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ORIGINAL RESEARCH

Survey of quantum mechanic calculations on combination of carbon nanotube and Methotrexate drug

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Abstract The combination of a carbon nanotube and Methotrexate (an ordinary form of anticancer drug) was investigated based on the Hartree–Fock theory calculations in the gas phase, water and ethanol environment. Thermodynamic functions including Gibbs free energy, entropy, enthalpy changes were computed at different temperatures. We found a relation between dipole moment of the solute and dielectric constant of the solvent. The Gibbs free energy of solvation is reduced by increasing the dielectric constant of solvents.

Keywords Dielectric constant · QM · Methotrexate or MTX · Carbon nanotube or CNT

Introduction

Methotrexate (MTX), an antimetabolite and antifolate drug, is generally applied to cure cancer cells and is well known like amethopterin [1–3]. In the 1950s, it began to be considered the more toxic antifolate aminopterin. The drug was originally synthesized by the Indian biochemist, Yellapragada Subbarow, and was developed clinically by the American pediatrician, Sidney Farber [4]. It was improved and is still utilized for chemotherapy, aloneorin combination with other factors. Methotrexate is used impressively for the therapy of certain cancers although it is prevalently utilized in the therapy of cancers, such as breast, head and neck, leukemia, lung and other neoplasias [5, 6] and ectopic pregnancies as well [7]. Methotrexate toxicity mechanisms are not yet fully identified but many assumptions might explain this neurotoxicity, like interference of Methotrexate with transmethylation reactions that are important for the formation of lipids, myelin and proteins [8]. By the way, Methotrexate works by inhibiting the metabolism of folic acid [1]. The intensification of new drug delivery system and the very well-organized drug delivery system is a critical point in the growing pharmaceutical profiles of large number of therapeutic molecule. Nowadays, there are individual sorts of drug delivery systems. A new alternative and effective device known for transporting therapeutic molecule in all nanomaterial is carbon nanotube. As functionalized carbon nanotube is not immunogenic, it exhibits weak toxicity, similar to systems that have a spacious potential in various fields such as nanobiotechnology and nanomedicine. When carbon nanotubes were discovered by Iijima, numerous examinations have been carried out to make clear the instruments and attributes of the new materials [9–13]. By additional research, the major dependence of electronic properties of carbon nanotubes on their structural topologies has been achieved. The results of studies indicated that materials classified as metal or semiconductors are carbon nanotubes [9]. Various sorts of carbon nanotubes that can be placed there are single multi-walled carbon nanotubes [14]. One of these types is single-walled carbon nanotubes (SWNTs) that have grapheme cylinders with a wall whose thickness is one atomic layers and whose diameter is around one nanometer. Their attributes, for example, include vast surface, hollow geometry, high aspect ratio [15], high prevalent transmitting ability, superior thermal attributes, excellent reversibility, and fast response [15–17]. Three

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main patterns of SWNTs are the following conditions: if the form is an armchair, it is $n = m$; if the form is zigzag, $n = 0$ or $m = 0$, and any other n and m, is chiral [18–20]. Therefore, each of these forms has its own characteristics. By two concentric cylindrical grapheme layers, double-walled carbon nanotubes (DWCNT) have been molded. Hence, both the higher mechanical power of MWNTs and fascinating electronic features of SWNTs have been observed in the carbon nanotubes [21]. In these investigations, we focused on the combination of carbon nanotubes with Methotrexate (MTX) drug. The carbon nanotubes have successfully indicated their ability to cross the cell shell in the medicament recently. For this reason, carbon nanotubes can be utilized to release active drug molecules in cells that researchers receive them specifically the most critical and fundamental molecule for specific disease similar to cancer. The results of studies by a number of researchers indicated a significant role for carbon nanotubes due to their unequaled optical, electrical, and thermal attributes [22, 23]. In the present paper, the combination of Methotrexate (MTX) with carbon nanotubes was examined by utilizing QM, in this place: the self-consistent reaction field technique to simulate the effects of dielectric constant of solvents used by quantum mechanics. Therefore, in the survey, by utilizing quantum mechanics, the effects of dielectric constant of the solvent on the thermodynamic parameters of the compound were explained. In the present paper, quantum chemical calculations based on the theory Hartree–Fock (HF) were conducted by the Gaussian 98 program. A theoretical analysis at the Hartree–Fock theory with the standard 6-31G basis set is utilized to discover thermodynamic parameters of MTX–CNT complex. We have shown the effects of dielectric constant solvent by Onsager method using Gaussian 98 program. The geometries of the combination of carbon nanotube with an MTX in different solvent are optimized utilizing the Onsager pattern at HF level of theory. This study investigates the combination of carbon nanotube with the MTX in various dielectric constants within the gas phase, aqueous, and ethanol solutions at different temperatures.

Computational detail

Self-consistent reaction field (SCRF) method

It is necessary to show the shape and volume of the solute molecule for any set of compounds demonstrated in the quantum chemical theory by SCRF model. A number of methods to calculate the characteristics are identified, but no nonempirical technique for their study is distinguished. However, the consequences of model computations indicate that the ordinary template assuming an ellipsoidal or a spherical form of cavities for the solute molecules is entirely appropriate for relatively very small and robust molecules, which, at the end, was our principal selection [24–27]. Self-consistent reaction field methods have been greatly used to survey solvent effects in chemical interactions. These methods are designed to determining solvation-free energy that is the reversible work necessary to move a molecule from gas phase to solution [28].Thus, in the present study, applying the Gaussian 98 program package, the quantum chemical computations were done on the combination of MTX with the carbon nanotube [29] and Hartree–Fock theory in level of 6-31G. Using the program, we applied ordinary approximations in the Hartree–Fock level and utilized the volume of the solute for calculating the radius of the cavity that molds the hypothetical surface of molecules, [30, 31]. The effect of dielectric constant solvent compliant with SCRF technique was believed to be derived from the Onsager reaction field theory of electrostatic solutions. In the desired pattern, solvents are like constant dielectric with the given dielectric constant. Subsequently, we researched the effect of dielectric constant of the solvent on the values of the parameters of G, H, S, E and μ of aqueous solution and ethanol solution encircling MTX–carbon nanotube complex within the SCRF pattern and applying an HF method and also the various temperature effects on MTX–carbon nanotube. Eventually, we appraised the obtained thermodynamic parameters of MTX–carbon nanotube in various media such as the gas phase, aqueous solution, and ethanol solution.

Results and discussion

The main purpose of the present study is to investigate the combination of carbon nanotube and Methotrexate (MTX) as an ordinary form of anticancer drug which, with inhibition of dihydrofolate reductase activities, is believed to prevent synthesis of the nucleotide and the cell cycle. Thus, values of thermodynamic parameters on combination of MTX with the carbon nanotube in various environments were investigated. Figure 1 exhibits the interaction of MTX and carbon nanotube. We have got the mentioned calculations to investigate the following reaction:

$$\text{MTX} + \text{Carbon nanotube} \rightarrow \text{MTX}-\text{Carbon nanotube} \quad (1)$$

We investigated parameters of G, H, S, E and μ of MTX–carbon nanotube in dielectric constant solvent similar to the gas phase, aqueous solution, and ethanol solution which were compared. Thus, the values of dipole moment for MTX and carbon nanotube, MTX–carbon nanotube complex in various dielectric constant environments such

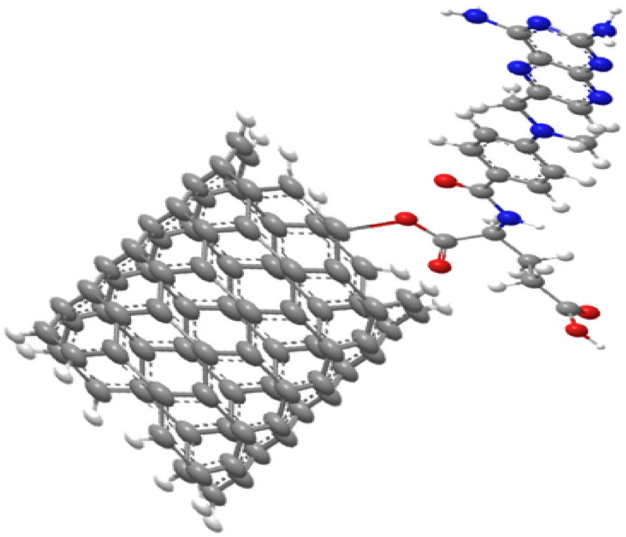

Fig. 1 Complex of MTX–CNT

Table 1 Values of [μ/(Debye)] in different solvents and temperatures

T/K	μ/(Debye)			$\Delta\mu$ (Debye)
	MTX	CNT	MTX–CNT	
Gas phase				
298	5.765	0.0095	809.2441	803.4696
303	5.768	0.0095	809.2480	803.4705
307	5.770	0.0096	809.2513	803.4717
312	5.776	0.0097	809.2580	803.4723
Aqueous solution or water				
298	7.885	0.0101	981.4289	973.5338
303	7.886	0.0101	981.4303	973.5342
307	7.887	0.0102	981.4327	973.5355
312	7.891	0.0103	981.4383	973.5370
Ethanol solution				
298	6.825	0.0095	865.265	858.4323
303	6.826	0.0096	865.261	858.4330
307	6.829	0.0097	865.267	858.4335
312	6.831	0.0099	865.268	858.4341

as the gas phase, aqueous solution, and ethanol solution in various temperatures have been surveyed. Values of dipole moment in different environments such as gas phase, aqueous solution, and ethanol solution were obtained which showed a positive correlation with dielectric constant (Table 1). A continuing dielectric constant exhibits solvent with the given dielectric constant in the SCRF method. Solute of cavities with radius in the electric field and the molecule that is relevant to solute through dipole of solvent will collaborate with dipole of molecular and directly to the net stabilization. Thus, first, salvation energy computed by the self-consistent reaction field technique is the distribution of electrostatic to the free energy of salvation. Therefore, radius of the cavities of MTX, CNT, and MTX–CNT complex has been measured and subsequently obtained values were replaced, while the productivity was extending. Here, we utilized the key word of "volume" and we obtained quantities of volume of MTX, CNT, and MTX–CNT complex. The consequences of computing show that the obtained volume of MTX, CNT, and MTX–CNT complex is equal to 4.15, 5.48 and 6.87 Å (Angstrom). Thus, it is obvious that with increasing dielectric constant of solvent, the dipole moment for MTX, CNT, and MTX–CNT complex in different temperatures, such as 298, 303, 307, and 312 K, will also be increased. Then, with computed Onsager template, researchers can demonstrate which values of G, E, H and S for MTX, CNT, and MTX–CNT complex are sensitive polarities of surrounding of the solvent. Based on this approach, in Table 2, we illustrated that the values of G, E, H, and S are relevant to dielectric constant of the solvent. Table 2 clearly shows that when the temperature increases from 298 to 312 K, the values of G parameter of MTX, CNT, and complex of MTX–CNT in gas phase, water and ethanol solutions will be reduced so that we have the lowest value of G parameter at 312 K. If the dielectric constant of the solvent increases, the achieved Gibbs free energy at various temperatures will decrease. Thus, the Gibbs free energy is the most negative value when MTX, CNT, and the complex of MTX–CNT are placed in water solvent. Table 2 also shows obtained values of thermodynamic parameters G, H, E, and S in different solvents. When the temperature changes between 298 and 312 K, the alterations of E, H, and S of MTX, CNT, and the complex of MTX–CNT in different environments such as the gas phase, aqueous solution, and ethanol solution occur. If the temperature is increased from 298 to 312 K, the results show what the most positive value of E, H, and S is for 312 K we think to be true. It should be noted that by calculating E, H, and S according to the dielectric constant of the solvent and enhancing the values of temperatures such as 298, 303, 307, and 312 K, the value of E and S changes to negative amounts. As the lowest values of parameters of E and H and the positive value of the parameter S could be obtained, here the most positive value of parameter of S takes place when MTX, CNT, and complex of MTX–CNT are in aqueous solution. In survey reaction of Eq. (1), Table 2 points out everything about combination of MTX–CNT system. Values of the Gibbs free energy of the combination between solute and solvent molecule are reduced if the dielectric constant solvent increases. As long as the dielectric constant of solvent increases, the values of enthalpy of combination between solute molecule and solvent molecule are moving toward a negative value because combination of solvent molecule and solute molecule is strong. Therefore, considering the Eq. (1), the

Table 2 Values of thermodynamic parameters in various environments and temperatures at 6-31G level for MTX, CNT, and complex of MTX-CNT

System	Media	Quantities	T/K			
			298	303	307	312
			Values of theoretical thermodynamic parameters (kcal/mol)			
MTX	Gas phase	*G*	−712,383.514	−712,384.007	−712,384.430	−712,384.9442
		H	−712,353.374	−712,353.167	−712,352.949	−712,352.729
		E	−712,353.921	−712,353.714	−712,353.496	−712,353.276
		S	0.101132	0.101771	0.102538	0.103254
	Aqueous solution or water	*G*	−712,385.708	−712,386.201	−712,386.625	−712,387.1364
		H	−712,355.53	−712,355.323	−712,355.105	−712,354.885
		E	−712,456.121	−712,455.915	−712,455.697	−712,455.477
		S	0.101258	0.101897	0.102664	0.10337
	Ethanol solution	*G*	−712,385.623	−712,386.120	−712,386.504	−712,387.0184
		H	−712,355.450	−712,355.248	−712,355.03	−712,354.81
		E	−712,374.871	−712,374.665	−712,374.447	−712,374.227
		S	0.101243	0.101879	0.102510	0.103232
CNT	Gas phase	*G*	−1,319,201.048	−1,319,201.465	−1,319,201.756	−1,319,202.123
		H	−1,319,167.77	−1,319,167.583	−1,319,167.394	−1,319,167.182
		E	−1,319,167.784	−1,319,167.645	−1,319,167.46	−1,319,167.32
		S	0.111661	0.111815	0.111917	0.111983
	Aqueous solution or water	*G*	−1,319,210.211	−1,319,210.630	−1,319,210.876	−1,319,211.288
		H	−1,319,176.855	−1,319,176.668	−1,319,176.434	−1,319,176.267
		E	−1,319,176.9	−1,319,176.761	−1,319,176.576	−1,319,176.436
		S	0.111924	0.112078	0.11218	0.112246
	Ethanol solution	*G*	−1,319,208.281	−1,319,208.725	−1,319,209.008	−1,319,209.361
		H	−1,319,175.004	−1,319,174.832	−1,319,174.626	−1,319,174.405
		E	−1,319,175.056	−1,319,174.92	−1,319,174.769	−1,319,174.573
		S	0.111661	0.111848	0.111975	0.112039
MTX–CNT	Gas phase	*G*	−2,133,768.310	−2,133,768.820	−2,133,768.867	−2,133,769.202
		H	−2,133,735.387	−2,133,735.195	−2,133,734.781	−2,133,734.501
		E	−2,133,735.473	−2,133,735.314	−2,133,735.038	−2,133,734.808
		S	0.11077	0.110975	0.111028	0.111220
	Aqueous solution or water	*G*	−2,133,831.954	−2,133,832.411	−2,133,832.605	−2,133,832.968
		H	−2,133,798.805	−2,133,798.623	−2,133,798.348	−2,133,798.141
		E	−2,133,799.107	−2,133,798.832	−2,133,798.538	−2,133,798.362
		S	0.111231	0.111499	0.111564	0.111625
	Ethanol solution	*G*	−2,133,818.329	−2,133,818.763	−2,133,819.046	−2,133,819.520
		H	−2,133,785.263	−2,133,785.104	−2,133,784.896	−2,133,784.769
		E	−2,133,785.262	−2,133,785.036	−2,133,784.833	−2,133,784.643
		S	0.110959	0.111085	0.111237	0.111381
Gas phase		Δ*G* (reaction)	−102,183.748	−102,183.348	−102,182.681	−102,182.1348
		Δ*H* (reaction)	−102,214.243	−102,214.445	−102,214.438	−102,214.59
		Δ*E* (reaction)	−102,213.768	−102,213.955	−102,214.082	−102,214.212
		Δ*S* (reaction)	−0.102023	−0.102611	−0.103427	−0.104017
Aqueous solution or water		Δ*G* (reaction)	−102,236.035	−102,235.580	−102,235.104	−102,234.5436
		Δ*H* (reaction)	−102,266.42	−102,266.632	−102,266.809	−102,266.989
		Δ*E* (reaction)	−102,166.086	−102,166.157	−102,166.265	−102,166.449
		Δ*S* (reaction)	−0.102151	−0.102876	−0.10328	−0.104191
Ethanol solution		Δ*G* (reaction)	−102,224.425	−102,223.918	−102,223.534	−102,223.1406
		Δ*H* (reaction)	−102,254.809	−102,255.024	−102,255.24	−102,255.554
		Δ*E* (reaction)	−102,235.335	−102,235.451	−102,235.617	−102,235.843
		Δ*S* (reaction)	−0.101945	−0.102645	−0.103248	−0.10389

amounts of denoted entropy are reasonable. With coupling of MTX with CNT, the entropy decreases which is clear in the above-mentioned reaction. Here, you can observe the assessment and survey of the information from another status toward Eq. (1). In Figs. 2, 3, 4, and 5, the diagrams of parameters like dipole moment, Gibbs free energy, enthalpy, and entropy alterations according to the temperature alerts reveal that the changes in the value of η, G, H and S are achieved by the function of $\Delta\eta = \Delta\eta_{\text{MTX-CNT}} - (\Delta\eta_{\text{MTX}} + \Delta\eta_{\text{CNT}})$. In this function η, G, H, and S are equal to the dipole moment, Gibbs free energy, enthalpy, and enthalpy parameter separately. Figure 2 shows that $\Delta\mu_{\text{reaction}}$ will be changed through increasing dielectric constant of solvent when temperature is increased to 312 K. Figure 3 reveals that the value of $\Delta G_{\text{reaction}}$ will rise by the increase of temperature. The lowest value of $\Delta G_{\text{reaction}}$ was in 298 K which led to the highest resistance in the Eq. (1). Figure 5 shows that the value of $\Delta S_{\text{reaction}}$ is reduced with increasing temperature. This is the more resistant rate because here the most positive amount of $\Delta S_{\text{reaction}}$ can be seen in Eq. (1). The values of thermodynamic parameters of reaction was mentioned in Table 2. Based on the dielectric constant of solvent, the value of the mentioned $\Delta G_{\text{reaction}}$ will decrease; moreover, the most negative amounts of $\Delta G_{\text{reaction}}$ are for water

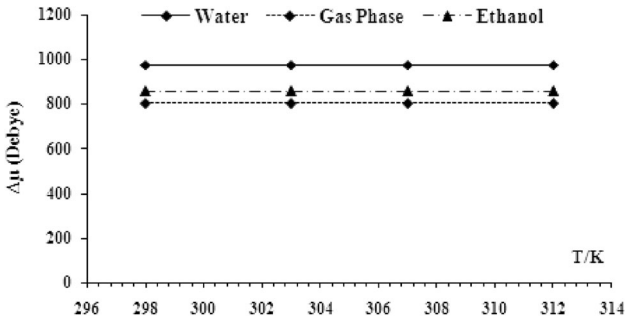

Fig. 2 Theoretical dipole moment alterations computed versus temperature according to MTX + CNT → MTX–CNT

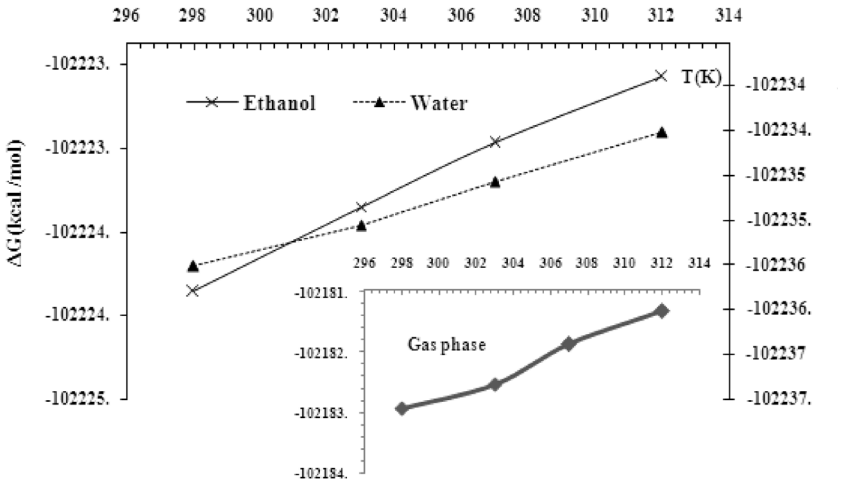

Fig. 3 Computed changes of Gibbs free energy for MTX + CNT → MTX–CNT at different temperature

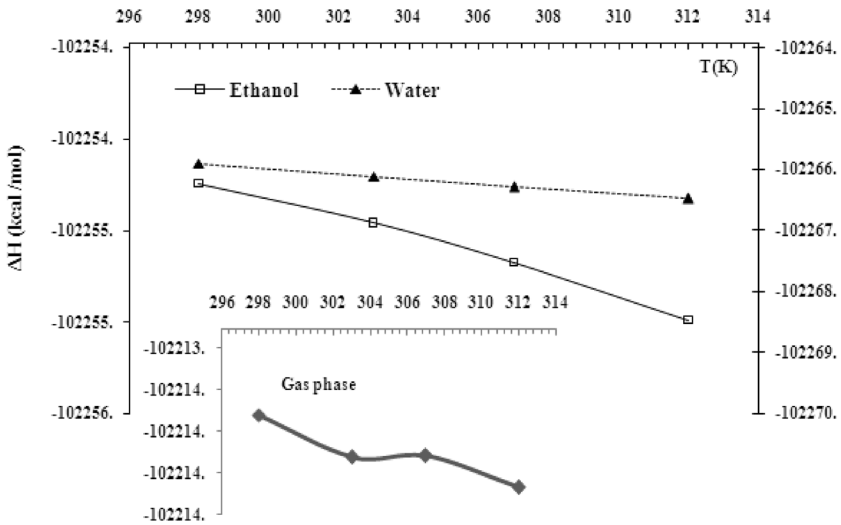

Fig. 4 Computed changes of enthalpy for MTX + CNT → MTX–CNT at different temperature

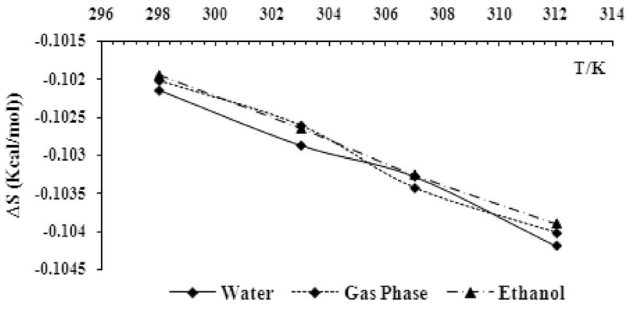

Fig. 5 Computed changes of entropy for MTX + CNT → MTX–CNT at different temperature

solution which is the best medium for Eq. (1). Also in Table 2, we can observe via increasing dielectric constant solvent in different temperatures (298, 303,307, and 312 K), values of $\Delta H_{\text{reaction}}$ and $\Delta S_{\text{reaction}}$ reduce. Table 2 illustrates that the amount of $\Delta S_{\text{reaction}}$ has the most positive value in 298 K; therefore, in these situations temperature of 298 K is the best selection for Fig. 1.

Conclusion

In this project, combination of Methotrexate (MTX), carbon nanotube, and (MTX–CNT) complex has been done by applying the method of quantum mechanics simulation. The results show that values of thermodynamic parameters in the mentioned reaction (Eq. 1) depend on the dielectric constant solvent. In other words, it shows a relation between dipole moment of the solute and dielectric constant of the solvent. Hence, the obtained results of the study, using Gaussian 98 program with 6-31G basis set, suggest that the best solvent is an aqueous solution (water solvent) when Methotrexate (MTX), carbon nanotube, and (MTX–CNT) complex are placed in it. They have the most negative Gibbs free energy and the most positive entropy.

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