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A theoretical survey of the ability of nanocarbon layers to deliver anti-cancer drug temozolomide to the target cancer cells

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Density functional theory with the basis set of 6-31+G(d) was used to investigate on the carbon nano layers, C(sp2), potential as a drug delivery system for transferring of anti-cancer drug temozolomide to the target tissue. In order to elucidate the possibility of drug transmission by utilizing a carrier, the mechanisms of direct drug degradation, and loaded drug on the carrier are analyzed and examined completely. Two possible and different pathways for direct drug hydrolysis have been considered. According to obtained results activation barriers of these two pathways are 62.17 and 72.10 kcal mol^{-1}, and 64.30 and 70.10 kcal mol^{-1} for two gas mode and also two aqueous solvent conditions respectively. By comparison of outcomes, it can be found out that these activation barriers for both degradation pathways are significantly greater than the activation barriers for drug separation from the surface of carbon carrier (18.59 and 51.92 kcal mol^{-1} for gas mode and 11.79 and 44.67 kcal mol^{-1} for aqueous solvent). Therefore, by studying the achieved outcomes, it can be deduced that separation and releasing of the drug from the carrier occurs faster kinetically than direct degradation of temozolomide, so the drug can reach to the target before direct decomposition.

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1. Introduction

One of the significant issues which attract the attention of researchers is finding the new and efficient drug delivery systems. The affection of cancer chemotherapy is restricted by intense detrimental side effects induced by anticancer drugs and the incapability of drugs to access tumor sites specifically.[1-3] In order to decrease the harmful and dangerous cytotoxic effect on healthy organs and destruct the cancerous cells with minimum harm to normal body tissue special drug delivery systems targeted specifically to cancer cells can be applied.[4-10] Using an appropriate drug delivery system can contribute to patients to be cured better and faster. Nowadays various sorts of drug delivery systems are available and applied.[11, 12] Nanomaterials such as carbon nanotubes (CNT) and fullerenes are suitable materials and effective tools for drug delivery and transporting drug, molecules and other materials.[13] Application and role of CNTs for the delivery of drugs to their special site of action has become one of the principals

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and significant areas of interest for a large number of researchers and specialists. This significant role is mostly due to the characteristics of these materials, including their unique chemical and physical properties, a nano needle shape, hollow monolithic structure, and their capability to obtain the favorable functional groups on their outer layers.[14-16] One of the important advantages of the CNT is its capability to deliver drugs directly to damaged organs and cancer cells.[17] Another important and useful application of CNTs for drug delivery is intravenous injection. One of the problems with injecting drugs into the body is the hazard of blood vessels becoming blocked due to the large size of the drugs, which would lead to tissue toxicity and detrimental effects on organs. It has been offered that CNTs could be applied as nano carriers for delivering drugs into the body via injectable paths.[17-19] Many benefits obtain from CNTs, but alongside the positives, they have some drawbacks. One of the principals and serious concerns for researchers is toxicity of nanoparticles.[20, 21] One of the suitable and efficient methods to make these materials less toxic and more biocompatible is the functionalization process. According to some investigations, the attachment of appropriate molecules and materials to the CNT surface can decline the toxicity of CNTs.[22, 23] These materials can be functionalized with different sort of agents such as proteins, peptides, nucleic acids and drugs, and applied to deliver their cargos to targets.[24-26] These functionalized nanomaterials can transport their cargos across cell membranes with little cytotoxicity.[27, 28] Also, nanomaterials have another privilege; they have a very high surface area per unit weight for high drug loading.[7, 29-32] The noncovalent interaction of doxorubicin which is an anticancer medicine, with CNTs have been investigated by Ali-Boucetta and co-worker and its cytotoxic activity has been studied.[33] Various ways and methods have been utilized in order to load drug molecules to the side walls of functionalized CNTs by covalent or noncovalent connections.[14, 30, 34] Temozolomide (**Fig. 1**) which is known as an alkylating agent can be applied for the treatment of a wide spectrum of malignant, gliomas.[35-40] The activation mechanism of temozolomide was reported by M. F. G. Stevens and co-workers and has been declared that the mechanism of degradation vary depends on pH. The rate of temozolomide degradation enhances with an increase in pH.[41] The ring-opening of temozolomide have been investigated by A. A. Taherpour and co-workers,[42] and two different pathways for the ring-opening reaction have been considered, in addition, the protonation of all possible sites were studied in order to show the significant role of acidic conditions on the increased stability and mechanism of the medicine. The obtained outcomes have illustrated the preferable site for protonation is the oxygen of the amide group that would stabilize the system more than the next favourable protonation site.[43] This article aims to elucidate the capability of nano carbon layers as drug delivery base. We have investigated the ability of nano carbon layers (sp^2 carbons) to deliver anti-cancer drug temozolomide to the target. Temozolomide was linked to carbon layers carrier and degradation mechanism under both neutral and acidic conditions have been studied in order to show that degradation of the drug would happen before or after reaching to target.

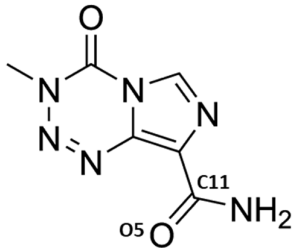


Fig. 1. Temozolomide structure

2. Computational Details

The complete geometrical optimization of all structures and transition states has been carried out with density functional theory[44, 45] by using the B3LYP[46] functional and the 6-31+G(d) basis set. To confirm that the systems are at a minimum point or transition state of potential energy surface, all the systems were confirmed by vibrational frequency calculations in the same basis set. Calculations of intrinsic reaction coordinates (IRC)[47] were also performed on transition states to confirm that such structures are indeed connecting two minima. The computation was carried out for water as the solvent

utilizing the SM8 (SCRF) model.[48, 49] All the analysis of molecular orbital composition, bond order analysis, and spin density analysis are performed on the .chf format of Multiwfn package.[50] All the calculations were performed with ORCA,[51] and Spartan 10 software suite of programs.[52]

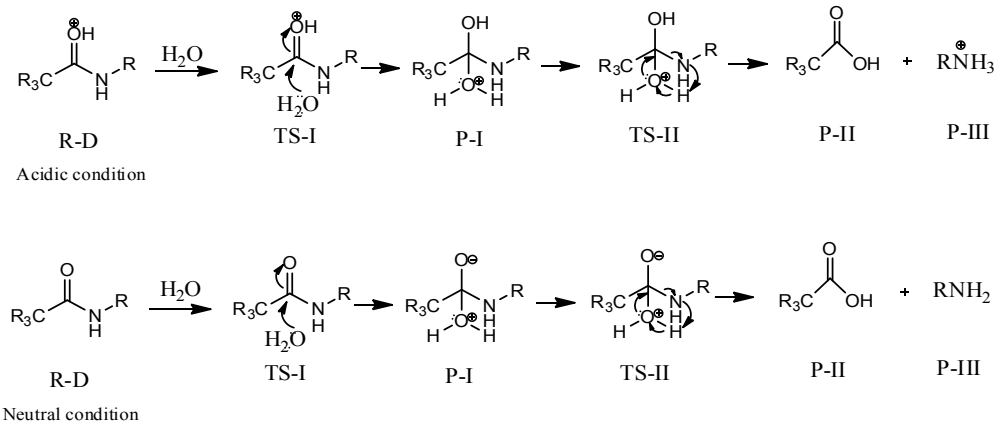
3. Results and discussion

In this study, the potential of temozolomide drug transfer to the target by applying the sp^2 carbon base has been analyzed. This survey can be performed by studying the following subjects and under various pH conditions. I. Investigation of hydrolysis process of the loaded drug on CF-C(sp^2) (Carboxylic group Functionalized on C(sp^2)) under acidic and neutral pH conditions; due to the interactive agent group of amine on temozolomide for interaction with the CF- C(sp^2); this part is investigated by studying of hydrolysis process of the amine groups (R-NH_2 components) from the carboxylic site of CF-C(sp^2). II. Selection of optimized conditions with minimum activation barrier for amine hydrolysis in the previous step and examination of different degradation mechanisms of temozolomide from CF-C(sp^2) under selected pH condition. III. Study of the activation barrier for hydrolysis and decomposition of temozolomide without the presence of a carrier substrate for possible paths of direct drug degradation. IV. Potential determination of drug transfer by CF-C(sp^2) with comparison of activation energies in stages II and III; if the required energy for drug degradation is lower than the amount of this energy for separation from the CF-C(sp^2) base, the drug would be decomposed just before leaving the CF-C(sp^2), and so the CF-C(sp^2) base does not have the high capability to transfer drug to the target tissue. In contrast, if the required energy for drug degradation is greater than the amount of this energy to separate from the CF-C(sp^2) base, the drug is able to separate from the CF-C(sp^2) at lower energies and this can be a guarantee of transferring of the drug before of hydrolysis.

3.1 Study of hydrolysis mechanism of R-NH_2 component connected to CF-C(sp^2)

Drugs and materials with active amine group which have interaction with a carboxylic agent on CF-C(sp^2) surfaces can be hydrolyzed and separated from CF-C(sp^2) under various pH conditions.[53] Due to the physiological buffering environment, hydrolysis generally occurs in neutral conditions, but studies have shown that in special parts of damaged tissues such as cancer cells, the situation is different and pH is lower than neutral rang and located in the acidic region.[54,55] Therefore, drugs which are utilized to transfer to these special parts should have the ability to release their active component in these acidic tissues. The main purpose of this study is to investigate the transfer potential of temozolomide drug under acidic and neutral conditions. In order to generalize the work and with respect to the active amine group in temozolomide drug, in the first section, the hydrolysis potential of amine groups from the carboxylic acid agent is generally investigated and the effects of acidic and neutral conditions on the hydrolysis of these compounds are examined. Hydrolysis of [CF-(sp^2)]-RNH_2 under two neutral and acidic conditions has been summarized in **Scheme 1**. In both conditions, the reactions can be accomplished by passing through two transition states and intermediates leads to hydrolysis of amine group on the CF-C(sp^2) base (**Fig. 2**). Under the neutral condition, water molecule attack to the carbon of the carbonyl group and by passing through two transition states (N-TS-I and N-TS-II), the drug is separated from CF-C(sp^2). The value relative Gibbs free energy barrier in gas and aqueous phases for N-TS-II are 52.4 and 56.9 kcal mol^{-1} respectively. This separation in aqueous phase has more activation barrier energy (4.3 kcal mol^{-1}) compared to the gas phase. Also, this separation under acidic condition by protonation of oxygen of the carbonyl group has been studied.

Based on **Fig. 2.** hydrolysis under acidic condition passes through two transition states H+TS-I and H+TS-II that H+TS-II has the most activation barrier with 39.2 and 49.1 56.9 kcal mol^{-1} in gas and aqueous phases respectively. By comparison of activation barriers in neutral and acidic conditions, it can be concluded that acidic conditions decrease significantly the values of activation barriers by 93.4 in the gas phase and 7.9 in the aqueous phase. This outcome is because of the catalytic role of hydrogen on carbon of carbonyl group.[56] Due to the connection of hydrogen to carbon this site would be activated compared to the neutral condition.



Scheme 1. Degradation mechanism of $R_3C(CO)NH_2$ compounds at neutral and acidic conditions

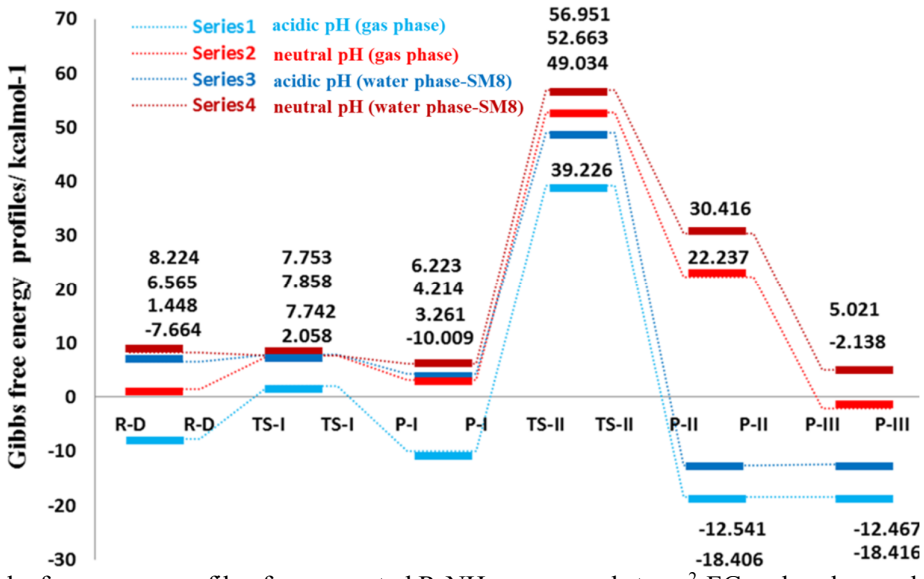


Fig. 2. Gibbs free energy profiles for connected R-NH_2 compounds to sp^2-FG carbon layers decomposition pathways in the gas and SM8 models. (The abbreviation symbols (R-D, P-I etc...) are indicated in **Schema 1**)

3.2 Degradation mechanism of connected temozolomide to CF-C(sp^2) in two possible pathways and at acidic condition

There are two possible protonation sites (O1 and O5) on connected drug to the CF-C(sp^2) (**Fig. 3**). Therefore, we investigate the degradation of the drug when these two sites are protonated. So the degradation mechanism of linked temozolomide to CF-(sp^2) can be studied in the following two ways. I. when O1 is protonated and II. when O5 is protonated (**Scheme 2** and **Fig. 4.**).

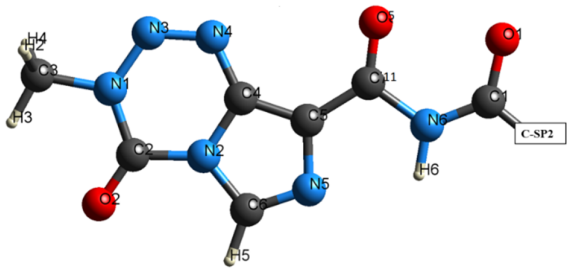
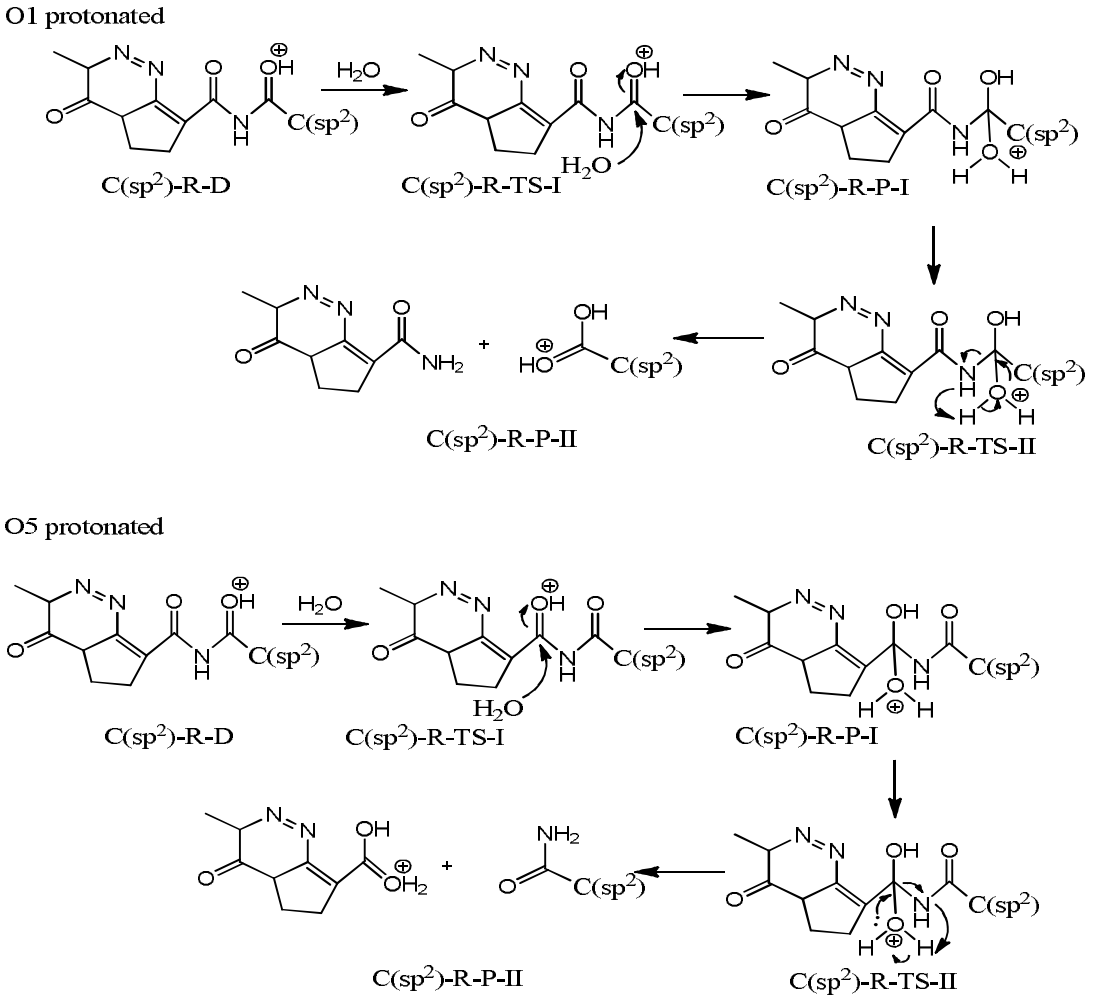


Fig. 1. Connected temozolomide to C(sp^2)



Scheme 2. Degradation mechanism of connected temozolomide to $C(sp^2)$-FG carbon layers in two possible pathways at acidic condition.

In the first case when O1 site is protonated, proton (H^+) is located on carboxyl which is attached to the CF-$C(sp^2)$ base. Due to this action, carbon site of this group would be activated and the electrophilicity potential of this site reaches to 116.22 kcal mol^{-1} which has 13 kcal mol^{-1} more electrophilicity potential comared to the carbon site of the second carbonyl at C14 with 103.22 kcal mol^{-1} (support information, SI 8). The main reason for increasing of electrophilicity potential is a major transfer of LUMO orbital portion from 0.00% to 51.01% at C1 and activation of this site for water attack (SI 10). This value of potential leads the reaction to attack to this site kinetically and the attack of a water molecule to this site would be facilitated. Due to this attack electron density transfers from double bond to OH^+ group and O1sp^2-R-TS-I with the energy of 9.08 kcal mol^{-1} is generated. This transition state with the complete transmission of electron density from double bond to OH and attachment of water molecule creates transition state of O1sp^2-R-P-I with an energy value of 3.18 kcal mol^{-1}.

This transition state is unstable and by some simultaneous transfers (simultaneous transfer of O-H at water molecule to oxygen and transmission of created O-C bond to carbon and finally, the transfer of N-C electron density to the nitrogen atom) by passing through O1sp^2-R-TS-II with energy of 18.59 kcal mol^{-1} generates O1 sp^2-R-P-II with energy value of -15.85 kcal mol^{-1}. This stage includes a separated drug from the CF- $C(sp^2)$ base. Due to this separation, the CF-$C(sp^2)$ base is separated with a protonated hydroxide agent. By analyzing the effect of the water solvent on O1sp^2-R-TS-II, we can observe the energy reduces to 11.79 kcal mol^{-1}. Since this transition state is the rate determining step, it can be clearly concluded that the aqueous solvent has a significant role on the reaction rate and can

reduce the activation barrier energy. On the other hand, the effect of adding solvent on the product is reversed and leads to increasing the energy to -11.72 kcal mol^{-1}. The reason for this behavior maybe is the difference between compound solvation before and after degradation.

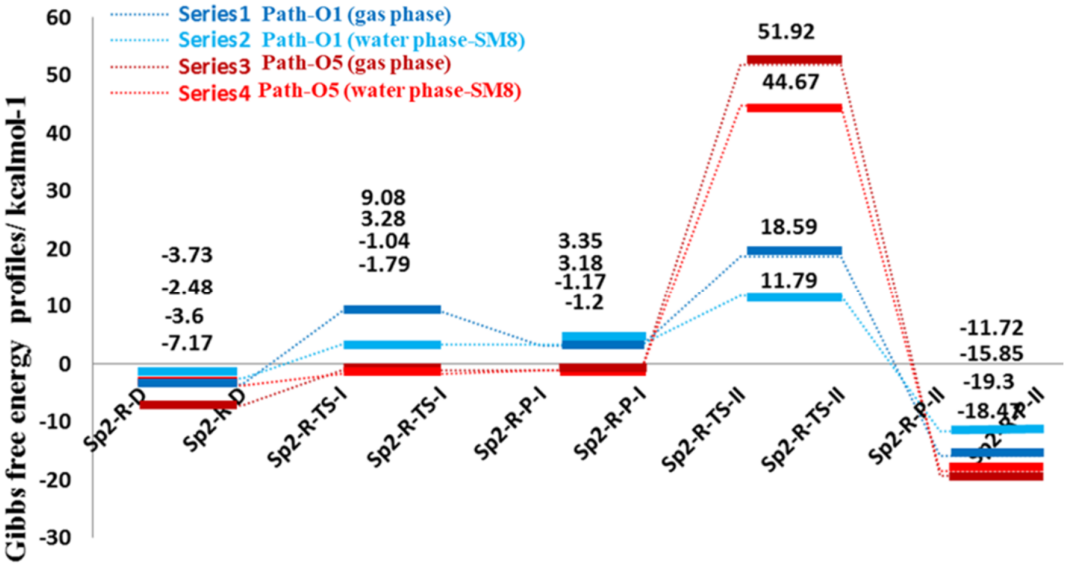
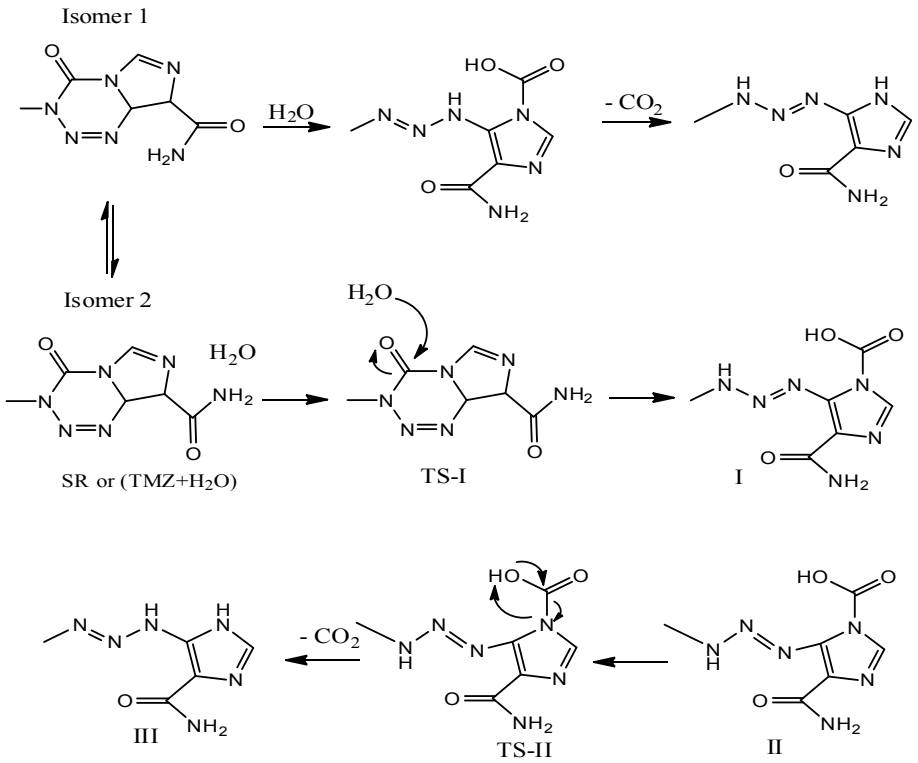


Fig. 4. Gibbs free energy profiles for connected temozolomide to C(sp^2)-FG carbon layers decomposition pathways in the gas and SM8 models. (The abbreviation symbols are indicated in **Scheme 2**)

The second path takes place with protonation of O5 which is related to the temozolomide carboxyl group, and adding of proton agent to this site can enhance electrophilicity potential about 4.65 kcal mol^{-1} relative to the carbon of carbonyl 1 (SI 4). It is noteworthy that potential of attack declines compared to the previous case and this is because of the transfer of lower LUMO orbital portion to carbon site 14 which only increases 0.28% (SI 6). This low potential is capable to change the trend of attack in the previous mechanism. Similar to the previous path by an attack of water and passes thorough O5sp^2-R-TS-I transition state with -1.04 kcal mol^{-1} energy, electron density transfers from carboxyl double bond to OH^+ group and by water attachment to this site, O5sp^2-R-P-I transition state with -1.20 kcal mol^{-1} of energy is generated. This transition state by providing energy of 51.92 kcal mol^{-1} and by passing through O5sp^2-R-TS-II (during transfer of O-H bond to positive oxygen at the water then density transfer of O-C related to water to C-OH bond and separation of C-N bond) reaches to product O5sp^2-R-P-II with -19.30 kcal mol^{-1}. The important point is the impact of water solvent on the second transition state which is the rate determining step and at model, SM8 decreases to the energy of 44.67 kcal mol^{-1}. The significant point in this mechanism is that with advancement of separation, the drug is hydrolysed and separated along with the carboxylic agent and the decomposed materials do not include the initial state of the drug. So by this way, the decomposed material has a negative effect on drug performance, and not only does not make effective drug transfer but also reduces the initial dosage. By comparison of activation barrier energies of rate determining step of two pathways, it is absolutely clear that with protonation of O1 activation barrier for gas phase 18.59 kcal mol^{-1} and for aqueous solvent 11.79 kcal mol^{-1} are obtained that would stabilize about 33.33 kcal mol^{-1} in gas mode and 32.88 kcal mol^{-1} in water solvent mode relative to O5 protonated and the reaction occurs faster kinetically.

Both of these activation barriers can be compared with activation barrier of direct drug hydrolysis which for gas mode and water solvent are 62.17 kcal mol^{-1} and 64.30 kcal mol^{-1} respectively and for path 2 obtained activation barrier are 72.10 kcal mol^{-1} and 70.17 kcal mol^{-1} for gas mode and water solvent respectively (**Fig. 5** and **Scheme 3**). By comparison of the activation barriers of drug decomposition with activation barriers of drug separation (from CF-C(sp^2)), it is clear, that separation should be more energetically favorable than decomposition. This indicates that before the separation

drug may not undergo the decomposition from the carbon base, and will be transmitted by the CNT-base to the target.



Scheme 3. The different pathways for the direct hydrolysis of temozolomide

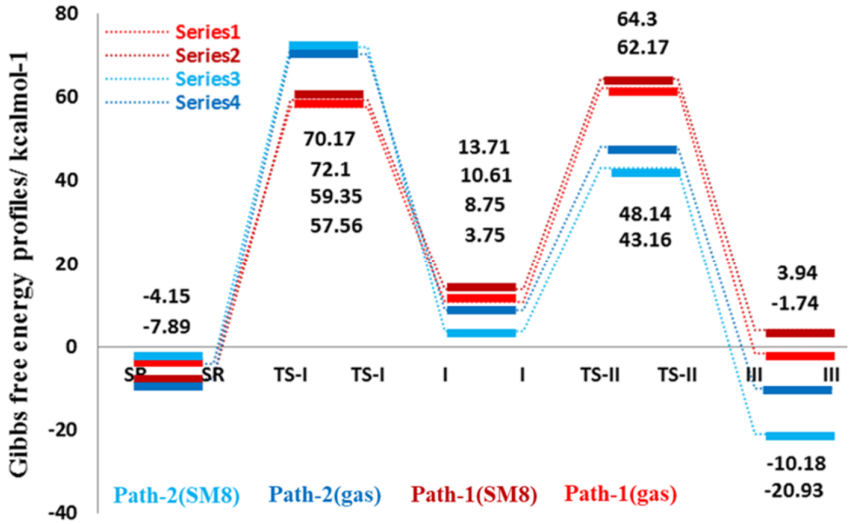


Fig. 5. Gibbs free energy profiles for temozolomide direct decomposition pathways in the gas and SM8 models. (The abbreviation symbols are indicated in **Schema 3**)

4. Conclusion

We have performed DFT calculations for carbon nano layers C(sp^2) in order to clarify their role as a nanocarrier for drug delivery of anti-cancer drug temozolomide. To compare mechanisms of direct temozolomide degradation and the separation of drug from carrier, possible mechanisms for each case have been investigated and analyzed. By comparison of the activation barriers of drug decomposition with activation barriers of drug separation (from CF-C(sp^2)), it is clear that separation should be more

energetically favourable than decomposition. This indicate, that the drug may not be decomposed before separation from the carbon base and will be transmitted by the base to the target. Also based on obtained outcomes, under the acidic condition, the drug separation from the carrier is faster than it direct degradation; therefore it could be expected that the sp2 carbon carrier can act as a suitable drug delivery vehicle, which has a potential and capability to transmit the anti-cancer drug temozolomide to the target tissue.

Financial interest

The authors declare no competing financial interest.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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