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Original Research Article

Theoretical Studies of Interaction Melphalan Anticancer Drug with Functionalized Carbon Nanotube: Thermodynamics Studies

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ABSTRACT

One of the advancements of the present century is the use of carbon nanotubes in the treatment of cancer. As the carbon nanotubes pass through the cell wall, the anticancer drug is transferred to the cancer tissue and released. The purpose of this project is to obtain the thermodynamic functions and potential energy of the interaction between melphalan anticancer drug and functionalized carbon nanotube. The potential energy of this interaction is obtained by Monte Carlo simulation at different temperatures in the gas, methanol and water phases and the thermodynamic functions of this interaction is obtained by quantum mechanics by the density function theory with B3LYP/6-311G basis set at different temperatures in the gas, methanol and water phases. The results show that the Gibbs free energy and entropy are a function of the solvent dielectric constant. So that the Gibbs free energy and entropy changes of reaction are decreases and increases respectively. Also the results of both methods indicate that the best environment for this interaction is water solvent.

Keywords: Monte Carlo simulation, melphalan, interaction, carbon nanotube, Thermodynamic

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Introduction

Since carbon nanotubes have extraordinary properties including physical, chemical, mechanical and biological. It has made carbon nanotubes widely used in industry and biomedicine and drug delivery [1-4].Until the 21st century, the use of carbon nanotubes has only been in the industry but in the 21st century, their first biological applications were also examined [5-6]. One of the characteristics of carbon nanotubes is their ability to carry drugs. These activities lead to the development of drug delivery based on the carbon nanotubes that it has attracted the attention of many researchers [7]. Carbon nanotubes are nanotubes made of single atom thick graphene sheets that it consists of a layer of carbon atoms in a two-dimensional honeycomb grid. There are two categories of carbon nanotubes, including single-walled carbon nanotubes and multi-wall carbon nanotubes [8]. One of the disadvantages of multi-walled nanotubes compared to single-walled nanotubes is that they are less robust because the interlayer bonds are weak. But since nanotube applications in polymer reinforcement improve thermal and electrical properties rather than improve mechanical properties, the use of multi-walled carbon nanotubes is high. There are several ways to make carbon nanotubes, including (1) carbon arc-discharge method [9] (2) laser-ablation technique [10] (3) chemical vapor deposition [11-12] (4) flame synthesis method [13-14] (5) spray pyrolysis method [13-15]. All carbon nanotubes have low solubility in aqueous and organic solvents.As a result, to increase their solubility, they must be functionalized that the functionalization of carbon nanotubes is done in three ways (1) covalent functionalization [16] (2) noncovalent adsorption of required molecules [17] (3) the endohedral filling of CNTs inner space [18] that The most important of these are covalently functionalized nanotubes that are excreted by the urine [18]. Melphalan is an anticancer drug that melphalan is used to treat multiple myeloma, ovarian cancer, AL amyloidosis and occasionally malignant melanoma. Melphalan modifies DNA nucleotide guanine by alkylation and creates linkage between DNA strands. This causes a chemical change in DNA synthesis and thus inhibits RNA synthesis. These changes cause toxicity in dividing and non-dividing tumor cells [19].we decided to investigate the interaction of melphalan anticancer drug with functionalized carbon nanotube. Initially, we obtain the potential energy by Monte Carlo simulation in force fields such as Amber, OPLS and MM $^{+}$. Then we obtain the thermodynamic values of this interaction by quantum mechanics with density function theory with B3LYP/6-311G basis set[20-21].

Computational Methods

The aim of the present study was to investigate the interaction of melphalan anticancer drug with carbon nanotube. So, we decided to investigate the interaction of melphalan anticancer drug with functionalized carbon nanotube. Initially, the potential energy of the anticancer drug interaction with functionalized carbon nanotube in the fields Amber, MM^{+}, OPLS was investigated by Monte Carlo simulation. Then this interaction was investigated using quantum mechanics calculations with density function theory with B3LYP / 6-311G basis set [22-23].

Results and discussions

All kinds of drug interactions with carbon nanotubes should be considered at the beginning of the calculations. This was done by quantum mechanics using the Gaussian 98 software with B3LYP/6-311G,B3LYP/6-31G,HF/6-31G basis set and the energy of these interactions was investigated. Any interaction that has less energy is more stable. The types of interactions are shown in Figure1 below:

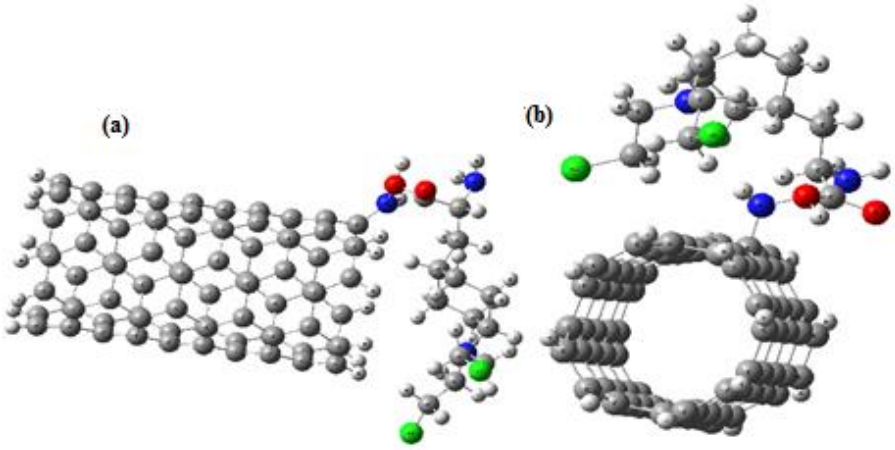

Figure 1. (a) Optimized structure of Interaction of the melphalan anticancer drug of the melphalan through the functionalized carbon nanotube head (b) Optimized structure of Interaction of melphalan anticancer drug through the functionalized carbon nanotube wall

Figure.1 with B3LYP/6-311G basis set has the lowest energy so it has the most stability. As a result, we use the interaction between the drug and the nanotube in Fig. 1 to perform the calculations. Table 1 reports the energy values.

Table (1): The energy of interaction of melphalan drug and the functionalized carbon nanotube (kCal/mol) in various basis sets

System	Energy(kCal/mol)			System	Energy(kCal/mol)		
Interaction of the melphalan through the functionalized carbon nanotube head	**HF/6-31G**	**B3LYP/6-31G**	**B3LYP/6-311G**	**Interaction of the melphalan through the functionalized carbon nanotube wall**	**HF/6-31G**	**B3LYP/6-31G**	**B3LYP/6-311G**
	-1216381.3395	-1216382.268	-1216385.355		-1216380.064	-1216381.7469	-1216382.86

Then in the next step we used Amber, MM^{+}, OPLS force fields to obtain the potential energy according to the following equation:

$$\text{Melphalan} + \text{CNT-NH}_2 \rightarrow \text{interaction of melphalan with CNT-NH}_2 \quad (1)$$

$$\Delta x = X_{\text{interaction of melphalan with CNT-NH2}} - (X_{\text{Melphalan}} + X_{\text{CNT-NH2}}) \quad (2)$$

In these fields the potential energy will not be the same. Figure 2 (a),(b) and (c) illustrate the potential energy changes in terms of temperature for the three fields mentioned that in these force fields such as: Amber, OPLS, MM+ is the lowest potential energy for the water solvent. By comparing all three graphs we can say that the best field for this interaction is MM^{+} that shown in Figure 2(d).

In the next step, the effects of the dielectric constant on this interaction are examined that in this project, the Onsager method is used for the constant dielectric effects on this interaction. First we have to calculate the radius of the cavity of the anticancer drug, the carbon nanotube and the interaction between them. The obtained values for them are equal to 5.31, 5.89, and 6.14 respectively. The results indicate that the anticancer drug, carbon nanotubes and their interactions are sensitive to solvent polarity. Thermodynamic values of Gibbs free energy and entropy is change with dielectric constant changes and is related to the solvent dielectric constant. According to Table2, the Gibbs free energy of the anticancer drug, carbon nanotubes, and the interactions between them decreases with increasing temperature from 298 to 320 K. So that the lowest amount of Gibbs free energy is for a temperature of 320 K. Also, if we examine the Gibbs free energy changes based on the dielectric constant, we find that the lowest Gibbs free energy is for the water solvent. In Table 2, the entropy values of the anticancer drug, carbon nanotubes and their interactions can be seen. According to this table, the maximum entropy for the temperature is 320 K and the most positive entropy values is for an anticancer drug, carbon nanotubes and their interactions in water solvents.

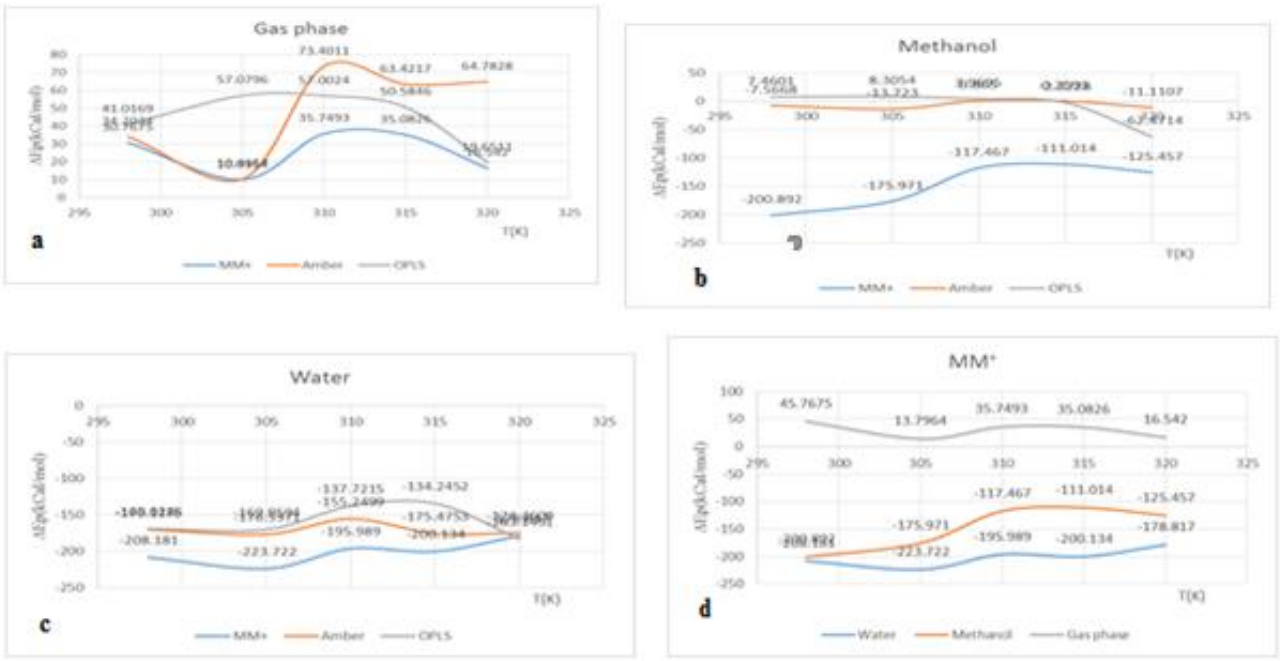

Figure 2. (a) Potential Energy changes versus Temperature Changes in Gas phase (b) Methanol(c) Water (d) Potential Energy changes versus Temperature Changes in various solvent

As shown in Table 3, The Gibbs free energy changes of the reaction and the entropy changes of the reaction are obtained by the equation 2.According to this table, as the temperature increases, the Gibbs free energy change values increase so that the lowest Gibbs free energy changes for 298 K. The table also shows that the reaction entropy decreased with increasing temperature, with the most positive reaction entropy being at 298 K. Also with increasing dielectric constant of solvent the lowest amount of Gibbs free energy of reaction and entropy changes of reaction is in water solvent. So the best environment for this chemical reaction is in the water solvent.

Table (2): Table 2Theoretical thermodynamic parameters in various temperatures for three phases at B3LYP/6-311G level of theory.

System	Media	Quantities	Temperature (K)				
			298	300	305	310	315
			Theoretical thermodynamic values				
Melphalan	Gas phase	G	-346812.213	-346812.388	-346812.425	-346812.678	-346812.931
		H	-346796.379	-346796.344	-346796.041	-346795.972	-346795.903
		S	0.0531	0.05348	0.05372	0.05389	0.05402
	Methanol	G	-347032.037	-347032.196	-347032.23	-347032.356	-347032.609
		H	-347012.506	-347012.454	-347012.095	-347011.804	-347011.735
		S	0.06554	0.06581	0.06602	0.0663	0.06645
	Water	G	-347065.459	-347065.565	-347065.59	-347065.839	-347066.092
		H	-347045.872	-347045.691	-347045.368	-347045.206	-347045.137
		S	0.065728	0.06625	0.06630	0.06656	0.06678
Carbon Nano tube-NH_2	Gas phase	G	-895099.95	-895100.006	-895100.532	-895100.903	-895101.274
		H	-895066.942	-895066.759	-895066.708	-895066.456	-895066.204
		S	0.110765	0.110800	0.110898	0.1111	0.1133
	Methanol	G	-895114.332	-895114.419	-895115.002	-895115.401	-895115.772
		H	-895081.212	-895081.052	-895080.998	-895080.746	-895080.494
		S	0.11114	0.11122	0.11149	0.1118	0.11197
	Water	G	-895123.595	-895123.756	-895124.426	-895125.032	-895125.403
		H	-895090.298	-895090.181	-895090.126	-895089.874	-895089.622
		S	0.1117	0.11192	0.1125	0.1134	0.1154

Interaction between Melphalan anticancer drug with carbon	Gas phase	G	-1241912.163	-1241922.87	-1241923.328	-1241923.876	-1241924.413
		H	-1241898.661	-1241898.59	-1241898.56	-1241898.461	-1241898.258
		S	0.080585	0.08091	0.081208	0.08197	0.08447
	Methanol	G	-1242157.039	-1242157.197	-1242157.675	-1242158.057	-1242158.652
		H	-1242129.07	-1242129.017	-1242128.927	-1242128.699	-1242128.512
		S	0.09385	0.09393	0.09426	0.09472	0.09485
	Water	G	-1242177.465	-1242200.836	-1242201.450	-1242202.184	-1242202.777
		H	-1242099.991	-1242172.317	-1242172.292	-1242172.231	-1242172.066
		S	0.09491	0.09506	0.09564	0.09647	0.09852

Table (3): Thermodynamic function alterations in various temperatures for three phases at B3LYP/6-311G level of theory.

System	Media	Quantities	Temperature (K)				
			298	300	305	310	315
			Theoretical thermodynamic values				
Δx	Gas phase	ΔG	-10.521	-10.476	-10.371	-10.295	-10.208
		ΔH	-35.340	-35.487	-35.811	-36.033	-36.151
		ΔS	-0.08328	-0.08337	-0.08341	-0.08302	-0.08285
	Methanol	ΔG	-10.67	-10.582	-10.443	-10.300	-10.271
		ΔH	-35.352	-35.511	-35.834	-36.149	-36.283
		ΔS	-0.08283	-0.08310	-0.08325	-0.08338	-0.08357
	Water	ΔG	-11.589	-11.515	-11.434	-11.313	-11.282
		ΔH	-36.179	-36.445	-36.798	-37.151	-37.307
		ΔS	-0.08252	-0.08311	-0.08316	-0.08349	-0.08366

Conclusion

In this study, we conclude from quantum mechanics calculations and Monte Carlo simulations that the best reaction environment for interaction of the melphalan anticancer drug and the functionalized carbon nanotube is water solvent. Because the potential energy changes of reaction by Monte Carlo simulations in Amber, OPLS and MM+ force fields and the Gibbs free energy changes of reaction by quantum mechanics with the density function theory and the B3LYP/6-311G basis set have the lowest values for the water solvent and the entropy changes of reaction by quantum mechanics with density function theory with B3LYP/6-311G basis set are the most positive values for water solvent. Also the Gibbs free energy and the entropy of reaction are a function of the solvent dielectric constant. Thus, when the dielectric constant of solvent increases, the Gibbs free energy changes of reaction are reduced so that the lowest value is for the water solvent and the entropy changes of reaction increased so that the most positive amount of reaction entropy is for the water solvent.

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