], as it only shows a response to a very narrow region of solar radiation due to its huge band



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Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). gap (\approx 3.20 eV). Different attempts have been made to reduce the bandwidth gap, such as through the doping of TiO₂ with metallic and non-metallic elements [17,24–27]. To this end, efforts in different areas of science have been made in bulk systems [24,25,28], films, and nanosystems, in order to determine the benefits obtained with different dopants [17,26,27]. The fundamental idea is to introduce electronic states in the middle of the band gap and this way enable the tune of the energy gap in a wider region of the solar radiation.

In the case of medical, biological or certain therapeutic applications (TiO₂) have been suggested as a carrier because of its biocompatibility and low toxicity observed [13,14]. The aforementioned research has opened a potential market for the possible use of TiO₂ for the delivery of biological molecules or drugs. For this reason, titanium dioxide nanostructures may serve as potential nanocarriers with applications in the pharmaceutical and biochemical industries. It turns out that the adsorption of organic molecules onto TiO₂ nanostructures also acts in a similar way as dopants and modifies the band gap, making it more sensitive to the electromagnetic spectrum [29]. In this way, it may serve a double purpose: as a carrier and for modification of the prohibited band gap.

Considering the above, in the current study, we focused on the electronic interactions between a designed $(TiO_2)_{20}$ nanocluster and various molecules with pharmaceutical and biochemical applications. This nanocluster has been recently reported by Cuko et al. [30], as a ground state structure presenting tetrahedral symmetry. An important advantage of using this cluster is that it does not require interactions within the site to present a band gap comparable to that of the bulk anatase and rutile phases, making this cluster a model emulating bulk structures. Although our main interest is the study of finite-size systems (i.e., molecules + cluster substrate), it is important to note that our research also provides some guidelines in the case of molecules adsorbed onto surfaces or volumetric phases of this oxide, due to the fact that the substrate presents a similar HOMO-LUMO gap. The set of biological molecules with multiple uses in everyday life and industry. Among the drugs studied here are Chloroquine, Hydroxychloroquine, and Favipiravir [31,32], which are considered useful against SARS-CoV-2 as they may promote the inhibition of this virus, which is the cause of the currently ongoing pandemic [33].

The remainder of this paper is organized as follows: In Section 2, the different theoretical methods used are presented, with the corresponding protocols defined for the DFT codes and their functionals. Section 3 provides the description, results, and discussion of the different groups of biological molecules adsorbed onto the $(TiO_2)_{20}$ nanocluster considered here. Finally, Section 4 discusses the main conclusions of this work.

2. Theoretical Approach and Computational Details

Considering that, in our work, we use different codes based on DFT, we briefly describe each one in this section, starting with the pure functional (PBE-SIESTA) [34,35] and, later, the hybrid functionals (B3LYP and M06-L) [36,37].

2.1. Pure Functional PBE-SIESTA

The calculations are based on the Density-Functional Theory (DFT), using the exchange-correlation functional developed by Perdew, Burke, and Ernzerhof (PBE) [34], within the Generalized Gradient Approximation (GGA), as implemented in the computational SIESTA package [35]. This package uses numerical pseudo-atomic orbitals as a basis to solve the single-particle Kohn–Sham equations, while the atomic cores are described by a non-local norm-conserving Troullier–Martins pseudo-potential [38] factorized in the Kleinman–Bylander form [39]. For the cluster substrate used in this work, $(TiO_2)_{20}$, the pseudo-potentials for O and Ti were generated using the following valence configurations: $2s^22p^4$ and $4s^23p^63d^2$, respectively. The *s* and *p* radii for O shared the value of 1.14 au, while the *s*, *p*, and *d* cut-off radii for Ti were all equal to 1.98 au. The valence states were described using double- ζ polarized basis sets. More details on the basis sets and pseudo-potentials

used for the different atoms that form the molecules, as well as the pertinent tests, can be found in our previous publications [40–43].

The calculations were performed using a orthorhombic cell (20 Å \times 34 Å \times 24 Å), the size of which guaranteed that interactions between the cluster and its replicas in neighboring cells were negligible. The shortest distance among the different images was \approx 12 Å. We performed several tests at different box sizes, in order to confirm the independence of the total energy values obtained in our calculations. Only the Γ -point was used for the Brillouin zone integration. A cut-off energy criterion of 250 Ry was used to define the real-space grid for the electron density. We employed the conjugate gradient method [44] for geometric optimization of the atomic structures, as implemented in the SIESTA code. The inter-atomic force criterion used for convergence, when below 0.006 eV/Å, was reached. We performed full geometrical relaxation without any constraints and full-spin polarization calculations in all of the optimizations.

2.2. Hybrid Functionals B3LYP and M06-L

After obtaining the putative minima corresponding to the configurations with the different adsorbed molecules using a pure functional (PBE [34] within the SIESTA package [35]), we performed an additional full electronic relaxation without any constraints in the optimization using two hybrid functionals, in order to determine the degree of soundness of our calculation and its reliability through the use of different functionals. The electronic properties of the optimized molecules were re-computed, using the Gaussian 09 (G09) package [36], through a single-point calculation. The functionals used for the re-optimization were B3LYP [37] and M06-L [45], two hybrid functionals with reported results close to experimental data, particularly in organic and some inorganic systems. At the same time, a double-zeta polarized basis set [46,47] and the LANL2DZ [48] pseudo-potential for the titanium atom were used. It is worth noting that the calculation with an additional functional was of relevant importance for us, given the lack of similar studies in the literature for comparison, as most of the previous calculations have been carried out on surfaces, fullerenes, wires, and tubes based on C, N, and B.

The results for all the molecules studied here using the hybrid functionals are presented in the Supplementary Materials, where the tables are named with respect to the functional used, and are also discussed throughout the text in comparison with the obtained PBE values using the SIESTA code.

2.3. Activity against SARS-CoV-2 (Docking)

To evaluate the activity against SARS-CoV-2, the optimized antiviral free drugs and drug– TiO₂ systems were considered as ligands coupled to the crystal structure of the SARS-CoV-2 main protease (SARS-CoV-2-M^{*Pro*}; PDB code 6LU7). The latter is generally used as one of the drug targets to understand and design novel molecules [49–54] for treatment of the virus that causes the coronavirus disease (COVID19). In silico molecular couplings were performed using the following molecules as reference: the co-crystallized molecule into the selected target and one of the outstanding molecules, in terms of performance, against SARS-CoV-2-M^{*Pro*}; that is, the so-called Prop8 proposed by Díaz-Cervantes et al. [55].

The Natural Bond Orbital (NBO) populations were considered, in order to assign a local charge to each atom of the ligands, which were computed at level M06-L [45] using the G09 [36] package. The biological targets were pH- and solvent-adjusted using the Chimera software [56]. Finally, a docking assay was performed using the Moldock score with the Molegro Virtual Docker (MVD) package [57], where the total energy of interactions was computed and decomposed into principal components as hydrogen bond interactions. Finally, the LE (=Total energy/#heavy atoms) was evaluated, which denotes the energy that each atom contributes to the total energy (where heavy atoms are all the atoms which are not hydrogens).

2.4. Chemical Energy Descriptors

The main goal of our work is to calculate the different energies presented in the considered complex (Molecule + Cluster). These include the binding energy of the free-standing molecules (E_B [(Molecule)]_{Free}), the binding energy of the formed complex (E_B [(Complex)]), the adsorption energy of the supported molecule ($E_{Ads.}$ [(Molecule)]) on the (TiO₂)₂₀ cluster, and the assistance binding energy of the adsorbed molecule (E_B [Molecule]), which is binding energy of the molecule in the presence of the substrate or cluster. In order to do so, we must define the following energies in terms of the total energies of the molecules, the cluster and the complex (Molecule+Cluster), and the atomic energies:

$$E_{\rm B}[({\rm Molecule})]_{\rm Free} = -\frac{E_{\rm Total}[({\rm Molecule})] - [\sum_{atoms} E_{\rm atoms}({\rm In \ the \ Molecule})]}{{\rm Nun. \ Atoms \ in \ Molecule}}, \qquad (1)$$

$$E_{\rm B}[(\rm Complex)] = -\frac{E_{\rm Total}[(\rm Molecule) + Cluster] - [\sum_{atoms} E_{\rm atoms}(\rm In \ the \ Complex)]}{\rm Nun. \ Atoms \ in \ Complex}, \quad (2)$$

 $E_{\text{Ads.}}[(\text{Molecule})] = E_{\text{Total}}[(\text{Molecule})]_{\text{free}} + E_{\text{Total}}(\text{Cluster}) - E_{\text{Total}}[(\text{Molecule}) + \text{Cluster}],$ (3)

$$E_{\rm B}^{*}[({\rm Molecule})] = E_{\rm B}[({\rm Molecule})]_{\rm free} + \frac{E_{\rm Ads.}[({\rm Molecule})]}{{\rm Nun. Atoms Molecule'}}$$
(4)

where "Cluster" denotes the $(TiO_2)_{20}$ cluster or substrate, "free" denotes the free-standing optimized molecule, and E(Cluster) denotes the total energy of the free-standing cluster. All of the energy values used in the previous definitions were obtained through optimizing the different systems within the framework of Density-Functional Theory.

2.5. Condensed Fukuis Functions

It is possible to discuss the local reactivity of a system using electronic parameters. The Fukui functions $(f^+, f^-, \text{ and } f^0)$ spatially determine the more- or less-favorable sites for the absorption (f^+) or removal (f^-) of electrons. These quantities are given by the expressions [58–60]:

$$f^{\pm}(\overrightarrow{r}) = \left(\frac{\partial\rho(\overrightarrow{r})}{\partial N_e}\right)_{v}^{\pm},\tag{5}$$

where $\rho(\vec{r})$ is the spatial charge, the number of electrons is N_e , and the subscript indicates that derivatives must be calculated with the external potential fixed (i.e., atomic coordinates fixed). The f^+ scalar field refers to the response upon addition of electrons in the density charge and, so, is an indicator of locally electrophilic regions within the system which are more susceptible to nucleophilic attack. In the same way, the f^- scalar function describes the response to subtraction of electrons in the density charge and, thus, locates the most nucleophilic regions within the system, which are more susceptible to an electrophilic attack than that expected when further oxygen is adsorbed to form a saturated oxide surface layer. Finally, f^0 , known as the radical attack Fukui function, is the arithmetic average of f^+ and f^- . Higher values $f^{\pm/0}$ of these functions indicate greater reactivity. Using a Mulliken population analysis, the values of these functions can be calculated locally for each atom [58]. Using a simple finite difference approximation of the derivatives, we obtained these simple expressions:

$$f_{N_e}^+(\vec{r}) = \rho_{N_{e+1}}(\vec{r}) - \rho_{N_e}(\vec{r}), \tag{6}$$

$$f_{N_e}^{-}(\vec{r}) = \rho_{N_e}(\vec{r}) - \rho_{N_{e-1}}(\vec{r}), \tag{7}$$

$$f_{N_e}^0(\vec{r}) = (1/2) \{ \rho_{N_{e+1}}(\vec{r}) - \rho_{N_{e-1}}(\vec{r}) \}.$$
(8)

3. Results

First, we provide details of the substrate used in our calculations. We considered the recently reported tetrahedral cluster $(TiO_2)_{20}$ [30,61] as the substrate to study the adsorption of different molecules onto a finite-size system. However, it can also be used as an approximate model for adsorption in bulk systems of TiO₂ [61]. The used cluster is shown in Figure 1a, from two different orientations. An advantage of using this cluster is that it does not require intra-site interactions (e.g., GGA + U or LDA + U) to present a band gap comparable to those of bulk anatase and rutile phases [29,62]. For this reason, the model cluster can be further used to mimic some of the adsorption properties of volumetric titanium dioxide systems, although our focus was on finite-size systems and their use as a vehicle for drug delivery. The $(TiO_2)_{20}$ cluster has the following electronic properties: Binding energy of 6.879 eV/atom, a HOMO-LUMO Gap (HLG) very similar to the bulk one (3.224 eV), electric dipole almost negligible (0.40 Dbys), and a Fermi level at -7.243 eV. The binding energy of our cluster was smaller than that of the corresponding bulk phase calculated within the same framework model (7.138 eV/atom). The corresponding values for the binding energy using the hybrid functional were 12% (B3LYP) and 4% (M06-L) lower than the PBE value. This energy showed the largest deviation, as detailed below, when compared to those of the molecules. In the case of the HLG, the B3LYP gave a higher value (4.818 eV) than PBE, while the M06-L slightly differed (3.286 eV). The difference between the HLG in the calculations can be attributed to the different amounts of Fock exchange considered by the hybrid functionals [29,62]:



Figure 1. In the upper-left part (**a**), different views of the $(TiO_2)_{20}$ substrate used in our adsorption studies of different molecules are presented. In (**b**–**d**), we present the different condensed Fukui fuctions, which inform us of the reactivity and its type at different sites of the cluster. Small and large balls represent Ti and O atoms, respectively.

It is worth noting that the most reactive sites in the cluster substrate $(TiO_2)_{20}$ correspond to vertices (Ti atoms). This causes all of the adsorbed molecules to be in top configurations (binding to the substrate through an O or N atom in all cases). Consequently, the structural deformations in the substrate cluster and in the adsorbed molecule

are relatively low. To support the above statement regarding the reactivity of the different cluster sites, in Figure 1b–d, we present the three different condensed Fukui functions: (b) Electrophilic f^+ , (c) Nucleophilic f^- , and (d) Radical f^0 of the pristine cluster substrate. The results of the three different Fukui functions (f^+ , f^- , and f^0) indicated that the values tend to shift to the right side of the scale, which strongly supports vertices as the most probable places for adsorption of different molecules presenting a top configuration.

In the case of the pristine molecules, the molecular weight and its respective binding energy (within the SIESTA code) are given as references in the tables throughout the paper. The atomic coordinates of the optimized complex system (molecule + cluster) in Tables 1–10 are given in the Supplementary Materials. We do not consider it necessary to give the coordinates of the free-standing molecules, as they did not present severe deformations or reconstruction. The reader may obtain them by simply extracting them from the complex and using these as input for further optimization.

The group of molecules considered in this work is large. For this reason, we only present some representative cases of the free-standing molecules with the largest binding energies for each one of the different groups (in Tables 1, 3, 5, 7 and 9). In Figure 2, we show some selected molecules with the largest binding energies. The corresponding values for $E_B[(Molecule)]_{Free}$ are provided under each figure (in units of eV/Atoms). The lowest value was obtained for Pyrazinamide (an antibiotic) in Figure 2e, while the largest was for Anthraquinone in Figure 2h, which is used as a polymerization inhibitor, as well as in photographic chemicals and paints. In the paper industry, it is used as a catalyst to increase production. In general, the values corresponding to the binding energy of all the free molecules here considered were practically the same with the three used functionals, and the differences were minimal (less than 2%), as presented in the coordinate tables in the Supplementary Materials.



(c)Pyrazinamide (4.845) (f)Favipiravir (4.913) (g)Aminoquinoline (4.986) (h)Anthraquinone (5.424)

Figure 2. Illustration of selected molecules for each of the different groups considered. Below every molecule, the binding energy of the free-standing molecule is shown (in units of eV/atoms).

Illustrations of the molecules that formed complexes with the highest binding energy values $E_B[(Complex)]$ are shown in Figure 3 The complex with the lowest binding energy was Diclofenac in Figure 3d, which is used to treat aches and pains, as well as problems with joints, muscles, and bones. The largest energy in complex was presented by Uracil, Vitamin B3, and Biotinidase, which had practically the same energy values (Figure 3a,b,h, respectively). Uracil is a pyrimidine, one of the four nitrogenous bases that are part of RNA and in the genetic code; B3 helps transform food into energy, and is important for the development and function of cells in the body; and, finally, Biotinidase plays an essential role in some human metabolic processes. In general, the values of the energy of formation of the complex satisfied PBE > M06-L> B3LYP, clearly reflecting the differences in binding energy reported in the cluster substratum noted above. All values are presented in the tables in the Supplementary Materials.



(e)Pyrazinamide (6.513) (f)Favipiravir(6.503) (g)Aminoquinoline (6.448) (h)Biotinidasa (6.566)

Figure 3. Illustration of selected complexes (formed by molecule + cluster). For each of the different groups considered, we only show those with the largest energy values. Below every molecule, the binding energy of the complex is shown (in units of eV/atoms).

Finally, the molecules with the highest adsorption energy $E_{Ads.}$ [(Molecule)] for the different groups are illustrated in Figure 4. The largest value was observed with Guanine, a basic amino acid bound by a Nitrogen atom, as shown in Figure 4b, which is used as a source of fertilizer. As shown Figure 4e, the lowest adsorption energy was presented in Isoniazid, an antibiotic that is used to fight bacteria and for the treatment and prevention of tuberculosis. In the case of the adsorption energy of the system, the PBE values were generally greater than or equal to those of M06-L; in a few cases, the differences were smaller (less than 6%). The adsorption energy values of M06-L were systematically higher than those of B3LYP. All the values are presented in the tables in the Supplementary Materials.

Table 1. Binding energies for the molecules Equations (1) and (4), binding energy of the complex (molecule-cluster) Equation (2), and adsorption energies Equation (3) for vitamin-like or precursors. Some numbers are emphasized (bold font) to facilitate discussion, since they correspond to the largest values of different physical properties in the different series.

Molecule/Weight	E _{Bind} (eV/atom) Molecule	E _{Bind} (eV/atom) Complex	Ads. Ene. (eV) Molecule
Vitamin-like			
B3(1) $C_6H_6N_2O_1/122.125$	4.862 (4.979)	6.499	1.749
B3(2) C ₆ H ₅ N ₁ O ₂ /123.109	5.014 (5.144)	6.551	1.825
B10 C ₇ H ₇ N ₁ O ₂ /137.136	4.875 (4.992)	6.463	1.996
B13 C ₅ H ₄ N ₂ O ₄ /156.096	5.071 (5.191)	6.542	1.801
B6(1) C ₈ H ₉ N ₁ O ₃ /167.164	4.718 (4.781)	6.335	1.315
B6(2) C ₈ H ₁₂ N ₂ O ₂ /168.196	4.474 (4.529)	6.208	1.324
K3 C ₁₁ H ₈ O ₂ /172.180	5.160 (5.225)	6.450	1.362
C C ₆ H ₈ O ₆ /176.124	4.573 (4.635)	6.318	1.242



(e) Isoniazid (1.561) (f) Chloroquine (1.897) (g) Aminoquinoline (1.885) (h)Galic Acid (1.804)

Figure 4. Illustration of the complexes with the largest adsorption energies. Molecules for each a different groups considered are shown. Below every molecule, the adsorption energy value is shown (in units of eV).

Next, we present more details of the electronic properties of the pristine molecules studied here, along with their changes after adsorption, as well as the electronic properties of the complexes formed during this process. To simplify the discussion, we emphasize the values of some of the molecular properties when the highest values were presented. The names, chemical formulae, and molecular weights of the studied molecules are given in the first column of the odd tables, while only the names and chemical formulae are given in the even tables.

Table 2. Some electronic properties for vitamin-like molecules or precursors. The system, Fermilevel, HOMO-LUMO gap of the complex (ratio of Gap(H-L) of complex to the pure molecule), and electric dipole of the molecule and of the complex. Some numbers are emphasized (bold font) to facilitate discussion, since they correspond to the largest values of different physical properties in the different series.

Molecule	E _{Fermi} (eV) Complex	Gap(H-L) (eV) Complex	Electric Dipole (Dbys) Molecule/Complex
Vitaminic-like			
B3(1) C ₆ H ₆ N ₂ O ₁	-5.842	2.897 (0.882)	(4.856, 10.306)
B3(2) $C_6H_5N_1O_2$	-5.461	2.634 (0.778)	(0.765, 4.697)
B10 $C_7H_7N_1O_2$	-5.089	2.133 (0.634)	(3.935, 1.681)
B13 $C_5H_4N_2O_4$	-6.061	1.911 (0.715)	(3.834, 0.840)
B6(1) $C_8H_9N_1O_3$	-6.246	2.129 (0.798)	(2.253, 11.052)
B6(2) $C_8H_{12}N_2O_2$	-5.549	2.129 (0.548)	(2.435, 10.731)
K3 $C_{11}H_8O_2$	-6.596	1.700 (0.878)	(1.042, 12.895)
$C C_6 H_8 O_6$	-5.895	2.983 (0.828)	(4.096, 16.337)

3.1. Vitamins

The first group to consider is vitamins. In Tables 1 and 2, some of their main properties are shown, in increasing order of their molecular weight. Table 1 displays the different vitamins considered here, the binding energy of the free molecules, the energy of the

complex, and the adsorption energy of the molecules. The binding energy of the freestanding vitamins ranged from 4.474 (B6(2)) to 5.160 (K3) eV/atom, while the binding energy of the complex ranged from 6.208 (B6(2)) to 6.551 (B3(2)) eV/atom (see columns 2 and 3). Overall, no correlation with molecular weight was observed in both energies; however, in the case of adsorption energy, a non-monotonous decrease was observed as a function of molecular weight. The assistance binding energy $E_{\rm B}^*[({\rm Molecule})]$ is listed in parentheses in the second column of Table 1, where its increment varied from 0.055 (B6(2)) to 0.130 (B3(2)) eV/atom. The largest increase was observed in Vitamins B3(2) and B13, although the largest adsorption energy occurred in vitamin B10 (see column 4). The largest increase in assistance binding energy did not correspond to the largest value of the adsorption energy, due to the different number of atoms in the molecules. The increase in $E_{\rm B}^{\rm c}$ [(Molecule)] with $E_{\rm Bind}$ indicates that the substrate improved the stability of molecules at relatively high values, with an average of approximately 0.093 eV/atoms. Regarding the use of different functionals (see Supplementary Materials), the largest differences in the adsorption energy values were observed between PBE and B3LYP, with an average of 16% higher in PBE. The case of vitamin B13 in PBE is highlighted, with value 40% and 24% larger than in B3LYP and in M06-L, respectively. Vitamin C was the only case where the adsorption energy in PBE was lower than the M06-L value (6%), while remaining comparable to that of B3LYP.

In Table 2, we present the Fermi level energy and HLG, as well as the electric dipole of the free-standing molecule and the corresponding one of the respective complex. In general, no correlation was observed between the Fermi level and atomic weight. In the third column, the HLG of the complex is shown; furthermore, in parentheses, we present the fraction to which the gap corresponds, compared to the free molecule one. In all the cases, the HLG of the complex was a fraction (<1) of that of the free molecule, and the smallest (largest) HLGs were observed for Vitamins K3 and B13 (C and B3(1)). In the fourth column, we present the electric dipole of the free molecule and its value after the adsorption process. In general, the electric dipole increased after adsorption, except in the case of vitamins B10 and B13, for which a decrease was observed. The smallest (largest) electric dipoles of the free vitamins were those of Vitamins B3(2) and K3 (B3(1) and C). After adsorption, the smallest electric dipole of the complex was observed for Vitamins B13 and B10, and the largest was for the complex with Vitamin C.

3.2. Amino Acids and/or Hormones

In Tables 3 and 4, some of the main properties of the amino acids and/or hormones are listed, in increasing order of molecular weight. Table 3 shows the binding energy of the free molecules in the second column, the energy of the complex in the third column, and the adsorption energy of the molecules in the fourth column. The binding energy of these free molecules ranged from 4.132 (DMG) to 4.924 (Guanine) eV/atom, while the binding energy of the complexes ranged from 6.262 (Dopamine) to 6.575 (Uracil) eV/atom. In general, no correlation with molecular weight was observed for both energies. In the second column of Table 3, the assistance binding energy $E_{\rm R}^{*}$ [(Molecule)] is presented in parentheses, which ranged from 0.052 (Dopamine) to 0.147 (Uracil) eV/atom. This group presented significantly high values in the increment of assistance binding energy, with an average of \approx 0.10 eV/atom. In particular, Uracil, Adenine, and Guanine presented the highest increments. The largest adsorption energy was observed for Adenine and Guanine bound by N (see Table 3, fourth column). For the comparison between different functionals (see Supplementary Materials), the largest differences in adsorption energy values were between PBE and B3LYP, with an average of 17% higher PBE values. Highlighting the cases of Guanine(N) and Dopamine, this value was much higher in PBE, being approximately 37% higher than the B3LYP case and 18% higher than the M06-L case. Cytosine was the only case where the adsorption energy in PBE was lower than in B3LYP and M06-L (\approx 10%).

In Table 4, we present the Fermi level energy and HLG, as well as the electric dipole of the free-standing molecules and the corresponding one for each complex in columns 1–4,

respectively. In general, no correlation between the Fermi level (second column) and the atomic weight of the molecules was detected. In the third column, the HLG of the complex is shown, while the fraction to which the gap corresponds compared to that of the free molecule is given in parentheses. In all cases, the HLG of the complex was a fraction (<1) of the HLG of the free molecule. The smallest (largest) HLGs were observed in DMG and Dopamine (Uracil(O), Thymine, and Guanine). In the fourth column, we present the electric dipole of the free molecule and its value after the adsorption process; in general, the electric dipole increased after adsorption, except for the case of Guanine bound by N, for which a decrease was observed. The smallest (largest) electric dipoles of the free molecules were observed for DMG and Phenylalanine (Cytosine and Guanine); meanwhile, after adsorption, the smallest (largest) electric dipoles of the free molecules of the smallest (largest) electric dipoles of the free molecules were for Guanine bound by N, DGM, and Phenylalanine (Cytosine and Guanine bound by O).

Table 3. Binding energies for the molecules Equation (1) and Equation (4), binding energy of the complex (molecule-cluster) Equation (2) and adsorption energies Equation (3) for amino acid and hormone. Some numbers are emphasized (bold font) to facilitate discussion, since they correspond to the largest values of different physical properties in the different series.

Molecule/Weight	E _{Bind} (eV/atom) Molecule	E _{Bind} (eV/atom) Complex	Ads. Ene. (eV) Molecule
Amino acid and/or Hormones			
DMG C ₄ H ₉ N ₁ O ₂ /103.120	4.132 (4.250)	6.326	1.884
Cytosine C ₄ H ₅ N ₃ O ₁ /111.100	4.708 (4.835)	6.515	1.653
Histamine $C_5H_9N_3/111.150$	4.318 (4.434)	6.340	1.976
Uracil C ₄ H ₄ N ₂ O ₂ /112.087 Bind O	4.905 (5.049)	6.574	1.735
Bind N	(5.052)	6.575	1.768
Thymine C ₆ H ₅ N ₂ O ₂ /126.113	4.765 (4.862)	6.475	1.456
Adenine C ₅ H ₅ N ₅ /135.130	4.917 (5.053)	6.514	2.037
Glutamic acid $C_5H_9N_1O_4/147.129$	4.415 (4.479)	6.302	1.230
Guanine C ₅ H ₅ N ₅ O ₁ /151.126 Bind O	4.924 (5.021)	6.488	1.549
Bind N	(5.053)	6.495	2.062
Dopamine C ₈ H ₁₁ N ₁ O ₂ /153.178	4.528 (4.580)	6.262	1.150
Histidine $C_6H_9N_3O_2/155.157$	4.525 (4.623)	6.315	1.953
Phenylalamine $C_9H_{11}N_1O_2/165.189$	4.663 (4.737)	6.285	1.708

Table 4. Some electronic properties for amino acid and hormone molecules. The system, Fermilevel, HOMO-LUMO gap of the complex (ratio of Gap(H-L) of complex to the pure molecule), and electric dipole of the molecule and of the complex. Some numbers are emphasized (bold font) to facilitate discussion, since they correspond to the largest values of different physical properties in the different series.

Molecule	E _{Fermi} (eV) Complex	Gap(H-L) (eV) Complex	Electric Dipole (Dbys) Molecule/Complex
Amino acid and/or Hormones			
DMG $C_4H_9N_1O_2$	-5.252	1.492 (0.397)	(1.824, 5.005)
Cytosine C ₄ H ₅ N ₃ O ₁	-5.562	3.068 (0.882)	(6.200, 20.067)
Histamine C ₅ H ₉ N ₃	-5.093	2.496 (0.511)	(2.662, 13.156)
Uracil C ₄ H ₄ N ₂ O ₂ Bind O	-6.236	3.184 (0.863)	(4.295, 11.535)
Bind N	-6.644	2.908 (0.788)	(4.295, 8.581)
Thymine C ₆ H ₅ N ₂ O ₂	-5.811	3.206 (0.886)	(4.316, 13.366)
Adenine C ₅ H ₅ N ₅	-6.265	2.467 (0.656)	(2.611, 7.411)
Glutamic acid C ₅ H ₉ N ₁ O ₄	-5.750	2.325 (0.559)	(2.420, 10.884)
Guanine C ₅ H ₅ N ₅ O ₁ Bind O	-5.670	3.200 (0.863)	(6.124, 19.890)
Bind N	-5.493	1.749 (0.472)	(6.124 , 3.097)
Dopamine C ₈ H ₁₁ N ₁ O ₂	-5.315	1.586 (0.394)	(2.275, 6.786)
Histidine C ₆ H ₉ N ₃ O ₂	-5.531	1.787 (0.426)	(5.384, 10.078)
Phenylalamine $C_9H_{11}N_1O_2$	-5.926	1.973 (0.478)	(1.901, 5.031)

3.3. Analgesics and Anti-Inflammatory Drugs

Tables 5 and 6 show some of the main properties of analgesics and anti-inflammatories, in increasing order of molecular weight. Table 5 shows the binding energies of the free molecules in the second column, the energy of the complex in the third column, and the adsorption energy of the molecules in the fourth column. The binding energy of the free molecules ranged from 4.391 (Tramadol) to 4.995 (Enantyum) eV/atom, while the binding energy of the complex ranged from 5.841 (Tramadol) to 6.499 (Salicylic Acid) eV/atom. A non-monotonic decrease was observed as a function of molecular weight, in general, in both energies for the analgesics. In the second column of Table 5, the assistance binding energy $E_{\rm B}^*$ (Molecule) is presented in parentheses, with increase ranging between 0.036 (Tramadol) and 0.088 (Salicylic) eV/atom. The increase in the assistance energy in this group was moderately low, with an average value of ≈ 0.06 eV/atoms, with Salicylic and Paracetamol presenting the highest increases. The largest adsorption energies were observed for Ibuprofen and Enantyum (see column 4). In the comparison between the different approaches (see Supplementary Materials), the largest differences in adsorption energy values were between PBE and B3LYP, particularly for molecules with high molecular weight. The strongest discrepancies were presented in Ibuprofen, Tramadol, Enantyum, and Diclofenac being \approx 44% higher in PBE with respect to the values obtained by B3LYP; this difference was smaller in the case of M06-L ($\approx 23\%$), but still significant. The other pain-relief (low molecular weight) molecules had similar adsorption energies with the three functionals used (within an \approx 3% range of difference).

In Table 6, we present molecules in the first column, the Fermi level energy in the second column, HLG in the third column, and the electric dipoles of the free-standing molecule and the corresponding complex in the last column. In general, no correlation in Fermi level was observed with the atomic weight of the molecules. In the third column, we indicate the HLG of the complex, as well as the fraction to which the gap corresponds compared to that of the free molecule in parentheses. In all the cases, the HLG of the complex was a fraction (<1) of the HLG of the free molecule. The smallest (largest) HLGs were observed in Tramadol, Ibuprofen, and Enantyum (Salicylic, Aspirin, and Diclofenac). In the fourth column, we present the electric dipole of the free molecule and its value after the adsorption process. In general, the electric dipole showed a complex dependence after adsorption but, in some cases, an increase was observed. The smallest (largest) electric dipoles of the free molecules were observed for Ibuprofen and Enantyum (Salicylic and Diclofenac), while, after adsorption, the smallest (largest) electric dipoles of the complex were observed for Ibuprofen and Enantyum (Paracetamol and Diclofenac).

Table 5. Binding energies for the molecules Equations (1) and (4), binding energy of the complex (molecule-cluster) Equation (2), and adsorption energies Equation (3) for analgesics and antiinflammatory drugs. Some numbers are emphasized (bold font) to facilitate discussion, since they correspond to the largest values of different physical properties in the different series.

Molecule/Weight	E _{Bind} (eV/atom) Molecule	E _{Bind} (eV/atom) Complex	Ads. Ene. (eV) Molecule
Analgesics			
Salicylic C ₇ H ₆ O ₃ /138.120	4.988 (5.076)	6.499	1.400
Paracetamol C ₈ H ₉ N ₁ O ₂ /151.163	4.744 (4.827)	6.366	1.651
Aspirin C ₉ H ₈ O ₄ /180.157	4.966 (5.033)	6.401	1.407
Ibuprofen C ₁₃ H ₁₈ O ₂ /206.281	4.536 (4.595)	6.068	1.936
Tramadol C ₁₆ H ₂₅ N ₁ O ₂ /263.375	4.391 (4.427)	5.841	1.575
Anti-inflammatory			
Enantyum C ₁₆ H ₁₄ O ₃ /254.285 Diclofenac C ₁₄ H ₁₁ N ₁ O ₂ Cl ₂ /296.147	4.995 (5.052) 4.897 (4.957)	6.231 6.238	1.890 1.811

Table 6. Some electronic properties for analgesics and anti-inflammatory molecules. The system, Fermi-level, HOMO-LUMO gap of the complex (ratio of Gap(H-L) of complex to the pure molecule), and electric dipole of the molecule and of the complex. Some numbers are emphasized (bold font) to facilitate discussion, since they correspond to the largest values of different physical properties in the different series.

Molecule	E _{Fermi} (eV) Complex	Gap(H-L) (eV) Complex	Electric Dipole (Dbys) Molecule/Complex
Analgesics			
Salicylic C ₇ H ₆ O ₃	-6.547	2.947 (0.799)	(6.352, 5.092)
Paracetamol C ₉ H ₈ N ₁ O ₂	-5.416	2.569 (0.729)	(3.362, 15.447)
Aspirin C ₉ H ₈ O ₄	-6.517	2.936 (0.806)	(4.570, 5.545)
Ibuprofen C ₁₃ H ₁₈ O ₂	-5.437	1.713 (0.408)	(1.708, 1.839)
Tramadol $C_{16}H_{25}N_1O_2$	-4.865	0.897 (0.268)	(2.136, 9.487)
Anti-inflammatory drugs			
Enantyum $C_{16}H_{14}O_3$	-5.3355	1.464 (0.517)	(1.759, 3.084)
Diciofenac $C_{14}H_{11}N_1O_2C_2$	-0.1151	2.811 (0.821)	(5.410, 18.412)

3.4. Antibiotis

Tables 7 and 8 show some of the main properties of drugs typically used against bacteria, viruses, and parasites, in increasing order of molecular weight. Table 7 shows the binding energy of the free molecules in the second column, the energy of the complex in the third column, and the adsorption energy of the molecules in the fourth column. The binding energies of the free-standing molecules belonging to the antibiotic group presented a relatively narrow range of values, from 4.440 (Chloroquine) to 4.986 (Aminoquinoline) eV/atom, while those of the binding energy of the complex are more dispersed in energy (similarly to the previous groups), ranging from 5.813 (Chloroquine) to 6.513 (Pyrazinamide) eV/atom. The fact that there were very few molecules with multiple different functions made it difficult to observe a general trend as a function of molecular weight. In the second column of Table 7, the assistance binding energy $E_{\rm B}^{\rm s}[({\rm Molecule})]$ is presented in parentheses, with increment ranging between 0.030 (Amodiaquinine) and 0.10 (Aminoquinoline) eV/atom; thus, the increase in the assistance energy was moderate, as observed by an intermediate increase in the values with an average of $\approx 0.07 \text{ eV}/\text{atom}$. In this regard, Pyrazinamide and Aminoquinoline showed the greatest increases. The largest adsorption energies were observed for Chloroquine, Aminoquinoline, and Isoniazid bound by N (see column 4), for each of the different subgroups in this table. Considering the different theoretical frameworks, the largest differences in the adsorption energy values were observed between PBE and B3LYP, as in the case of the pain-relief molecules. The strongest discrepancies were presented between PBE and B3LYP for Isoniazid(N) (\approx 28%), Chloroquine and Hydroxychloroquine (both \approx 41%), and Amodiaquinine, with larger values presented in the PBE approximation. In the case of M06-L, the difference in adsorption energies for the same previously cited molecules with respect to PBE was smaller ($\approx 10\%$). The other antibiotic molecules had similar adsorption energies with the three functionals used (ranging within $\approx 8\%$).

In Table 8, we present the Fermi level energy and HLG, as well as the electric dipole of the free-standing molecule and that of the corresponding complex. In general, no correlation was observed between the Fermi level and the atomic weight of the molecules. In the third column, the HLG of the complex is shown, as well as the fraction to which the gap corresponds compared to that of the free molecule in parentheses. In all cases, the HLG of the complex was a fraction (<1) of the HLG of the free molecule. The smallest (largest) HLGs were observed in Amodiaquine, Chloroquine, and Hidroxychloroquine (Isoniazid, Favipiravir, and Aminoquinoline, for each of the subgroups). In the fourth column, we present the electric dipole of the free molecule and its value after the adsorption process. In general, the electric dipole increased considerably after adsorption; the only exception

was Amodiaquine, for which a reduction was observed. The smallest (largest) electric dipoles of the free molecules were observed for the Antibiotic group (Chloroquine and Amodiaquine); meanwhile, after adsorption, the smallest (largest) electric dipole of the complex was observed with Amodiaquine (the Antiviral group).

Table 7. Binding energies for the molecules Equations (1) and (4), binding energy of the complex (molecule-cluster) Equation (2) and adsorption energies Equation (3) for the antibiotics group. Some numbers are emphasized (bold font) to facilitate discussion, since they correspond to the largest values of different physical properties in the different series.

Molecule/Weight	E _{Bind} (eV/atom) Molecule	E _{Bind} (eV/atom) Complex	Ads. Ene. (eV) Molecule
Antibiotics			
$\begin{array}{c} Pyrazinamide \ C_5H_5N_3O_1/123.113\\ Isoniazid \ C_6H_7N_3O_1/137.139 \ Bind \ O\\ Bind \ N \end{array}$	4.845 (4.944) 4.698 (4.788) (4.789)	6.513 6.418 6.418	1.379 1.544 1.561
Anti-virals			
Favipiravir C ₅ H ₄ N ₃ O ₂ F ₁ /157.103 Chloroquine (CH.) C ₁₈ H ₂₆ N ₂ Cl ₁ /319.872	4.913 (5.000) 4.440 (4.480)	6.503 5.813	1.298 1.897
Hydroxy CH. C ₁₈ H ₂₆ N ₃ O ₁ Cl ₁ /335.876	4.534 (4.572)	5.854	1.856
Anti-parasites			
$\begin{array}{c} \mbox{Aminoquinoline} \ \ C_9H_8N_2/144.173 \\ \mbox{Metrodinazole} \ \ \ C_6H_9N_3O_3/171.156 \\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ $	4.986 (5.085) 4.458 (4.510) 4.705 (4.735)	6.448 6.265 5.937	1.885 1.097 1.396

Table 8. Some electronic properties for anti-group molecules. The system, Fermi-level, HOMO-LUMO gap of the complex (ratio of Gap(H-L) of complex to the pure molecule), and electric dipole of the molecule and of the complex. Some numbers are emphasized (bold font) to facilitate discussion, since they correspond to the largest values of different physical properties in the different series.

Molecule	E _{Fermi} (eV)	Gap(H-L) (eV)	Electric Dipole (Dbys)
	Complex	Complex	Molecule/Complex
Antibiotics			
Pyrazinamide C ₅ H ₅ N ₃ O ₁	5.933	2.678 (0.923)	(3.233, 15.750)
Isoniazid C ₆ H ₇ N ₃ O ₁ Bind O	5.653	2.784 (0.822)	(2.238, 11.826)
Bind N	5.8097	2.557 (0.755)	(2.238, 9.994)
Anti-virals			
$ \begin{array}{c} \hline & \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$	- 5.7693	2.369 (0.883)	(5.432, 17.269)
	-4.8366	1.427 (0.510)	(6.213 , 17.606)
Hydroxy CH. C ₁₈ H ₂₆ N ₃ O ₁ Cl ₁ Anti-parasites	-4.9982	1.593 (0.538)	(4.281, 15.971)
$\begin{array}{c} Aminoquinoline \ C_9H_8N_2\\ Metrodinazole \ C_6H_9N_3O_3\\ Amodiaquinine \ C_{20}H_{22}N_3O_1Cl_1 \end{array}$	-5.5707	2.700 (0.852)	(3.543, 14.791)
	- 6.5734	2.034 (0.718)	(4.129, 14.665)
	-5.1099	1.259 (0.545)	(5.663 , 4.842)

3.5. Industry and/or Food

In Tables 9 and 10, some of the main properties of molecules commonly used in food and/or industry are shown, in increasing order of their molecular weight. Table 9 presents the binding energy of the free molecules in the second column, the energy of the complex in the third column, and the adsorption energy of the molecules in the fourth column.

The binding energies of these free-standing molecules ranged from 4.263 (Glucose) to 5.424 (Anthraquinone) eV/atom, while the binding energies of the complex ranged from 6.152 (Glucose) to 6.566 (Biotinidase) eV/atom. It was difficult to observe a general trend as a function of molecular weight, due to the very different characteristics and multiple different uses of these molecules. In the second column of Table 9, the assistance binding energy $E_{\rm B}^{\rm e}$ (Molecule) is presented in parentheses, with increment ranging from 0.012 (Biotinidase) to 0.10 (Gallic acid) eV/atom. As such, the increase in the assistance energy was relatively low, with an average value of $\approx 0.054 \text{ eV}/\text{atom}$, where Gallic acid presented the greatest increase. The largest adsorption energies were observed for Glucose and Gallic acid (see column 4). As in all previous cases, the largest differences in the adsorption energy values were between PBE and B3LYP functionals (see Supplementary Materials). The strongest discrepancies between PBE and B3LYP were presented for Thymol (\approx 27%), Glucose, Gallic acid, and Anthraquinone (the latter all presenting a difference of $\approx 24\%$), with the higher values presented for the PBE approximation. In the case of M06-L adsorption energies, this difference was about half that observed in B3LYP, with respect to the PBE values. It is important to highlight the case of Resveratrol, where the difference in E_{Ads} .[(Molecule)] was very large between the three functionals (see Supplementary Materials).

In Table 10, we present the Fermi level energy and HLG, as well as the electric dipole of the free-standing molecule and that of the corresponding complex. In general, no correlation was observed between the Fermi level and the atomic weight of molecules. In the third column, we present the HLG of the complex, as well as the fraction to which the gap corresponds compared to that of the free molecule in parentheses. In all cases, the HLG of the complex was a fraction (<1) of the HLG of the free molecule. The smallest (largest) HLGs were observed for Resveratrol and Anthraquinone (Biotindase). In the fourth column, we present the electric dipole of the free molecule and its value after the adsorption process. Overall, the electric dipole increased considerably after adsorption—in particular, it is worth noting the case of Anthraquinone, which changed from non-polar to a relatively high value. The only exception was Glucose, for which a reduction in the electric dipole was observed. The smallest (largest) electric dipoles of the free molecules were observed for Anthraquinone, Carbachole, and Thymol (Biotinidase, Gallic acid and Glucose); meanwhile, after adsorption, the smallest (largest) electric dipole of the complex was observed for Glucose (Biotinidase).

Molecule/Weight	E _{Bind} (eV/atom) Molecule	E _{Bind} (eV/atom) Complex	Ads. Ene. (eV) Molecule
Industry			
Biotinidase C ₃ H ₄ O ₃ /88.062	4.568 (4.580)	6.566	1.230
Thymol C ₁₀ H ₁₄ O ₁ /150.218	4.497 (4.545)	6.193	1.215
Carbachol C ₁₀ H ₁₄ O ₁ /150.218	4.498 (4.544)	6.192	1.163
Glucose C ₆ H ₁₂ O ₆ / 180.160	4.263 (4.334)	6.152	1.706
Gallic acid C ₇ H ₆ O ₅ /184.147	4.970 (5.070)	6.462	1.804
Anthraquinone $C_{14}H_8O_2/208.212$	5.424 (5.483)	6.480	1.427
Resveratrol C ₈ H ₁₂ N ₂ O ₂ /228.240	4.980 (5.023)	6.272	1.029

Table 9. Binding energies for the molecules (Equations (1) and (4)), binding energy of the complex (molecule-cluster) (Equation (2)) and adsorption energies (Equation (3)) for molecule of common use in industry. Some numbers are emphasized (bold font) to facilitate discussion, since they correspond to the largest values of different physical properties in the different series.

Table 10. Some electronic properties for various molecules. The system, Fermi-level, HOMO-LUMO gap of the complex (fraction of Gap(H-L) of pure molecule), and electric dipole of the molecule and of the complex. Some numbers are emphasized (bold font) to facilitate discussion, since they correspond to the largest values of different physical properties in the different series.

Molecule	E _{Fermi} (eV) Complex	Gap(H-L) (eV) Complex	Electric Dipole (Dbys) Molecule/Complex
Industry			
Biotinidasa C ₃ H ₄ O ₃	-6.289	3.202 (0.526)	(5.161, 16.954)
Thymol $C_{10}H_{14}O_1$	-5.127	2.246 (0.532)	(1.280, 7.136)
Carbachol C ₁₀ H ₁₄ O ₁	-5.733	2.424 (0.571)	(1.190, 8.897)
Glucose C ₆ H ₁₂ O ₆	-5.763	2.022 (0.401)	(3.270, 1.011)
Gallic acid $C_7H_6O_5$	-5.347	2.140 (0.662)	(3.658, 9.506)
Anthraquinone C ₁₄ H ₈ O ₂	-6.372	1.792 (0.829)	(0.000, 11.731)
Resveratrol C ₈ H ₁₂ N ₂ O ₂ 0	-5.264	1.390 (0.531)	(1.694, 2.966)

3.6. Chemical Bond Size

In this section, we briefly comment on the size of the chemical bonds in the complexes (molecule + cluster). The mean inter-atomic distance between the anchor point of the substrate (Ti atom) and the molecule linked by the X-atom (anchor) presented a slight dispersion (as shown in Table 11), with an average value of 2.12 Å. The bond was slightly larger when Nitrogen was the anchor, compared to oxygen. Similarly, the average adsorption energies were also larger when anchoring with Nitrogen than with an Oxygen atom. Regarding the inter-atomic distance between the anchor X-atom and the next atom in the chain (C), it was generally somewhat scattered (having a narrow distribution) with a mean value of 1.34 (Å), while we observed similar behavior as in the case of the Ti–X bond length with larger values, when considering Nitrogen with respect to the Oxygen. Although our sample of adsorbed molecules here was small, this behavior is relevant and suggests a trend. For a more detailed analysis of the size of the bond lengths, the coordinates of all the complexes are provided in the Supplementary Materials.

Table 11. Average bond length for the different groups of molecules studied here and its range in parentheses. We also include the average adsorption energies for the different groups and its range in parentheses. A distinction is made in each case on the type of anchor X-atom. The Antis- label is for Antibiotics, Anti-virals, and Anti-parasites.

Molecule Binding by X	Ti-X (Distance) (Å) Ave. First Bond	X-C (Distance) (Å) Ave. Second Bond	Ave. Ads. Energy (eV)
Vitamin			
X=O	2.07 (1.98–2.13)	1.31 (1.25–1.47)	1.577 (1.242, 1.996)
Amino acid			
X=O	2.07 (2.02-2.17)	1.29 (1.25-1.42)	1.590 (1.150, 1.953)
X=N	2.16 (2.14–2.18)	1.36 (1.36–1.37)	1.961 (1.768, 2.062)
Analgesic			
Х=О	2.07 (1.97–2.16)	1.32 (1.27–1.50)	1.667 (1.400, 1.936)
Antis-			
Х=О	2.09 (2.02-2.20)	1.31 (1.27–1.43)	1.343 (1.097, 1.544)
X=N	2.20 (2.18-2.24)	1.38 (1.36–1.40)	1.799 (1.561, 1.897)
Industry			
Х=О	2.13 (2.04–2.20)	1.37 (1.24–1.49)	1.368 (1.029, 1.804)

Once the selected molecules were optimized and the wave function was computed at three different levels (PBE, B3LYP, and M06-L), a Molecular Orbital (MO) analysis was performed. Here, we considered only the M06-L functional for the sake of simplicity. In Figure 5, we show the molecular orbital analysis only for those molecules which presented a higher energy of adsorption in molecule– TiO_2 complex, as illustrated in Figure 4. It is clear that the high occupied molecular orbital (HOMO) was located on the biological molecule (Figure 5A) in all cases, which demonstrates the electronic density distribution on both the TiO₂ and the biological molecule. These results corroborate the binding mode in the molecules and higher adsorption energies in these systems. In turn, as depicted in all the systems in Figure 5B, the LUMO was located systemically in the TiO_2 cluster, indicating the possibility that the TiO_2 cluster functions as a multi-adsorbent of more than one biological molecule, thus potentially promoting the delivery of more than one drug and presenting a multi-functional character. Although the localization characteristics of HOMO and LUMO (quoted above) are only presented for systems with higher adsorption energies, they are significant and suggest that this behavior is mainly due to the TiO_2 cluster; as such, it should be present in the other systems studied here.

3.8. Comparison with Other Calculations

Although our calculations for the adsorbed molecules are strictly valid only when the substrate is a cluster, it is noteworthy that our cluster (substrate) can be suggested as a possible model to imitate (mimic) the volumetric and surface behavior of TiO₂ surface substrates [29]. For this reason, we briefly comment on similar calculations for the adsorption energies carried out in different surfaces and finite-size systems (i.e., clusters and tubes).

We first examine the case of infinite systems, such as surfaces, and consider finitesize systems later. The main sources of differences in the adsorption energy values are the following: (i) Size effects and (ii) substrate used. Considering the former, regarding the finite-size effects for extended systems such as surfaces or solids, our values will be systematically larger as expected; meanwhile, in the case of tubes and clusters, the values are comparable. Considering the latter, the differences due to the substrate are more difficult to estimate, being the main reason for the differences in adsorption energies.

In the case of amino acids adsorbed on Silicate surfaces, such as Adenine, Cytosine, Guanine, Thymine, and Uracil, the reported values using VASP/PBE [63] were systematically smaller (by a factor of 1.5 to 2.5) than those obtained here. In the case of Uracil VASP/PW91 [64] on Au surfaces, the same behavior was also observed. For Guanine on Ge surfaces using VASP/PAW/vdW [65], the reported values were smaller, by a factor of 1.1 to 1.5, depending on whether the adsorption considers Nitrogen or Oxygen. In the case of Phenylalanine on quartz with QE/B86bPBE [66], the adsorption energy values were also smaller (by a factor of 1.4). For dopamine on anatase surface with VASP/PBE/GGA+U [67], the difference in the average adsorption energy from our energy value was on the order of 6%, while, in the case of Glucose QE/PBE [68], our value with a configuration equivalent to that proposed by them was 30% larger; in this case, our putative ground state was almost double.

Regarding the molecules of the Antibiotics group adsorbed on finite-size systems, Favipiravir adsorbed on $C_{19}M$ fullerene where M is an anchor impurity, such as Si (QTAIM-/M06/BSSE) [69] or Ti (G90/B3LYP) [70] has been investigated. For $C_{19}Si$, the difference in the average adsorption energy was smaller than 25% with M06-L and 36% for PBE; meanwhile, in the case of $C_{19}Ti$, the differences were less than 5%. For Pyrazinamide (Dmol3/PBE) [71] on graphene tubes doped with N, the reported values were very similar to our values with the three used functionals. Finally, for Isoniazid (SIESTA/PBE) [72] on BN tubes, the results differed by a factor of half, with respect to our values obtained with PBE.



Figure 5. Illustration of Molecular Orbitals of molecules with higher energy of adsorption (see also Figure 4): (**A**) The HOMO orbitals; and (**B**) LUMO orbitals for each one of the corresponding molecules are shown by (**A**) and (**B**), respectively. The blue surfaces represent positive values of the molecular orbital and the red surfaces correspond to negative values of the molecular orbital.

3.9. Activity against SARS-CoV-2 (Docking)

Following the above methods, docking assays against the SARS-CoV-2-M^{*Pro*} were performed, in order to evaluate the possible activity of some of the considered systems against COVID-19; in particular, the systems with Chloroquine (Clq), Hydroxychloroquine (Hclq), and favipiravir (Fav) were tested, due to their implication as possible antivirals.

As mentioned in the Methods section, the co-crystalized molecule on the protein and Prop8 was evaluated. We further tested the free drugs and the free TiO_2 cluster on the same biological target, in order to compare the effect of the TiO_2 cluster on the interaction of the drug with the selected target. Table 12 shows the main ligand–target interaction energies, which demonstrate that, in terms of Ligand Efficiency (the more negative the value, the

better the ligand of the molecule is), free Favipiravir presented the highest interaction, due to the more negative value (this being the best-studied ligand against SARS-CoV-2- M^{Pro}), followed by Chloroquine and Hydroxychloroquine, with values of -0.291, -0.266, and -0.265 eV (-6.73, -6.14, and -6.13 kcal/mol), respectively.

Table 12. Main interaction energies, in eV (kcal/mol), between the studied antiviral systems and the SARS-CoV-2- M^{Pro} . LE represents the ligand efficiency (LE = Energy/#Heavy Atoms), and HBond shows the hydrogen bond interaction energies, where Heavy Atoms indicate all atoms excluding hydrogen atoms.

Molecule	Total Energy	LE	HBond
Co-crystal	-8.73 (-201.31)	-0.175(-4.11)	-0.132 (-3.05)
Prop8	-11.09 (-255.79)	-0.236 (-5.44)	-0.346(-7.99)
Fav	-3.21(-74.00)	-0.292 (-6.73)	-0.046(-1.06)
Clq	-5.86 (-135.02)	-0.266(-6.14)	-0.075(-1.74)
Hclq	-6.12(-141.05)	-0.266 (-6.13)	-0.101(-2.33)
Fav-(TiO ₂)	-2.69(-62.10)	-0.038(-0.87)	-0.268 (-6.19)
Clq-(TiO ₂)	-3.78(-87.11)	-0.046(-1.06)	-0.291 (-6.72)
Hclq-(TiO ₂)	-3.65(-84.16)	-0.044(-1.01)	-0.327 (-7.55)
(TiO ₂)	0.30 (7.01)	0.005 (0.12)	-0.409 (-9.43)

In accordance with the ligand efficiency and whole interaction energies, the TiO_2 can interact with SARS-CoV-2-M^{*Pro*}, but in a much less efficient way than the free drug. However, by analyzing the results in Table 12, we can see that the TiO_2 cluster promoted a greater hydrogen bond interaction with the selected target, providing a means to anchor the cluster on the surface of the protein and then deliver the drug. The above is better explained by analyzing the target site depicted in Figure 6, which illustrates a TiO_2 cluster anchored on the protein surface (Figure 6A), delivering the drug into the cavity. Finally, by analyzing the hydrophobic surfaces of the ligand–target interactions, Figure 6B shows that the input channel to the active site presents a higher hydrophilic surface, which interacts with the hydrophobic surface. The anchorage of the complex suggests possible inactivation and spread of the virus through a steric blockade. The results above lead to the conclusion that titanium dioxide is a potential drug carrier of antiviral compounds against SARS-CoV-2, allowing for delivery of the drug into the active site.



Figure 6. Illustration of the Clq–TiO₂ system coupled to the SARS-CoV-2-M^{*Pro*}: (**A**) full view; and (**B**) hydrophobic interactions into the active site (zoom). Hydrophilic and hydrophobic surfaces are depicted in red and blue, respectively.

4. Conclusions

Our calculations showed that the adsorption energies of the biological molecules considered here ranged from 1.03 to 2.06 eV, with a mean value of 1.61 eV. The most significant adsorption energy values were presented in the amino acid and analgesic groups, followed by vitamins and antibiotics. The final group, with multiple applications (specifically in industry), was very heterogeneous and its average value was the lowest (1.37 eV), albeit with a range similar to that of the previous groups.

For all of the molecules studied here, we observed that the substrate increased the stability of the adsorbed molecules, with values ranging between 12 and 150 meV/atom, thus demonstrating the importance of the $(TiO_2)_{20}$ substrate in the stabilization of the complex; this is significant in consideration of its biological safety.

Comparison between the different functionals indicated that, in general, the binding energy values for free-standing molecules (E_B [(Molecule)]_{Free}) calculated with M06-L were systematically higher than those corresponding to B3LYP, while the PBE values were typically very similar to those of B3LYP. The values of the energy of formation of the complex (E_B [(Complex)]) met the following inequality: PBE > M06-L > B3LYP. This clearly reflects the differences in binding energy reported for the (TiO₂)₂₀ substrate cluster (as mentioned above) with the three functionals used here. In the case of the adsorption energy ($E_{Ads.}$ [(Molecule)]), the values of M06-L were systematically higher than those corresponding to B3LYP, and the PBE adsorption energies were mostly larger than those of M06-L; although, in a few cases, they were smaller, with differences of less than 10%.

The HLG of the complex system (molecule + substrate) was always a fraction of the value presented by the free-standing molecules. In all of the groups studied here, we found complexes with lower HLG values than the pristine substrate cluster— $(TiO_2)_{20}$ with 3.22 eV—allowing the complex (molecule + cluster) to respond to a much wider range of solar radiation, thereby increasing the efficiency of titanium dioxides in applications that require HLG reduction, such as solar devices and/or in photo-degradation processes, such as ecological packaging.

The large values in the electric dipole of the complex allow us to move it through the application of an electric field, which can be very useful in cases where the titanium dioxide cluster is to be used as a transporter or drug carrier in possible therapies. It is important to highlight the large values obtained in the electric dipole in the case of the group of antibiotics. Additionally, it is important to note the possible use of this kind of nanocluster for the delivery of drugs to biological targets, as was demonstrated in this study using the TiO_2 clusters as carriers of antiviral drugs against the main protease of SARS-CoV-2.

The results obtained in this paper should be considered as the first steps towards understanding real systems, which can help us to understand the behavior of molecules adsorbed onto nanoparticles of titanium dioxide, even though our considered substrate was considerably smaller than experimental nanoparticle TiO_2 . However, the presented results provide general trends within the range of variations that their properties could have. Furthermore, our results obtained on finite systems also provide guidance regarding which molecules can be tested in TiO_2 nanoparticle and surface systems in order to achieve the desired electronic properties.

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