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Original Research Article

Comparison of Thermodynamic Functions of Idarubicin Cancer Drug Interaction with Carbon Nanotube: QM/MM studies

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ABSTRACT

Due to the growing need of the scientific community to target drugs for Cancer whose use of drugs has many side effects for the patients, there are many studies that play an important role in better understanding and optimizing the laboratory processes for evaluating the drug delivery capability of drug carriers, using computational methods. Carbon nanotubes Improves drug performance and reduces side effects. In the project, the interaction of idarubicin, an anticancer drug, on carbon nanotubes was investigated using density functional calculations at B3LYP level and basis set (6-311G). The results show that the solvent dielectric constant is effective on the thermodynamic functions obtained from quantum calculations and energy from molecular dynamic calculations. Therefore, based on these results, the best environment for reaction in both methods is the water environment. Because the Gibbs free energy changes in the water environment are minimum value. And the entropy changes in this environment are highest value.

Keywords: Monte Carlo, Idarubicin, CNT, Thermodynamic, Functions.

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Introduction

We need smart drug delivery systems because the physical and chemical properties of drugs vary widely. In smart drug delivery, the drug is placed on the carbon nanotube as the carrier of the drug and reaches the patient's body tissue [1]. The drug carrier must be bio-compatible with the body so that it can be readily attached to the drug and removed from the body, and the manufacturing process is carefully controlled [2]. Among different drug carriers, carbon nanotubes have proven their ability to deliver targeted drug delivery [3]. Macromolecules, polymers, micelles, nanoparticles, metallic nanoparticles, and others are among the carriers used in drug delivery[4] Carbon nanotubes have received more attention than other nanoparticles due to their special mechanical properties, chemical stability, thermal stability, strength and most importantly high biocompatibility[5-6]. Because carbon nanotubes are not toxic, they do not damage biological molecules such as DNA and can be used as Nano carriers for toxic drugs and with clinical adverse effects [7-8]. In this study, we investigate the complexion of idarubicin and CNT using density functional density quantum calculations which, as a Nano carrier, can bring idarubicin to the target site [9]. Idarubicin is an anthracycline antileukemic drug. Idarubicin binds to DNA and prevents DNA interference with topoisomerase II [10].This is the analogue of daunorubicin, but the absence of a methoxy group results in increased fat solubility and cellular uptake.it pulls the histone out of the chromatin and it is related to anti-tumor antibiotics. Idarubicin is used to treat acute myeloid leukemia [11]. Carbon nanotubes are also nanotubes (5, 0). Due to the side effects of idarubicin, the drug is combined with carbon nanotubes to reduce its side effects and to reach the target cell in a targeted manner. Nano drug delivery systems improve therapeutic activity by increasing the half-life of the drug, improving the solubility of non-water soluble drugs or controlled drug release [12-13]. The purpose of this study is to use density functional calculations at B3LYP level and the basis set 6-311G to investigate the thermodynamic functions of the idarubicin anticancer drug on carbon nanotube [14].

Computing methods for simulation

In this study B_3LYP hybrid method [15, 16] in conjunction with the exchange function B_3 and LYP correlation function [17-18] was used. For these project different structures of Idarubicin Cancer Drug, carbon nanotube and interaction of (Idarubicin-CNT) optimized, then at the same computational level Thermodynamic Functions performed to confirm spontaneously or non-

spontaneously of reaction. The calculations were performed with Software Gaussian 09 [19-20]. Then, the energy of the Idarubicin anticancer drug interaction with CNT in the fields Amber, MM+, and OPLS was investigated by molecular dynamic calculations.

1. Internal energy:

Internal energy is:

$$E = NK_B T^2 (\frac{\partial lnq}{\partial T})_V \qquad (1)$$

2. Entropy is:

$$S = Rln(q(V,Y)e) + RT(\frac{dlnq}{dT})_p \qquad (2)$$

3. Enthalpy is :

$$H = RT\left[T(\frac{\partial lnq}{\partial T})_{N,V} + 1\right] \qquad (3)$$

4. Finally, Gibbs free energy is:

$$\Delta G(T) = \Delta H(T) - T\Delta S(T) \qquad (4)$$

Results and discussions

In this study, carbon nanotube (5,0) were used which have chirality characteristics, length 12 angstrom and length carbon-carbon bond 1.41 angstrom and idarubicin anticancer drug was used. The idarubicin anticancer drug binds to the open end of the carbon nanotube. As shown in Figure 1.

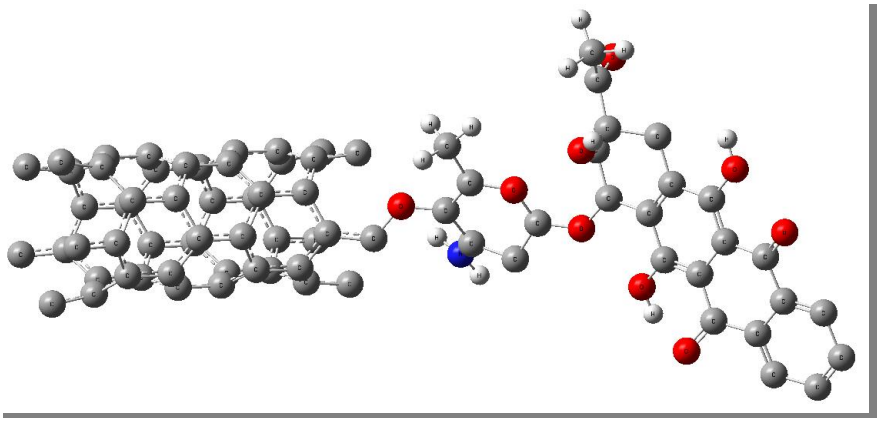

Figure 1. Optimized structure of interaction of the idarubicin anticancer drug of carbon nanotube head.

First, the energy calculation is based on three methods of calculating the molecular dynamic, namely MM^{+}, AMBER, OPLS for the interaction of a carbon nanotube and the idarubicin anticancer drug. This interaction is done by the following reaction:

$$Idarubicin + CNT \rightarrow Idarubicin - CNT \qquad (5)$$

The values of energy for the three force fields such as: $MM^{+,}$ AMBER, OPLS are obtained by the following formula:

$$\Delta E = E_{idarubicin} - \left(E_{idarubicine} - E_{CNT}\right) \qquad (6)$$

The calculated energy changes in terms of various dielectric constants in the MM^{+}, AMBER, and OPLS force fields for the reaction are shown in Figure 2.

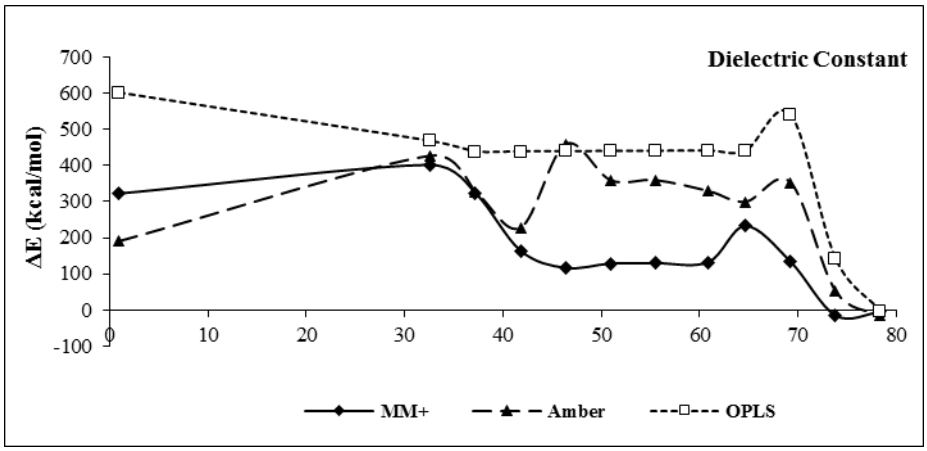

Figure 2. Calculated energy changes in terms of constant dielectrics at MM +, AMBER, OPLS force fields.

In general, the energy increases with decreasing dielectric constant of solvent and, in some cases, irregularities are due to the proximity of the dielectrics. Due to the Amber, OPLS, MM^{+} force fields we find that the lowest energy is for the water solvent. By comparing all three graphs we can say that the best force field for this interaction is MM+. In quantum computing, volume required for idarubicin anticancer drug and CNT and complex of (idarubucin / open-end of CNT) using volume keyword is obtained and the values obtained are, respectively, 5.65, 5.81 and 6.35 angstrom. The results of the Onsager method prove that the Gibbs free energy, enthalpy and entropy values of the idarubucin anticancer drug and CNT and complex of idurobicin / open-end system of CNT are sensitive to the polarity of the surrounding solvent. The results show that by increasing the temperature from 298 K to 310 K, the Gibbs free energy of the idarubucin anticancer drug and CNT and complex of idarubucin / open-end of CNT will decrease in the gas, water and methanol phases. It is observed that with increasing temperature from 298 K to 310 K the most positive enthalpy and entropy is at 310 K. The water solvent is the best environment for the idarubucin anticancer drug, CNT and interaction between them.

Table 1. Theoretical thermodynamic parameters in various temperatures for three phases at B3LYP/6-311G level of theory for idarubicin anticancer drug.

System	Media	Quantities	Temperature (K)			
			298	300	305	310
			Theoretical thermodynamic values			
idarubicin	Gas phase	G(kcal / mol)	-359157.634	-359157.809	-359157.846	-359158.099
		H(kcal / mol)	-359141.700	-359141.665	-359141.362	-359141.293
		S(kcal / mol.K)	0.05347	0.05381	0.054046	0.054213
	Methanol	G(kcal / mol)	-359377.458	-359377.617	-359377.651	-359377.777
		H(kcal / mol)	-359357.820	-359357.775	-359357.416	-359357.125
		S(kcal / mol.K)	0.0659	0.06614	0.06634	0.06662
	Water	G(kcal / mol)	-359410.88	-359410.986	-359411.011	-359411.26
		H(kcal / mol)	-359391.193	-359391.012	-359390.688	-359390.520
		S(kcal / mol.K)	0.06606	0.0666	0.0667	0.06691

Table 2. Theoretical thermodynamic parameters in various temperatures for three phases at B_3LYP/6-311G level of theory for Carbon nanotube.

System	Media	Quantities	Temperature (K)			
			298	300	305	310
			Theoretical thermodynamic values			
Carbon Nanotube	Gas phase	G(kcal / mol)	-907445.371	-907445.427	-907445.953	-907446.324
		H(kcal / mol)	-907412.263	-907412.08	-907412.029	-359141.293
		S(kcal / mol.K)	0.1111	0.11120	0.11123	0.11144
	Methanol	G(kcal / mol)	-907459.753	-907459.840	-907460.079	-907460.204
		H(kcal / mol)	-907426.533	-907426.373	-907426.319	-907426.067
		S(kcal / mol.K)	0.11148	0.11156	0.11182	0.1121
	Water	G(kcal / mol)	-907469.016	-907469.177	-907469.847	-907470.453
		H(kcal / mol)	-907435.619	-907435.502	-907435.447	-907435.195
		S(kcal / mol.K)	0.11207	0.11225	0.11279	0.11374

Table 3. Theoretical thermodynamic parameters in various temperatures for three phases at B_3LYP/6-311G level of theory for (idarubicin-CNT) complex.

System	Media	Quantities	Temperature (K)			
			298	300	305	310
			Theoretical thermodynamic values			
(idarubicin-CNT) complex	Gas phase	G(kcal / mol)	-1266614.238	-1266614.394	-1266614.885	-1266615.394
		H(kcal / mol)	-1266590.084	-1266590.02	-1266589.706	-1266589.475
		S(kcal / mol.K)	0.08105	0.08125	0.081446	0.08168
	Methanol	G(kcal / mol)	-1266848.672	-1266848.78	-1266849.035	-1266849.250
		H(kcal / mol)	-1266820.608	-1266820.513	-1266820.158	-1266819.729
		S(kcal / mol.K)	0.094174	0.094223	0.09468	0.09523
	Water	G(kcal / mol)	-1266892.753	-1266892.899	-1266893.275	-1266893.769
		H(kcal / mol)	-1266864.606	-1266864.369	-1266864.099	-1266863.82
		S(kcal / mol.K)	0.09445	0.0951	0.09566	0.09661

On changes of enthalpy, entropy, and free Gibbs energy it can be stated that by increasing the dielectric constant the Gibbs free energy values decrease and move to negative values and the system is more stable. By increasing the dielectric constant of solvent, the enthalpy values move to negative values. And as the idarubicin anticancer drug is coupled to functionalized carbon nanotubes, entropy decreases.

Table (4): Thermodynamic function alterations in various temperatures for three phases at $B_3LYP/6$-311G level of theory for reaction 5.

System	Media	Quantities	Temperature (K)			
			298	300	305	310
			Theoretical thermodynamic values			
Δx	Gas phase	ΔG(kcal / mol)	-11.233	-11.158	-11.086	-10.971
		ΔH(kcal / mol)	-36.121	-36.275	-36.315	-36.405
		ΔS(kcal / mol.K)	-0.08352	-0.08376	-0.08383	-0.08397
	Methanol	ΔG(kcal / mol)	-11.461	-11.323	-11.305	-11.269
		ΔH(kcal / mol)	-36.255	-36.365	-36.423	-36.537
		ΔS(kcal / mol.K)	-0.08321	-0.08348	-0.08348	-0.08349
	Water	ΔG(kcal / mol)	-12.857	-12.736	-12.417	-12.056
		ΔH(kcal / mol)	-37.794	-37.855	-37.964	-38.105
		ΔS(kcal / mol.K)	-0.0837	-0.08375	-0.08383	-0.08405

Conclusion

In this study, the results obtained using the Onsager method are sensitive to the polarity of the surrounding solvent. When the solvent dielectric constant increases, the Gibbs and enthalpy free energy values decrease but the entropy values increase. And entropy of complex of idarubicin-CNT are reduced. And given $\Delta G_{reaction}$ values so that it is the lowest for 298 K which has the highest stability. The most positive $\Delta S_{reaction}$ value is 298 K.

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