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A computational molecular approach on chitosan vehicle for metformin

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Abstract

Density functional theory (DFT) calculations have been performed to study properties of chitosan (Chit) as a possible vehicle for carrying metformin (Met) drug. To this aim, the singular molecules of Met and Chit have been first optimized and, then, sixteen possible bimolecular complexes have been subsequently constructed and optimized to obtaine the stabilized interacting structures. Two bimolecular complexs have been seen as the most powerful interacting systems among all complexes. N_5 and N_8 atoms of Met are very important atoms for interacting with Chit counterpart. Molecular parameters such as molecular orbital energies and dipole moments approved the effects of interations on both Chit and Met counterparts. Atomic scale quadrupole coupling constants demonstrated the effects of interactions on the electronic atomic sites. As a final remark, although the Chit could be used as a vehicle for Met; further investigations are still required to see what's happening inside the molecular systems.

Keywords: Chitosan; metformin; density functional theory; molecular vehicle.

Introduction

Metformin (Met) is a medicine for those people who are diagnosed with diabetes type–2 to control their sugar level in blood [1]. Although Met has been introduced as one of the most efficient anti–diabetes; low bioavailability and small absorption yield to high dosage administration for patients have been witnessed [2]. Therefore, hybridization with other biocompatible materials or carriers may increase the efficacy of Met with lower dosage administrations with higher bioavailability [3]. Earlier works have introduced chitosan (Chit) as a proper vehicle to carry Met inside the body; however, further investigations are still required to achieve the purpose [4]. Chit is initially a biocompatible structure consisting of biological familiar glucose amine constructing monomers, which could be proposed as a good choice for applications in living systems [5]. Despite several experimental and theoretical achievements on Chit–Met hybrid systems; there is still a lack of information on molecular-scale details of interactions between Chit and Met molecules [6]. In an earlier work [7], the advantage of Chit as a gene carrier

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has been very well investigated at the molecular scale based on examining the intermolecular interactions. The intermolecular interactions e.g. hydrogen bonds, are dominant factors to maintain the stability of hybrid structures and also to predict their corresponding activities [8–12]. Therefore, molecular–scale studies could reveal important information about the nature of interacting systems [13]. Among the methodologies, computer–assisted investigations could generate information with high accuracy for the considered systems [14-23]. It is worth to note that the structure is very much important for the desired activity of a chemical compound or medicine; known as SAR [24].

This work has been established to investigate the characteristic properties of Chit as a vehicle for Met by careful examination of their intermolecular interactions employing density functional theory (DFT) approach. Although several computational approaches have been established from molecular mechanics to high-level quantum mechanics in order to investigate molecular systems, DFT could be considered as a helpful approach to solve problems in the computational molecular scales [9,25,26]. Each singular structure of Met and Chit has been separately optimized and possible bimolecular complexes have been subsequently optimized and characterized to evaluate the interacting positions between two hetero molecular counterparts (Figures 1 and 2). Molecular and atomic scale electronic properties have been evaluated in addition to structural properties to see the details of Chit vehicle for carrying Met counterpart (Tables 1–3).

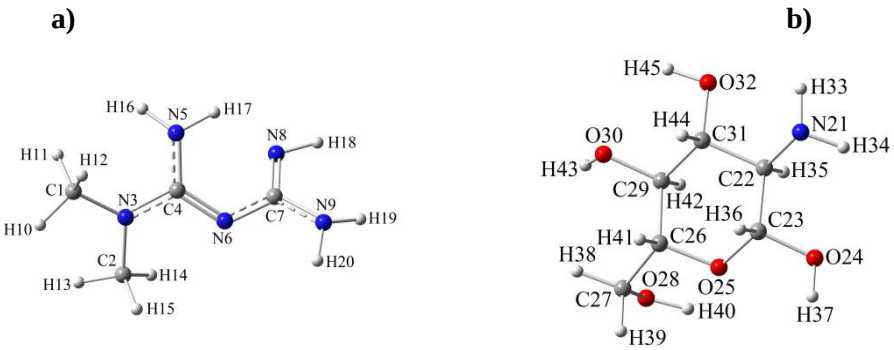

Figure 1. The singular structures of a) Met ($C_4H_{11}N_5$) and b) Chit ($C_6H_{13}NO_5$)

Computational details

The B3LYP exchange-correlation functional [27] and the 6–311++G** standard basis set [28] have been employed as DFT approach of all calculations of this work. It is worth to note that the varaities of computational approaches always make a difficult task to choose the best method for calculations. In this case, earlier works indicated that our employed method could generate reliable results for such systesm [25,26,29]; therefore, we have chosen the method for our work. Furthermore, our work has been done in the gas-phase system to show the original properties of Chit and Met structures avoiding the effects of solvents or any other media [9,29]. It is important to note that the Chit is originally a polymer structure; however, we employed glucosamine

molecule as the monomer of Chit in our molecular-scale computations in accordance to the earlier works [7,30,31]. First, each of the singular Met and Chit structures and their possible interacting bimolecular complexes have been optimized to obtain the minium energy geometeris (Figures 1 and 2). Subsequently, the global minimum optimized structures have been also examined by the frequency calculations at the same level of theory. The Grimme dispersion correction has been included in all of the optimization calculations by adding IOp=(3/124=3) to the calculation route [32]. Furthermore, the basis set superposition errors (BSSE) have been examined for the bimolecular complexes by adding Counterpoise=2 to the calculation route [33]. As a result, minimized energy structures and their corresponding properties have been evaluated for the molecular counterparts of singular and complex structures. Table 1 demonstrates the values of total energies (E_T), BBSE, binding energies (E_B) (eq. 1), energies of the highest occupied and the lowest unoccupied molecular orbitals (E_{HOMO} and E_{LUMO}), energy gaps (E_G) (eq. 2), and dipole moments (D_M) for the investigated molecular systems.

$$E_B = E_{Complex} - E_{Met} - E_{Chit} \quad (1)$$

$$E_G = E_{LUMO} - E_{HOMO} \quad (2)$$

Table 2 exhibits the interaction information including the interacting atoms and distances for the Met···Chit complexes. By the designed intermolecular geometries, sixteen bimolecular complexes have been constructed to cover all the possible interactions for the Met and Chit counterparts. The interacting atoms of Chit with Met molecule are shown in Figure 2 for all sixteen models. Furthermore, the atomic-scale quadrupole coupling constants (C_Q) have been evaluated (eq. 3) (Table 3) by the electric field gradient (EFG) calculations of the nitrogen and oxygen atoms of the optimized structures.

$$C_Q = e^2 Q q_{zz} h^{-1} \quad (3)$$

The components of eq. 3 are e: electronic charge, Q: the nuclear quadruple moment, q_{zz}: the EFG eigenvalue, and h: the Planck's constant [34–36]. All calculations of this work have been performed employing the Gaussian 09 package of program [37].

Results and discussion

Within this work, the capability of Chit vehicle for carrying Met drug has been examined based on DFT calculated results for singular and interacting bimolecular complex systems. All possible interacting positions have been first designed for the optimization processes to find the best intermolecular geometries and the corresponding properties for the Met···Chit bimolecular complexes. In addition to the interacting positions for molecular counterparts, their corresponding atomic scale C_Q properties have been also evaluated for the investigated models (Tables 1–3 and Figures 1 and 2).

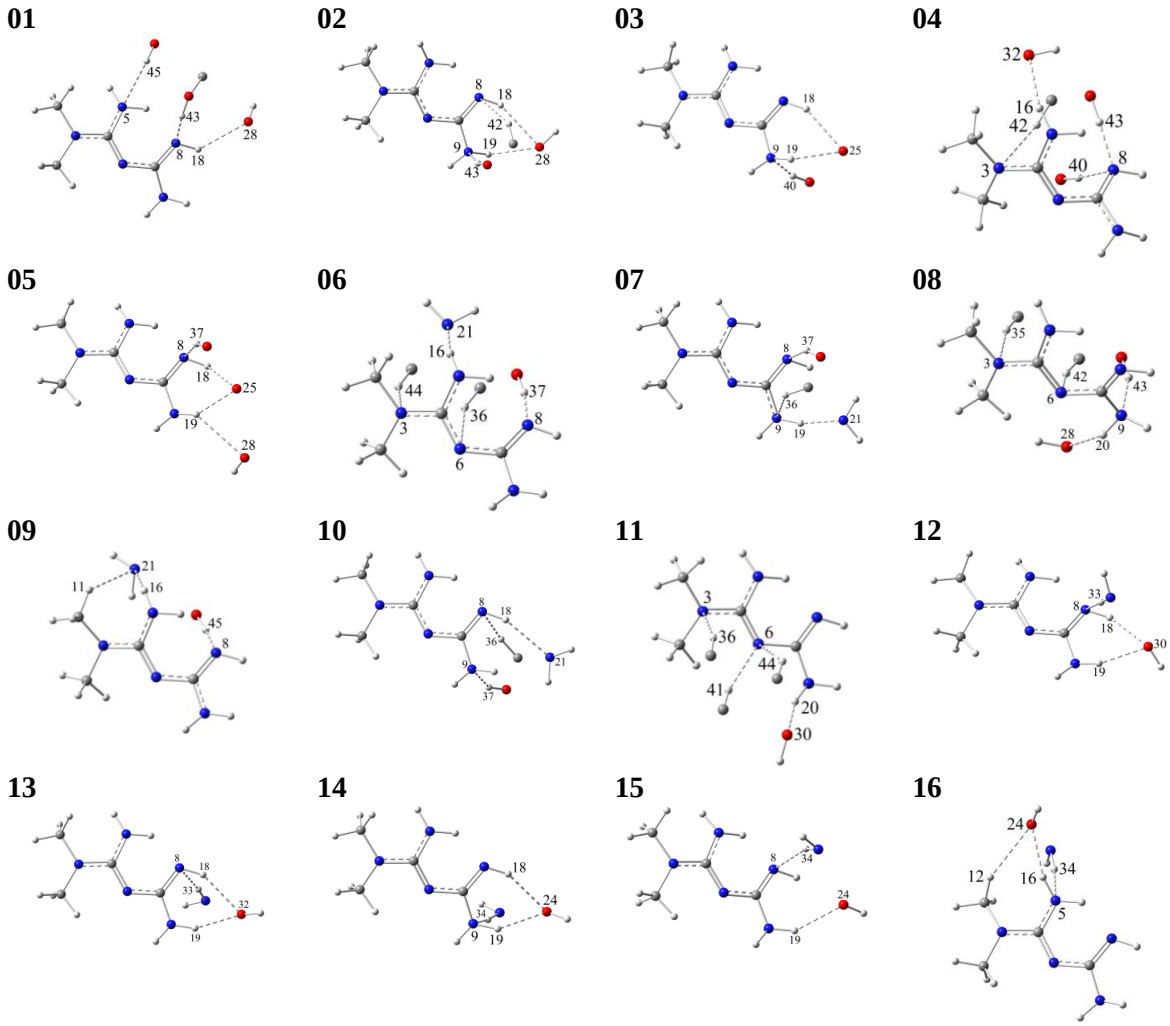

Figure 2. Met···Chit bimolecular complexes; the Met structure and the interacting atoms of Chit are shown to ease.

The results of Table 1 present the evaluated molecular properties for both of singular and complex optimized structures (Figs. 1 and 2). Based on the obtained E_T values, the bimolecular complex structures could be distinguished regarding their stabilities and the corresponding E_B values. As a result, the bimolecular complexes have been ranked by these values in this work; rank 01 represents the best interacting situation among all possibilities. Small values of BSSE have been obtained for the E_T and E_B parameters, in which they could be neglected for consideration in energy temrs. Careful examinations of E_B values could indicate that the intermolecular geometries of bimolecular complexes are very much important to achieve a strong interacting complex.

Table 1. Molecular properties for Met and Chit in singular and complex structures*

Structure	E_T (kcal/mol)	BSSE (kcal/mol)	E_B (kcal/mol)	E_{HOMO} (eV)	E_{LUMO} (eV)	E_G (eV)	D_M (Debye)
Met	–271399	—	—	–5.87	–0.49	5.38	2.81
Chit	–418437	—	—	–6.82	–0.54	6.28	1.50
Met···Chit_01	–689846	1.39	–10.1	–6.21	–0.55	5.66	3.29
Met···Chit_02	–689845	1.53	–9.21	–6.04	–0.55	5.49	2.95
Met···Chit_03	–689845	1.37	–8.33	–5.99	–0.56	5.44	4.84
Met···Chit_04	–689844	2.44	–7.65	–6.41	–0.57	5.84	2.07
Met···Chit_05	–689842	1.28	–6.12	–5.97	–0.6	5.38	5.08
Met···Chit_06	–689842	2.19	–5.68	–6.12	–0.55	5.57	3.41
Met···Chit_07	–689842	1.65	–5.55	–6.08	–0.6	5.49	5.81
Met···Chit_08	–689841	2.21	–4.69	–6.02	–0.51	5.51	2.77
Met···Chit_09	–689840	1.63	–4.05	–6.09	–0.46	5.63	2.55
Met···Chit_10	–689839	1.47	–2.45	–5.94	–0.58	5.36	5.24
Met···Chit_11	–689839	1.75	–2.36	–5.89	–0.66	5.24	4.32
Met···Chit_12	–689838	0.94	–2.22	–5.58	–0.69	4.89	2.80
Met···Chit_13	–689838	1.02	–1.75	–5.57	–0.68	4.89	3.07
Met···Chit_14	–689838	1.11	–1.58	–5.62	–0.61	5.01	2.56
Met···Chit_15	–689838	1.28	–1.56	–5.62	–0.66	4.96	2.99
Met···Chit_16	–689837	1.26	–0.99	–5.69	–0.77	4.93	6.03

* See Figures 1-3 for the model structures.

The information of Table 2 and Figure 2 show that the atoms N_5 and N_8 of Met are very much important atomic sites for the formation of interactions with H_{45} and H_{43} of Chit to make strong interacting complexes. None of other bimolecular complexes have such situations as their interactions are weaker than the 01 complex. Up to Met···Chit_16 bimolecular complex, the E_B value reaches to –0.99 kcal/mol; ten times weaker than 01 complex. This is an important task for the molecular level studies, in which the characteristic properties are very well recognized for the investigated molecular systems in the lowest possible molecular scale.

Table 2. Molecular interaction properties for Met···Chit complexes*

Interacting Molecules	Interacting Atoms	Interacting Distances Å	Interacting Molecules	Interacting Atoms	Interacting Distances Å
Met···Chit_01	$N_5\cdots H_{45}$	2.50	**Met···Chit_09**	$N_8\cdots H_{45}$	1.75
	$N_8\cdots H_{43}$	1.76		$H_{11}\cdots N_{21}$	2.58
	$H_{18}\cdots O_{28}$	2.39		$H_{16}\cdots N_{21}$	2.12
Met···Chit_02	$N_8\cdots H_{42}$	2.59	**Met···Chit_10**	$N_8\cdots H_{36}$	2.50
	$N_9\cdots H_{43}$	1.89		$H_{18}\cdots N_{21}$	2.41
	$H_{18}\cdots O_{28}$	2.44		$N_9\cdots H_{37}$	1.99
	$H_{19}\cdots O_{28}$	2.24			
Met···Chit_03	$N_9\cdots H_{40}$	1.90	**Met···Chit_11**	$N_3\ldots H_{36}$	2.46
	$H_{18}\cdots O_{25}$	2.31		$N_6\cdots H_{41}$	2.35
	$H_{19}\cdots O_{25}$	2.16		$N_6\cdots H_{44}$	2.66
				$H_{20}\cdots O_{30}$	2.10
Met···Chit_04	$N_3\cdots H_{42}$	2.61	**Met···Chit_12**	$N_8\cdots H_{33}$	2.31
	$N_8\cdots H_{40}$	1.98		$H_{18}\cdots O_{30}$	2.42
	$N_8\cdots H_{43}$	1.76		$H_{19}\cdots O_{30}$	2.07
	$H_{16}\cdots O_{32}$	2.13			
Met···Chit_05	$N_8\cdots H_{37}$	1.96	**Met···Chit_13**	$N_8\cdots H_{33}$	2.39
	$H_{18}\ldots O_{25}$	2.35		$H_{18}\cdots O_{32}$	2.33
	$H_{19}\cdots O_{25}$	2.08		$H_{19}\cdots O_{32}$	2.12
	$H_{19}\ldots O_{28}$	2.64			
Met···Chit_06	$N_3\cdots H_{44}$	2.73	**Met···Chit_14**	$N_9\cdots H_{34}$	2.20
	$N_6\cdots H_{36}$	2.69		$H_{18}\cdots O_{24}$	2.37
	$N_8\cdots H_{37}$	1.75		$H_{19}\cdots O_{24}$	2.25
	$H_{16}\cdots N_{21}$	1.98			
Met···Chit_07	$N_8\cdots H_{37}$	1.90	**Met···Chit_15**	$N_8\cdots H_{34}$	2.22
	$N_9\cdots H_{36}$	2.71		$H_{19}\cdots O_{24}$	2.17
	$H_{19}\cdots N_{21}$	2.09			
Met···Chit_08	$N_3\cdots H_{35}$	2.55	**Met···Chit_16**	$N_5\cdots H_{34}$	2.34
	$N_6\cdots H_{42}$	2.25		$H_{12}\cdots O_{24}$	2.53
	$N_9\cdots H_{43}$	1.95		$H_{16}\cdots O_{24}$	2.05
	$H_{20}\cdots O_{28}$	2.18			

* See **Figures** 1 and 2 for the atoms numbers and model structures. All possible interactions are considered for the complex Met···Chit bimolecular complexes

Based on the obtained intermolecular E_B values and geometries, it could be concluded that the interaction is possible for Met and Chit bimolecular complexes; however, the strength quality of interacting systems could be measured by quantities of energies and distances showing the variations of integration situations.

As a concluding remark of this section, the Chit could be proposed as a carrier for Met, but it is better to protect other interacting atomic sites of Chit not to interact with Met counterpart.

Further examinations of contents of Table 1 could show the effects of molecular interactions on the HOMO and LUMO energies. Comparing the results of bimolecular complexes with those of singular Met and Chit could show the changes of molecular orbital energies in the bimolecular complexes, in which the effects on the HOMO levels are more significant in comparison to the LUMO levels. The corresponding E_G values also approve the obtained results by variations of values of different bimolecular complexes. The E_G values are notable for 01 complex in comparison to other complexes as that of the 16 complex has very small meaning and more reactivity but possesses less stability of the mentioned structure among other complexes as indicated before by the values of E_T and E_B. The D_M values also refer to the different electronic environments for the bimolecular complexes, in which the values are varied among the models. As a final conclusion of the results of Tables 1 and 2, it could be mentioned that the Chit structure could be seen as a vehicle for carrying Met drug; however, further information are still required to maintain the most proper vehicle for the most efficient carrying of Met drug. The experimental works have already reported the advantage of Chit for carrying several biological materials and here, within this work, we have shown the molecular intermolecular interactions of Met···Chit complexes based on computational chemistry methodologies.

The atomic scale C_Q properties for N and O atoms of Met and Chit molecular systems in the singular and bimolecular complexes have been evaluated for better interpretation of the investigated systems (Table 3). NQR (nuclear quadrupole resonance) spectroscopy is among the most versatile techniques to investigate the properties of matters at the atomic scales [34, 38]. Within this technique, the electronic environment of those atoms with meaningful Q could be detected by the calculated EFG tensors.

Afterwards, these tensors could be converted to C_Q (eq. 3) as a measurable parameter in both of experimental and computational approaches [39]. The importance of C_Q is for careful examination of the electronic properties of atomic sites, which are very important especially in the intermolecular interacting systems [40-44]. A quick look at the results of Table 3 could reveal that the electronic atomic sites could detect the effects of complex structures formation by comparing the C_Q values of each atomic counterpart in the singular and complex forms. The magnitudes of changes of parameters could also reveal the amount of the employed effect on the atomic site, in which the significant changes of C_Q values in singular and complex structures could imply for the significant detection of effects. Interestingly, atoms directly contributing to intermolecular interactions are not the only atoms with effects detections, but other atoms also

detect the effects. This is because of the floating nature of electrons in short and long ranges of integrations. The atomic scale properties for all bimolecular complexes could be very well tracked by the changes of C_Q values in the singular and complex forms.

Table 3. C_Q (kHz) properties for N and O atoms of singular Met and Chit and their complexes

Structure	N_3 ; N_5 ; N_6 ; N_8 ; N_9	O_{24} ; O_{25} ; O_{28} ; O_{30} ; O_{32} ; N_{21}
Met	5222; 3732; 3372; 2580; 4352	
Chit		10112; 10593; 10425; 10197; 10477; 4616
Met···Chit_01	5083; 3754; 3435; 2479; 4525	10133; 10564; 10468; 8801; 10252; 4612
Met···Chit_02	5180; 3699 3362; 2381; 3850	10101; 10566; 10393; 9146; 10448; 4602
Met···Chit_03	5165; 3690; 3378; 2383; 3828	9988; 10335; 9495; 10170; 10454; 4613
Met···Chit_04	4729; 4012; 3448; 2710; 4479	10237; 10610; 9675; 9139; 10013; 4628
Met···Chit_05	5160; 3664; 3362; 2552; 3996	9475; 10499; 10563; 10177; 10451; 4595
Met···Chit_06	4888; 3499; 3443; 2729; 4538	9041; 10743; 10628; 10090; 10344; 4166
Met···Chit_07	5144; 3679; 3364; 2622; 3958	9297; 10798; 10639; 10114; 10416; 4188
Met···Chit_08	5026; 3777; 3409; 2406; 3897	10059; 10604; 10470; 9152; 10420; 4630
Met···Chit_09	4833; 3612; 3358; 2669; 4566	10216; 10737; 10713; 10429; 9360; 4161
Met···Chit_10	5185; 3691; 3371; 2369; 3921	9358; 10851; 10644; 10137; 10416; 4290
Met···Chit_11	5353; 3684; 3342; 2646; 4272	10261; 10709; 10601; 9932; 10493; 4619
Met···Chit_12	5224; 3638; 3343; 2516; 4192	10170; 10760; 10650; 10039; 10064; 4502
Met···Chit_13	5249; 3668; 3364; 2531; 4388	10166; 10735; 10651; 10109; 10195; 4535
Met···Chit_14	5225; 3665; 3360; 2438; 4280	10195; 10746; 10663; 10141; 10463; 4453
Met···Chit_15	5219; 3659; 3353; 2530; 4250	10007; 10686; 10656; 10157; 10459; 4438
Met···Chit_16	5076; 3375; 3347; 2646; 4548	10214; 10748; 10655; 10158; 10460; 4585

* See Figures 1 and 2 for the atoms numbers and model structures.

Conclusion

This work has been performed based on DFT approach to investigate the properties of Chit vehicle for carrying the Met drug. Based on the purpose, singular molecules and all possible interacting bimolecular complexes have been constructed and optimized to obtain the minimized energy structures. Some trends could be highlighted as final remarks of this work. First; the Chit vehicle could be considered for carrying the Met drug in two efficient intermolecular positions with proper corresponding binding energies. Second; N_5 and N_8 atoms of Met and H_{45} and H_{43} of Chit are those atoms with the highest contributions to intermolecular interactions. Third; for more proper interactions of Met···Chit bimolecular complexes, it could be proposed to mask other interacting atoms of Chit not to contribute to interactions with Met counterpart. Fourth; HOMO, LUMO and dipole moments values show the effects of interactions on the electronic distributions of molecular systems.

Fifth; parallel effects are seen for the electronic atomic sites by exploring the atomic scale quadrupole coupling constants. And finally, the Chit could be proposes as a vehicle for carrying the Met counterpart, in which the detailed information of this work could increase the efficiency of achievements of purpose.

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