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Chitosan Ibuprofen Interaction: Modeling Approach

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Semiempirical quantum mechanical calculations were carried out at PM6 to study possible interactions between chitosan and ibuprofen. Four active sites exist which dedicate them as possible sites of interaction while the fifth one is following a complex state between amine group of chitosan and COOH of ibuprofen. The same interactions were tried in the existence of three water molecules. QSAR descriptors were also utilized to describe each interaction. Results indicated there is no charge transfer in such interactions. In addition, there are changes in the partial charge is followed with a change in total dipole moment. The interaction is likely to take place through OH…HO that is confirmed by both total dipole moment and HOMO/LUMO band gap energies.

Keywords: Chitosan, Ibuprofen, PM6, QSAR, Hydration.

RESEARCH ARTICLE

1. INTRODUCTION

Quantum mechanical calculations continue to be the hot topic for analyzing several systems and molecules. Although there are many level of theories but semiempirical methods still provide, structural, electronic, spectroscopic data for many systems and molecules.[1–5] It is widely applied to understand the reactivity and interactions of biological interactions. Recently, molecular modeling at different levels is supporting the study of molecular structure of biological molecules to understand their interactions. Assessment of the genotoxicity of dioxins in the marine environment was subjected to several techniques while confirmation is carried out with *ab initio* quantum mechanical calculations.[6] Molecular modeling together with fluorescence spectroscopy, circular dichroism spectroscopy were applied to understand the sucralose with whey protein interactions.[7] Molecular modeling at density functional theory (DFT) level was utilized with several spectroscopic tools as confirming tool to describe the interaction of bovine serum albumin (BSA) with and darunavir.[8] For the interaction between cholesterol derivatives and the Mce4A, spectroscopic tools were combined with molecular dynamics to carry out this task.[9] Molecular docking was confirming the spectroscopic tools for understanding the *in vitro* cytotoxicity of organometallic palladium complexes with biologically active β-diketones.[10] Based on these knowledge molecular modeling is a useful tool to describe the interaction of different biological molecules. Biomaterials have been widely applied according to their amazing chemical, biological and industrial properties; among them chitosan which obtained from natural sources.[11] It is derived from chitin, the second most abundant after cellulose.[12] While crude chitosan is not of big concern, it needs some kind of modifications to meet the emerging demands.[13–15] Pharmaceuticals at trace level are early detected in wastewater as well as different types of water.[16] It is reported later that these levels could be toxic for different aquatic life.[17] Ibuprofen (IBP) is classified among the most highly toxic pharmaceutical residues according to its fatal and chronic risk.[18] Many reports indicated that IBP is detected in rivers as well as some wastewater treatment stations in Europa.[19–21]

Therefore, many attempts are tried to remove IBP with different techniques, some examples will be given as in the following. Nano TiO_2 is utilized as a tool for photocatalysis of IBP;[22] the problem is how to efficiently remove the TiO_2. Sol–gel technique is followed to prepare magnetic-core titanium dioxide then IBP is subjected to photocatalytic removal.[23] A study is conducted to compare IBP removal efficiency and kinetics. The study is applied for three wetland designs. It is indicated that the removal process could be according to the microbial degradation by the fixed bed biofilm.[24]

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The present work is conducted to apply PM6 quantum mechanical calculations to study the possible interaction between chitosan and IBP.

2. CALCULATION DETAILS

Molecular model molecules of chitosan monomer (Cs), chitosan four units (4Cs) and ibuprofen molecule (IBP) were built up as shown in Figure 1. Then, these model molecules were energetically optimized using semiempirical quantum mechanical calculations at PM6 level using SCIGRESS 3.0 soft code which is implemented at Spectroscopy Department, Physics Division, National Research Centre, NRC.[25] The interaction probabilities of chitosan monomer (Cs) and ibuprofen molecule (IBP) in the absence of water were constructed as illustrated in Figure 2. These interaction probabilities were energetically optimized at the same theoretical level. Furthermore, these interaction probabilities were reconstructed in the presence of water as presented in Figure 3 and then, optimized using the same method. The electronic, QSAR, and thermodynamics properties are calculated at the same level. The infrared transitions of the geometry optimized compounds are calculated using MO-G at PM6 level of theory in order to confirm that the investigated compounds are optimized corresponding to energy minimum.

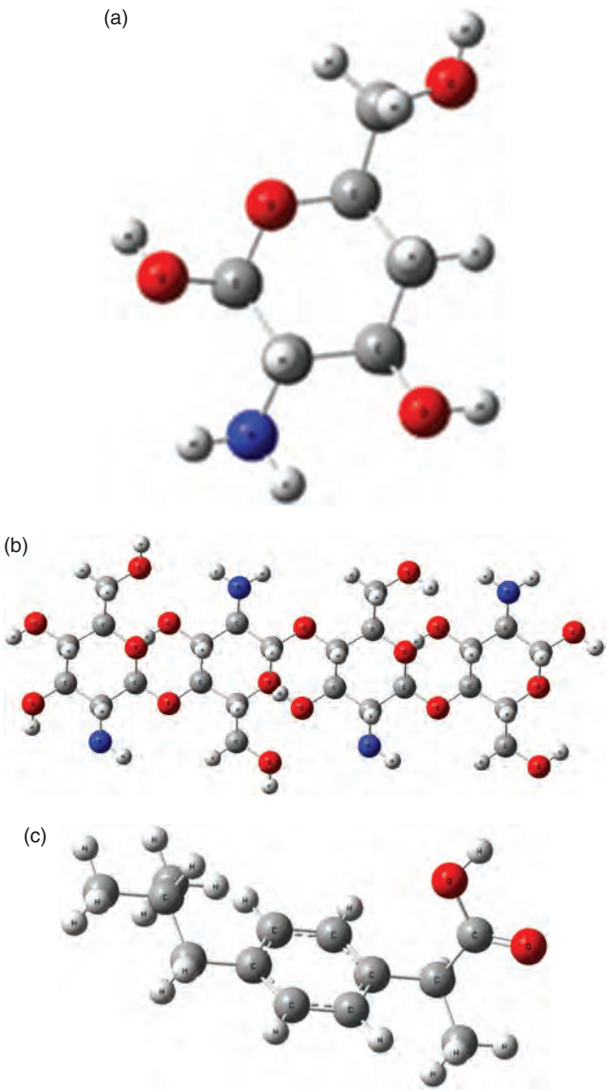

Fig. 1. Molecular model molecules of (a) chitosan monomer (Cs), (b) chitosan four units (4Cs) and (c) ibuprofen molecule (IBP) optimized at PM6 semiempirical quantum mechanical calculation.

3. RESULTS AND DISCUSSION

3.1. Building Model Molecules

Chitosan monomer (Cs) is built up as shown in Figure 1(a). It consists of a heterocyclic benzene ring of five carbon atoms and an oxygen one (glucopyranose unit). The first carbon atom binds to a hydroxymethyl group (CH_2OH) which is considered as the first active site that can be noted as 1st S. The second as well as the fifth carbon atoms are always involved in formation of the β-glycoside linkage with other monomers to form linear polysaccharide chain. The third carbon atom binds to a hydroxyl group (OH), the second active site (2nd S). The fourth carbon one binds to an amine group (NH_2), the third active site (3rd S) and finally the fifth carbon atom binds to a hydroxyl group (OH), the fourth active site (4th S). Thus, chitosan monomer has four active sites as shown in Figure 1(a); three hydroxyl groups and only one amine one.

The four units chitosan molecule (4Cs) is illustrated in Figure 1(b). It is built in this form in order to simulate the whole polymer. It consists of four units linked together by 1–4 β-glycoside linkage.[26] The fifth carbon atom of the first unit (at left) binds to the second one of the adjacent unit while its fifth carbon one attached to the second one of the third unit and so on. Hence, the constructed molecule contains three glucosidic bonds. The two units at ends represent the terminals of the whole polymer and those between them represent the polymer core. Thus, we can say that this four units model molecule can simulate the whole polymer.

Ibuprofen (IBP) model molecule is built as presented in Figure 1(c). Ibuprofen structure can be divided into two parts, one large hydrophobic chain containing a benzene ring bound to 2-methyl propane chain and hydrophilic polar one ends with a carboxyl (COOH) reactive group. Thus, ibuprofen can be considered as an amphiphilic molecule; composed of two different parts hydrophobic and hydrophilic ones.

The structures of both chitosan monomer (Cs) and ibuprofen molecule (IBP) suggest a number of possible interactions between them. In this work, five interaction probabilities are proposed as shown in Figure 2. The first interaction probability (P_1) is a covalent bond formation at the third active site (3rd S) of chitosan, the amine group

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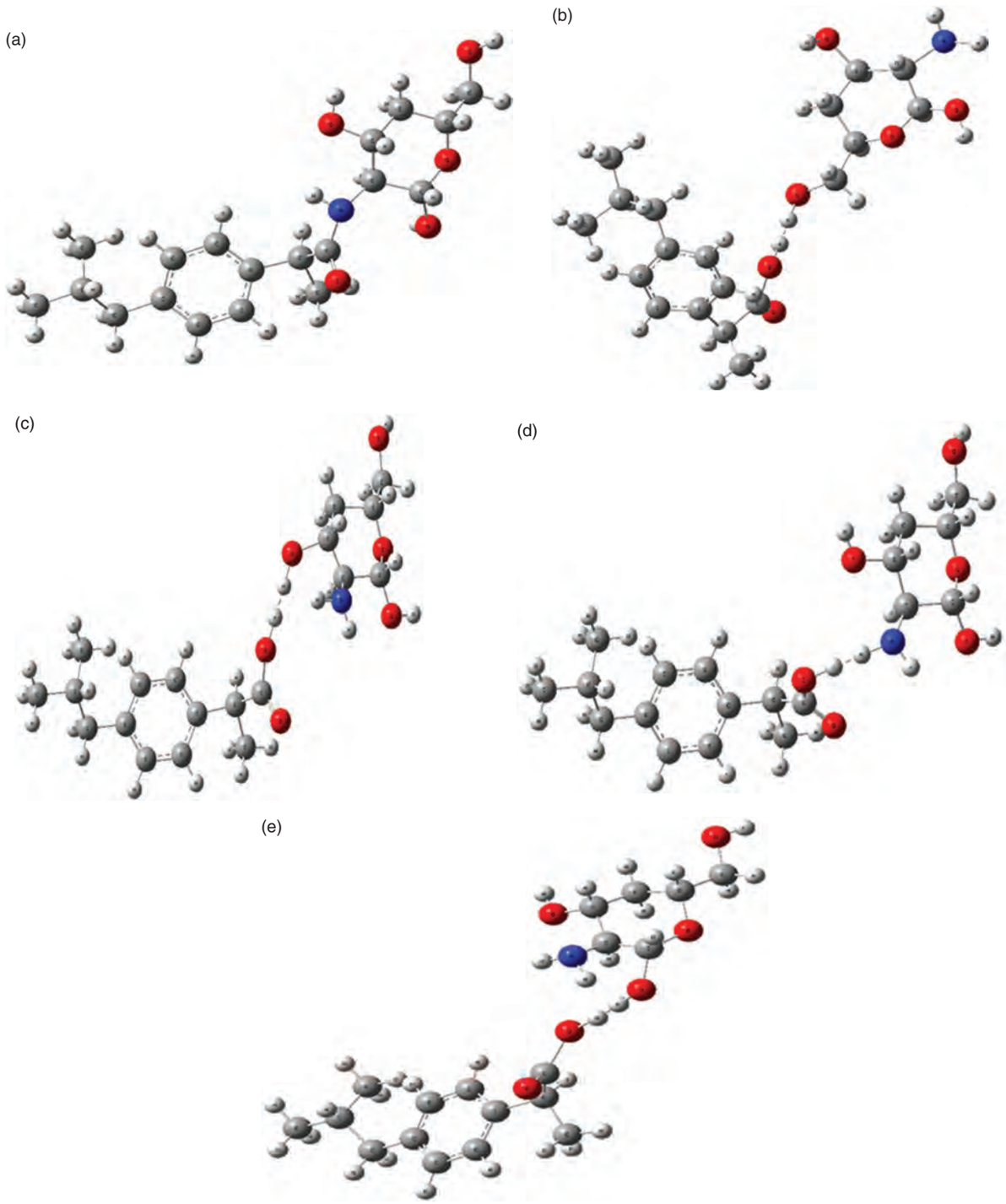

Fig. 2. Interaction probabilities of Cs and IBP in the absence of water (a) IBP-Cs first interaction probability (P_1), (b) IBP-Cs second interaction probability (P_2), (c) IBP-Cs third interaction probability (P_3), (d) IBP-Cs fourth interaction probability (P_4) and (e) IBP-Cs fifth interaction probability (P_5) optimized at PM6 semiempirical quantum mechanical calculation.

(NH_2). It involves the formation of a peptide bond (–NH–CO–) as illustrated in Figure 2(a). The other probabilities involve the formation of a hydrogen bond between the hydroxyl group (OH) of ibuprofen and the various active sites of chitosan monomer as shown in Figures 2(b)–(e). The second interaction probability (P_2) involves OH…HO interaction at 1st S of chitosan (Cs) (Fig. 2(b)). Similarly, the third (P_3) and fifth (P_5) ones involve the formation of

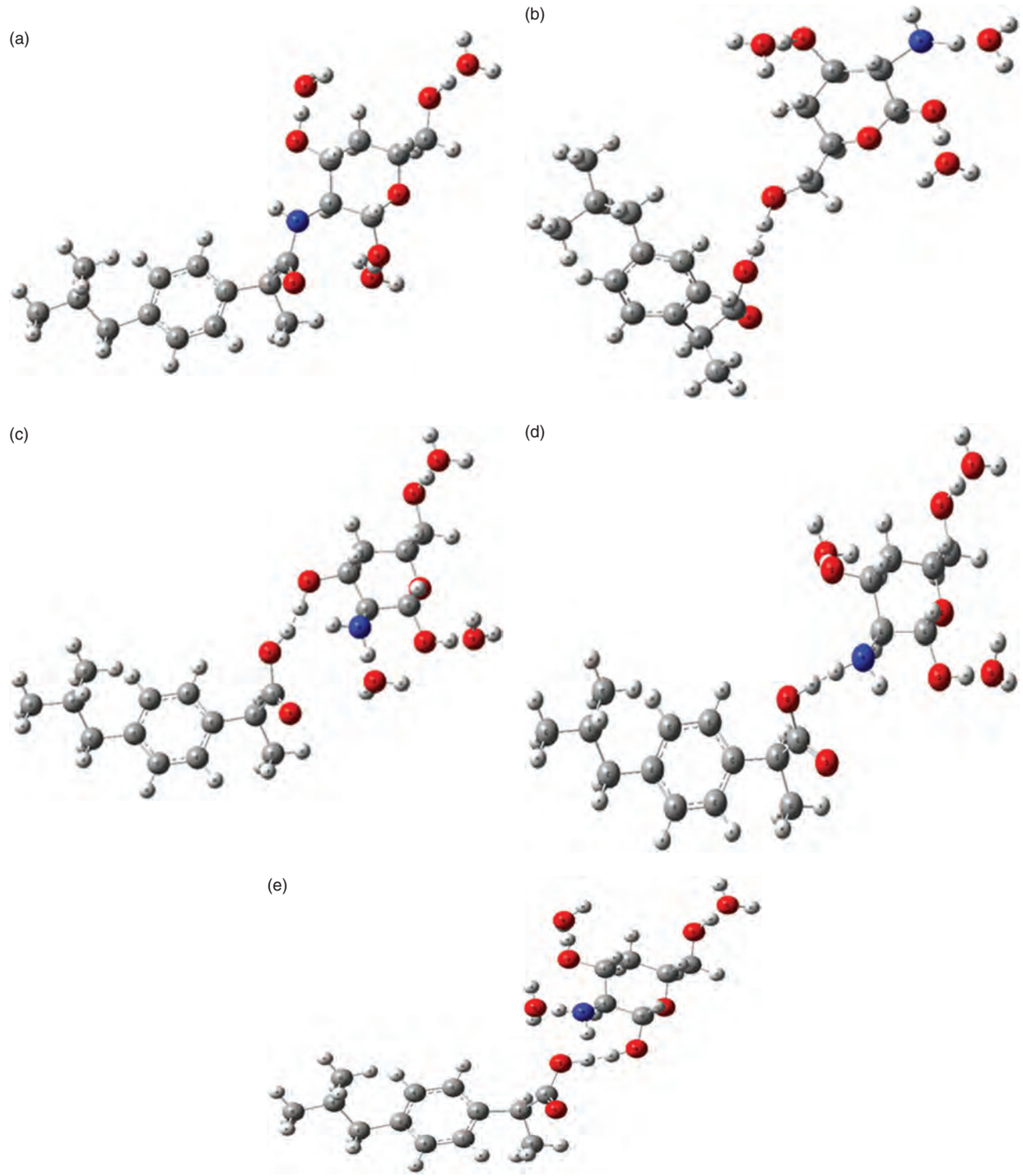

Fig. 3. Interaction probabilities of Cs and IBP molecule in the presence of water (a) IBP-Cs first interaction probability (P_1'), (b) IBP-Cs second interaction probability (P_2'), (c) IBP-Cs third interaction probability (P_3'), (d) IBP-Cs fourth interaction probability (P_4') and (e) IBP-Cs fifth interaction probability (P_5') optimized at PM6 semiempirical quantum mechanical calculation.

OH…HO bond at the 2nd and 4th S off chitosan (Cs), respectively as shown in Figures 2(c) and (e). While the fourth one (P_4) involves NH…HO interaction at the 3rd S of chitosan (Cs) (Fig. 2(d)).

Figure 3 presents the same interaction probabilities in the presence of water molecules to simulate the real interaction environment. Three water molecules are added in each probability at the non-reacting active sites of

Table I. Some of the physical, electronic and QSAR properties, total energy (E), frontier molecular orbital energy gap (ΔE), total dipole moment (TDM), ionization potential (IP), Log P, polarizabililty, volume and surface area of the four units chitosan (4Cs), chitosan monomer (Cs), ibuprofen molecule (IBP), their proposed interactions in the absence of water denoted as P_1 for first probability, P_2 for the second probability, P_3 for the third probability, P_4 for the fourth probability and P_5 for the fifth probability and in the presence of water that denoted as P_1' for first probability, P_2' for the second probability, P_3' for the third probability, P_4' for the fourth probability and P_5' for the fifth probability calculated at PM6 semiempirical level.

Structure	E (eV)	ΔE (eV)	TDM (Debye)	IP (eV)	Log P	Polarizability (A^3)	Volume (A^3)	Surface area (A^2)
4Cs	−9241.104	10.057	5.499	−9.925	−6.800	41.297	505.33	577.07
Cs	−2258.218	10.883	2.916	−9.717	−1.683	9.353	138.37	170.93
IBP	−2420.941	9.475	2.071	−9.270	3.830	15.789	205.35	240.1
P_1	−4304.659	9.472	2.714	−9.183	2.141	25.791	323.26	363.96
P_1'	−5318.227	9.436	5.021	−9.263	0.999	26.400	366.33	392.24
P_2	−4651.509	9.475	3.276	−9.252	2.147	25.683	338.92	391.22
P_2'	−5637.536	9.475	3.276	−9.252	2.147	25.683	338.92	391.22
P_3	−4706.848	8.978	4.339	−9.306	2.030	26.520	327.800	366.540
P_3'	−5665.011	9.475	3.276	−9.252	2.147	25.683	338.92	391.22
P_4	−4651.433	8.978	4.339	−9.306	2.030	26.520	327.8	366.54
P_4'	−5637.570	9.475	3.276	−9.252	2.147	25.683	338.92	391.22
P_5	−4665.012	9.441	2.716	−9.334	2.147	25.819	341.48	387.47
P_5'	−5623.187	7.255	8.883	−8.346	2.636	38.756	425.63	490.26

chitosan. The first interaction possibility (P_1') needs three water molecules at the first, second and fourth active sites of chitosan (Fig. 3(a)). While the second (P_2') one at the second, third and fourth active sites (Fig. 3(b)). Similarly, the others are built in the same manner as shown in Figures 3(c)–(e).

3.2. QSAR Properties

The optimization processes of all the constructed model molecules and interaction possibilities result in some physical electronic and QSAR properties. Such properties are summarized in Table I. The listed properties are charge, total energy (E), frontier molecular orbital energy gap (ΔE), total dipole moment (TDM) and ionization potential (IP), Log P, polarizabililty, volume and surface area. Since, all the proposed structures are in the ground state, so the charge of each of them is zero. The total energy (E) of the individual compounds are −9241.1040 eV for the chitosan four units (4Cs), −2258.2178 eV for the chitosan monomer (Cs) and −2420.9411 eV for the ibuprofen molecule (IBP). The four units chitosan molecule (4Cs) has the lowest energy and hence the highest stability among the three individuals. Depending on the results of energy (E), ibuprofen molecule is more stable than chitosan monomer. This can be attributed to having only one active functional group (–COOH) rather than four active ones in chitosan (three –OH and one $–NH_2$ groups). The ibuprofen-chitosan monomer interactions (IBP-Cs) result in structures of lower optimization energy indicating more stable structures than the individuals do. The total energy of the first interaction probability (P_1) is −4304.6592 eV. It is the largest value among the calculated interactions indicating a less stable structure. Both the second (P_2) and fourth (P_4) possibilities have the same total energy and equals to −4651.5087 eV and −4651.4332 eV, respectively. However, the third possibility (P_3) results in a lowest energy structure with energy value −4706.8475 eV. The structure of the fifth probability (P_5) has a higher energy value of −4665.0118 eV.

In addition, Table I shows that adding three water molecules for the proposed probabilities lower their energies. This means that having an aqueous medium is preferred for them. The energy of all the proposed interactions becomes much lower than those in the absence of water by about 1 KeV. The values of the total energy have the same behavior that is previously mentioned in the absence of water where the first possibility (P_1') has a value of −5318.2272 eV. It is the highest energy result indicating a lowest stable structure. Again, both of the second (P_2') and fourth (P_4') probabilities have the same energy values that equal −5637.5358 eV and −5637.5697 eV, respectively. Similarly, the third interaction probability (P_3') has the lowest energy value that equals −5665.0106 eV indicating high stability. However, the fifth possibility (P_5') has a higher energy value of −5623.1869 eV.

Second for the calculated frontier molecular orbital binding gap energy (ΔE), as the ΔE value decreases, the structure becomes more reactive with its surrounding molecules. Ibuprofen molecule (IBP) has the lowest ΔE value when compared to both chitosan monomer (Cs) and chitosan four units (4Cs). It indicates more reactivity for ibuprofen as compared with the other two structures. Besides, the interaction between the chitosan monomer (Cs) and ibuprofen molecule (IBP) in the absence of water does not affect their energy gap (ΔE) significantly except for the third (P_3) and fourth (P_4) interaction probabilities. They have the same value of ΔE that equals 8.978 eV. Thus, they can be considered the most reactive ones among the proposed interactions. The presence of water also does not affect greatly the energy gap (ΔE) of all of the second (P_2'), the third (P_3') as well as the fourth (P_4') probabilities. They acquired the same ΔE value of ibuprofen (IBP) except for the fifth interaction probabilities (P_5') whose ΔE equals 7.255 eV which in turn the lowest one. However,

the ΔE result of the first possibility (P_1') decreases slightly to 9.436 eV.

The other calculated parameters, total dipole moment (TDM) and ionization potential (IP) represent solid indicators of reactivity of compounds. The higher the total dipole moment is, the higher the reactivity of the compound with its surroundings. The ionization potential (i.e., the electron detachment energy) is the amount of energy needed to remove an electron from the molecule to infinite distance. It represents how we can remove an electron from its molecule in order to be ionized. Hence, being able to interact with its surrounding compounds and be reactive. The lower the ionization potential is, the higher the reactivity of the compound will be. The results of the total dipole moment (TDM) of the three individual structures, four units chitosan (4Cs), chitosan monomer and ibuprofen molecule (IBP), are in the order of chitosan four units (4Cs), chitosan monomer (Cs) then ibuprofen (IBP). Thus, they follow the same order of reactivity and the four units chitosan one is of the highest activity among them. This is due to the existence of largest number of reactive functional groups. The interaction between the ibuprofen (IBP) and chitosan monomer (Cs) results in quite higher reactive structures of higher total dipole moments whose values vary due to the interaction site. In the absence of water, both the first (P_1) and fifth (P_5) interaction possibilities have the same resultant and lowest dipole moment values of 2.714 and 2.716 Debye, respectively. Similarly, both of the third (P_3) and fourth (P_4) ones have the same and highest results of 4.339 Debye. The presence of water in such proposed interactions increases the total dipole moment values and hence the reactivity of only the first (P_1') and fifth (P_5') possibilities. Their TDM values become 5.021 and 8.883 Debye, respectively. However, it decreases for the third one as well as for the fourth probability from 4.339 to 3.276 Debye. Moreover, the presence of water in the second possibility does not affect their dipole moment where its value remains constant at 3.276 Debye. It is also noticed that all of P_2', P_3' and P_4' interaction possibilities have the same TDM that equals 3.276 Debye. Thus, the presence of water does not affect positively our interactions in all cases and depends on the site of interaction. Regarding the calculated ionization potential, those of the three individual compounds obey the same order mentioned for total dipole moment; the four units chitosan (4Cs) followed by chitosan monomer (Cs) and ibuprofen (IBP). On the same manner of ΔE results, the interaction between ibuprofen (IBP) and chitosan monomer (Cs) in either absence or presence of water has a small influence on the values of ionization potential except for the fifth interaction probability (P_5). It increased to be the largest among all the proposed interactions. Other results of ionization potential are similar to that of ibuprofen molecule (IBP) which equals −9.270 eV.

The fifth property listed in Table I is the Log P one which is the logarithm of the partition coefficient that determine whether the molecule is hydrophilic (water soluble) or hydrophobic (lipophilic). Positive value of Log P indicates a hydrophilic molecule which is more soluble in water while negative one represents a hydrophobic one which is more soluble in organic solvent. Due to the results illustrated in Table I, both chitosan monomer (Cs) and chitosan four units (4Cs) have negative Log P values referring to have two hydrophobic structures. However, the ibuprofen molecule has a positive value indicating a hydrophilic one. The interaction of ibuprofen (IBP) and chitosan monomer (Cs) results in hydrophilic structures of positive Log P values. The addition of water to the various interactions does not affect their hydrophilic properties. However being hydrophilic, the first interaction probability in the presence of water (P_1') has the smallest Log P result.

Surface area and volume results are listed in Table I. As expected the four units of chitosan (4Cs) has the largest volume and surface area due to its largest structure. Interactions of ibuprofen (IBP) and chitosan monomer (Cs) increase the surface area of the resultant structure except for the second interaction probability whose surface area remains constant at 391.22 A^2. Similarly, the volume results have the same behavior of surface area for both individual structures as well as those resultant ones. The fifth interaction probability has the largest surface area and volume in either absence or presence of water among the proposed interactions. Finally, polarizability property is shown in the table. Since polarizability depends on the volume, the polarizability of chitosan four units is the largest one while that of chitosan monomer is the smallest. The proposed interactions have larger polarizability results than the individual molecules. The addition of water does not increase the polarizability in all cases. It remains constant at the same value for the second interaction probability. While it lowers for both the third and fourth possibilities.

In addition, some of the electrical properties of the atoms involved in the proposed interactions in both cases of absence and presence of water molecules are listed in Table II. The net atomic charge (C) of these atoms is calculated at the same theoretical level of PM6 semiempirical quantum mechanical calculation. The positive charge of hydrogen atom of chitosan monomer (Cs) is higher than that of the four units molecule (4Cs). While the negative charge of nitrogen atoms of both is nearly the same. The net charge of hydrogen and oxygen atoms in ibuprofen molecule (IBP) is 0.3388 and −0.5398, respectively. The interaction of ibuprofen (IBP) with chitosan monomer (Cs) increases the charge of hydrogen and oxygen atoms which form its active site. The charge of hydrogen atom has a minimum value of 0.3578 and 0.3580 for the third (P_3) and fourth (P_4) probabilities, respectively and a maximum of 0.3756 and 0.3701 for the second (P_2) and fifth (P_5) possibilities, respectively. In the same manner of hydrogen atoms, the negativity of oxygen atoms

Table II. The net atomic charges (C) of active site of the four units chitosan (4Cs), chitosan monomer (Cs), ibuprofen molecule (IBP), their proposed interactions in the absence of water denoted as P_1 for first probability P_2 for the second probability, P_3 for the third probability, P_4 for the fourth probability and P_5 for the fifth probability and in the presence of water that denoted as P_1' for first probability, P_2' for the second probability, P_3' for the third probability, P_4' for the fourth probability and P_5' for the fifth probability calculated at PM6 semiempirical level.

Structure	Atom's no.	C
4Cs	H_{82}	0.2254
	N_{41}	−0.5196
Cs	H_{13}	0.3388
	N_{11}	−0.5135
IBP	H_{33}	0.3388
	O_{15}	−0.5398
P_1 Cs side	H_{43}	0.2804
	N_{42}	−0.4572
P_1 IBP side	C_{13}	0.5876
	O_{14}	−0.5431
P_1' Cs side	H_{43}	0.2804
	N_{42}	−0.4572
P_1' IBP side	C_{13}	0.5876
	O_{14}	−0.5431
P_2 Cs side	H_{55}	0.3591
	O_{54}	−0.5610
P_2 IBP side	H_{33}	0.3756
	O_{15}	−0.5468
P_2' Cs side	H_{55}	0.3591
	O_{56}	−0.5397
P_2' IBP side	H_{33}	0.3756
	O_{15}	−0.5468
P_3 Cs side	H_{53}	0.3452
	O_{43}	−0.5697
P_3 IBP side	H_{33}	0.3578
	O_{15}	−0.6336
P_3' Cs side	H_{53}	0.3452
	O_{43}	−0.5697
P_3' IBP side	H_{33}	0.3578
	O_{15}	−0.6336
P_4 Cs side	H_{45}	0.2246
	N_{45}	−0.4932
P_4 IBP side	H_{33}	0.3580
	O_{15}	−0.6110
P_4' Cs side	H_{45}	0.2246
	N_{45}	−0.4932
P_4' IBP side	H_{33}	0.3580
	O_{15}	−0.6110
P_5 Cs side	H_{51}	0.3878
	O_{50}	−0.5015
P_5 IBP side	H_{33}	0.3701
	O_{15}	−0.5263
P_5' Cs side	H_{51}	0.3878
	O_{50}	−0.5015
P_5' IBP side	H_{33}	0.3701
	O_{15}	−0.5263

of ibuprofen increases upon the interaction with chitosan monomer. The third interaction probability (P_3) has the largest value which equals −0.6336 while the fifth one (P_5) has a charge of −0.5263 as a minimum one. The addition of water to the different possible reactions between chitosan monomer (Cs) and ibuprofen (IBP) doesn't alter the charge of the interacting atoms except for the oxygen atom of chitosan monomer in the second interaction probability (P_2'). Its negativity decreases from −0.5610 to −0.5397. Such result may be reasonable since water molecules are added away from the reacting active site, so they have no effect on their electrical properties.

3.3. Thermodynamical Properties

Thermal parameters including heat of formation, heat capacity, enthalpy, entropy, and free energy for the studied structures using PM6 at 298 Kelvin are calculated and listed as in Table III.

The calculated parameters are important for describing the physical behavior of a system, in terms of its possible interaction with its surrounding media in the presence of heat. They are also indicators for a given chemical structure for its ability, behavior when it is subjected and/or exchange heat with or from its surroundings. Regarding the heat of formation, it can be defined as the change in the enthalpy which accompanying the creation of one mole of a substance from its components in their natural and stable states, under atmospheric standard conditions at a given temperature.[27] For the heat of formation, for a given compound it is defined as the amount of evolved or absorbed heat forming one mole. Heat capacity of a given substance is equal to the amount of energy required to raise its temperature by one degree. The heat capacity, Cp, of gas-phase systems could be defined using vibrational frequencies and moments of inertia and the translational contributions. Then one can be defined as the heat capacity at constant volume, Cv, can be derived from $Cv = Cp - R$, where $R = 1.987$ calories.[28] Another thermal parameters which is used to measure the total energy of a system is called Enthalpy. Then the entropy is a measure of the number of specific ways in which the system may be arranged. Free energy is the energy in system that can be converted to do work.[29]

The heat of formation of the four units chitosan (4Cs) is the lowest one and equals −752.889 Kcal/mol. While that of ibuprofen molecule (IBP) is the highest one and equals −102.633 Kcal/mol. Similarly, all the other thermal properties of the four units chitosan (4Cs) are the highest for heat capacity, enthalpy and entropy. Their values are 191.530 cal/mol/Kelvin, 32.490 Kcal/mol and 301.412 cal/mol/Kelvin, respectively while has the lowest result of free energy quantity which equals −467.601 Kcal/mol. These results can be attributed to the large structure of the four units chitosan with respect to all other proposed structures. Chitosan monomer (Cs) has the lowest value for heat capacity which equals 48.526 Cal/mol/Kelvin. This would suggest that it requires small amount of heat to raise its temperature by one degree relative to others. Also chitosan monomer (Cs) has the lowest amount of enthalpy that equals 8.723 Kcal/mol. as well as the lowest value of entropy whose amount is 113.756 Cal/mol/Kelvin. Ibuprofen molecule (IBP) possesses the highest amount of free

Table III. Calculated heat of formation (HF), heat capacity (HC), enthalpy (En), entropy (ET), and free energy (FE) for the four units chitosan (4Cs), chitosan monomer (Cs), ibuprofen molecule (IBP), their proposed interactions in the absence of water denoted as P_1 for first probability, P_2 for the second probability, P_3 for the third probability, P_4 for the fourth probability and P_5 for the fifth probability and in the presence of water that denoted as P_1' for first probability, P_2' for the second probability, P_3' for the third probability, P_4' for the fourth probability and P_5' for the fifth probability calculated at PM6 semiempirical level at 298 Kelvin.

Structure	HF (Kcal/mol)	HC (cal/mol/Kelvin)	En (Kcal/mol)	ET (cal/mol/Kelvin)	FE (Kcal/mol)
4Cs	−752.889	191.530	32.490	301.412	−467.601
Cs	−187.520	48.526	8.723	113.756	−122.493
IBP	−102.633	62.603	10.914	133.560	−38.819
P_1	−302.333	111.923	19.285	205.667	−161.080
P_1'	−302.669	112.785	19.654	209.641	−162.601
P_2	−295.576	113.639	19.801	212.989	−156.505
P_2'	−301.580	112.293	19.394	207.126	−160.762
P_3	−244.804	105.142	17.865	188.847	−115.140
P_3'	−479.962	143.415	25.920	263.477	−306.133
P_4	−492.594	141.211	24.453	234.871	−310.241
P_4'	−479.019	144.479	25.988	261.038	−304.463
P_5	−127.416	145.191	26.110	264.164	20.762
P_5'	−431.568	134.706	23.433	225.574	−263.045

energy which is −38.819 Kcal/mol. The presence of water molecules does not influence significantly the thermal properties of the first, second and fourth interaction probabilities. However, those of the third and fifth probabilities are enhanced by the addition of water molecules except for the heat capacity (HC), enthalpy (En) and entropy (ET) of the fifth one that are lowered.

3.4. The Calculated Vibrational Spectra

Figure 4 shows the calculated vibrational spectra of the three individual structures and their proposed interaction probabilities in either absence or presence of water. The obtained spectral bands which are all indicating positive frequencies, these could be a good sign for the given structures. Having positive frequencies prove that all compounds under investigation correspond to energy minimum, that ensures the validity of our calculations and propositions.

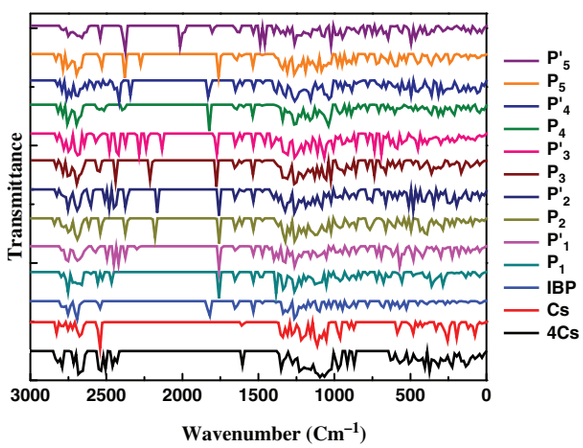

Fig. 4. Calculated PM6 IR spectra for four units chitosan (4Cs), chitosan monomer (Cs), ibuprofen molecule (IBP), their proposed interactions in the absence of water denoted as P_1 for first probability, P_2 for the second probability, P_3 for the third probability, P_4 for the fourth probability and P_5 for the fifth probability and in the presence of water that denoted as P_1' for first probability, P_2' for the second probability, P_3' for the third probability, P_4' for the fourth probability and P_5' for the fifth probability.

4. CONCLUSION

Possible structures indicating the interaction between chitosan and ibuprofen are given with PM6. Five probabilities for interactions were given with and without three water molecules.

The interaction between chitosan and ibuprofen is followed by a change in the partial charge this in turn leads to a possible change in the total dipole moment. The calculated ionization potential is nearly unchanged for all the studied interaction. It is stated earlier that, the higher calculated dipole moment reflect the reactivity of the given interaction, which could be further interacting with its surrounding molecules. Results showed that in the absence of water, the OH…HO weak interaction through the second and third active sites of chitosan named P_3 and P_4 are the most probable interaction scheme, where they have the highest TDM, the lowest HOMO/LUMO band gap energy and total energies. Moreover, results indicate that the interaction through OH…HO which is termed (P_5') is most probable as it possess higher calculated total dipole moment. This result is confirmed with lower HOMO/LUMO band gap energy of the same interaction. Finally, the calculated vibrational spectra indicate the occurrence of each studied structure as optimized one. All the calculated QSAR descriptors, such as Log P, polarizability, surface area and volume, increased as a result of interacting Cs with IBP. The last interaction probability named P_5' is found to have the highest values of QSAR descriptors.

The present work is an indication for the suitability of PM6 for describing different interactions of biological molecules in appropriate computational time. It could be concluded that, PM6 is an efficient model for refining the different possibilities while this work needs some kind of verifications at higher level of theory and/or experimental scale.

The change in the physical properties of chitosan after interaction indicate the possible application of chitosan as sensor for Ibuprofen.

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