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Ab Initio Study of Vinblastine-Tubulin Anticancer Complex

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ABSTRACT

Vinblastine is an important anticancer agent known to diminish microtubule assembly. *Ab initio* calculations are applied to examine the structural properties and different energies of vinblastine-tubulin complex in different dielectric constants and temperatures. The aims of this work are discovery the best optimized structure and thermodynamic properties of vinblastine-tubulin complex and comparing the structure of the complex under in and out of in vivo conditions. Discovery dipole moment, frequency and intensity of vibration of the vinblastine-tubulin complex in different dielectric constants, finding free energy, enthalpy and entropy in different media that have been prepared in this paper could be useful in undrestanding the structural and thermodynamic properties of the complex. Results show the structure is more stable in water than the other media. The dipole moment of the structure at dielectric constant of 24.55 is larger than that in the other media. The intensity of vibration of the structure decreases by decreasing dielectric constant. Enthalpy and entropy energies have direct relationship with temperature. *In vivo* condition changes the structure and increases the affinity of vinblastine to tubulin. To confirm the reliability of the obtained data, the parameters were calculated by two methods, Hartree-Fock (HF) and Becke, three-parameter, Lee-Yang-Parr (B3LYP). The results indicated that the acquired data from these two methods are in good agreement.

Keywords: Vinblastine-tubulin, Anticancer, *Ab initio*, HF, B3LYP

INTRODUCTION

Microtubules are composed of α-tubulin and β-tubulin heterodimers. These heterodimers organize the form of slender filamentous tubes, which can be many micrometres long. They are highly dynamic polymers. Microtubules are extremely important in the process of mitosis, during which the duplicated chromosomes of a cell are separated into two identical sets before cleavage of the cell into two daughter cells. Because of its importance in mitosis and cell division, microtubule is an important target for anticancer drugs.

Vinblastine as an antimitotic drug was obtained from the plant (*Catharanthus roseus*) [1,2]. The antineoplastic properties of vinblastine arise from its interaction with tubulin. Vinblastine binds to β-subunit of tubulin dimers at a distinct region called the *Vinca*-binding domain [3-5]. The mechanism of vinblastine in therapy of cancer, the desire to develop orally available analogues and the need to overcome its neurotoxicity and the development of resistance, which occurs with this drug has been motivated us to study the structure and energy of vinblastine-tubulin complex.

β-Tubulin is bound to vinblastine *via* its 175-213 residues [6]. This sequence is included these amino acids, respectively from N- to C-terminal, as found in PDB entry 4EB6: Pro^{175}-Gln^{176}-Val^{177}-Ser^{178}-Thr^{179}-Ala^{180}-Val^{181}-Val^{182}-Glu^{183}-Pro^{184}-Tyr^{185}-Asn^{186}-Ser^{187}-Ile^{188}-Leu^{189}-Thr^{190}-Thr^{191}-His^{192}-Thr^{193}-Thr^{194}-Leu^{195}-Glu^{196}-His^{197}-Ser^{198}-Asp^{199}-Cys^{200}-Ala^{201}-Phe^{202}-Met^{203}-Val^{204}-Asp^{205}-Asn^{206}-Glu^{207}-Ala^{208}-Ile^{209}-Tyr^{210}-Asp^{211}-Ile^{212}-Cys^{213} Coderch *et al.* [7] have published the model complex of Vinblastine-Tubulin. In *Vinca*-binding domain, Tyr-210 is the most effective amino acid

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interacting with vinblastine [7]. Results of Nuclear Magnetic Resonance (NMR) computation specified the active site of vinblastine molecule whereas this site has the most shifting at indicated model [8].

In this study, we analyze the best optimized structure of vinblastine-tubulin complex in different media and temperatures by theoretical methods.

COMPUTATIONAL METHODS

Gaussian 98 computational package was applied by B3LYP [9] and HF to optimize vinblastine-tubulin complex using STO-3G, 3-21G, 6-31G and 6-31G* basis sets (set of functions were used to create the molecular orbitals with polarization functions to hydrogens added to improve the total energy of the system) in various solvents (water, methanol and ethanol) by Self-Consistent Reaction Field (SCRF-Onsager) methods [10-12]. In this investigation, B3LYP and HF methods were employed using 6-31G* and 6-31G** basis sets to obtain thermodynamic properties, vibrational frequency ratios, intensity and dipole moment of the complex in different dielectric constants including 78.39, 32.63 and 24.55, which are similar to the dielectric constants of water, methanol and ethanol, respectively. In fact the structure input into the Gaussian programe alone, without any solvent molecules, and we just change the dielectric constant in the route section of the program. We selected the dielectric constant similar to ethanol and methanol in order to understand the effect of less polar media on the complex. All optimizations started *in vacuum* (Table 1), and then the obtained structures were optimized in solvents. The effects of temperature (300, 305, 310, 315 and 320 K) on Gibbs free energy, enthalpy and entropy of the complex were characterized by B3LYP and HF methods. For all methods used in Gaussian, the atomic unit of energy is the *Hartree*: 1 Hartree = 627.509391 kcal mol^{-1}.

Table 1. Optimization Energy, Dipole Moment (μ (debye)), Intensity (Ln[I] (km mol^{-1})), Vibrational Frequency (Ln[F] (cm^{-1})) of Vinblastine-Tubulin Complex in Different Media by B3LYP and HF Methods

	B3LYP								
Dielectric constant	78.39			32.63			24.55		
Basis set	μ	Ln[*I*]	Ln[*F*]	μ	Ln[*I*]	Ln[*F*]	μ	Ln[*I*]	Ln[*F*]
6-31G*	9.166	6.256	8.198	9.135	6.25	8.205	9.113	6.249	8.2
		5.874	7.519		5.873	7.518		5.873	7.52
		5.235	7.156		5.232	7.156		5.238	7.156
6-31G**	9.147	6.301	8.202	9.115	6.293	8.208	9.093	6.293	8.204
		5.871	7.519		5.87	7.517		5.869	7.519

	E (kcal mol^{-1})							
	HF				B3LYP			
Media	Sto-3g	3-21g	6-31g	6-31g*	Sto-3g	3-21g	6-31g	6-31g*
Gas	-482697.763	-486205.117	-488717.302	-488929.547	-485492.59	-489147.487	-491707.675	-491854.029
Water	-482698.829	-486215.781	-488726.46	-488940.775	-485497.928	-489153.969	-491714.215	-491858.764
Methanol	-482698.79	-486215.498	-488726.181	-488940.45	-485497.756	-489153.703	-491713.962	-491858.545
Ethanol	-482698.769	-486215.343	-488726.028	-488940.271	-485497.661	-489153.558	-491713.823	-491858.425

Table 2. Thermodynamic Parameters of Vinblastine-Tubulin Complex in Different Dielectric Constants and Temperatures by B3LYP and HF Methods. Gibbs Free Energy (G) and Enthalpy (H) are in kcal mol^{-1} and Entropy (S) is in cal mol^{-1} K^{-1}

		B3LYP								
Dielectric constant		78.39			32.63			24.55		
Basis set	T(K)	G	H	S	G	H	S	G	H	S
6-31G*	300	-491720.366	-491676.707	145.533	-491718.586	-491677.33	137.521	-491719.877	-491676.778	143.666
	305	-491721.095	-491676.391	146.572	-491719.276	-491677.025	138.53	-491720.597	-491676.462	144.708
	310	-491721.83	-491676.071	147.612	-491719.971	-491676.715	139.538	-491721.323	-491676.143	145.747
	315	-491722.571	-491675.748	148.647	-491720.671	-491676.401	140.542	-491722.054	-491675.819	146.783
	320	-491723.318	-491675.42	149.684	-491721.377	-491676.083	141.545	-491722.792	-491675.491	147.816
6-31G**	300	-491739.386	-491694.939	148.156	-491737.847	-491695.569	140.929	-491739.641	-491695.007	148.784
	305	-491740.128	-491694.614	149.228	-491738.554	-491695.253	141.971	-491740.385	-491694.681	149.852
	310	-491740.877	-491694.284	150.299	-491739.266	-491694.933	143.011	-491741.137	-491694.351	150.923
	315	-491741.631	-491693.951	151.367	-491739.984	-491694.61	144.047	-491741.894	-491694.018	151.99
	320	-491742.392	-491693.614	152.434	-491740.707	-491694.282	145.081	-491742.659	-491693.681	153.061
		HF								
6-31G*	300	-488784.954	-488743.665	137.634	-488783.863	-488744.3	131.877	-488783.954	-488744.358	131.991
	305	-488785.645	-488743.37	138.609	-488784.524	-488744.015	132.819	-488784.616	-488744.072	132.934
	310	-488786.341	-488743.072	139.58	-488785.19	-488743.726	133.759	-488785.283	-488743.783	133.874
	315	-488787.041	-488742.769	140.547	-488785.862	-488743.433	134.695	-488785.955	-488743.49	134.811
	320	-488787.746	-488742.463	141.511	-488786.538	-488743.137	135.628	-488786.632	-488743.194	135.744
6-31G**	300	-488805.659	-488766.144	131.717	-488805.808	-488766.181	132.089	-488805.907	-488766.242	132.218
	305	-488806.32	-488765.859	132.66	-488806.471	-488765.897	133.032	-488806.571	-488765.957	133.162
	310	-488806.985	-488765.57	133.599	-488807.138	-488765.607	133.971	-488807.238	-488765.668	134.102
	315	-488807.656	-488765.278	134.535	-488807.811	-488765.315	134.908	-488807.912	-488765.374	135.039
	320	-488808.331	-488764.982	135.468	-488808.487	-488765.018	135.842	-488808.589	-488765.078	135.973

RESULTS AND DISCUSSION

As geometry optimization shows, there is an intermolecular hydrogen bonding interaction in vinblastine-tubulin complex between H23 and O26 (Fig. 1). In spite of the results of 6-31G**, the free energies obtained by 6-31G* exhibit the vinblastine-tubulin is more stable in water than the other solvents. Because the results of 6-31G* are in agreement with the geometry optimisation energies and frequency calculations, it is concluded that 6-31G* is a valid basis set in this case (Table 1). The relation of dielectric constant and orientation of atoms in the complex displays the higher dielectric constant of solvent, the more change in the orientation of atoms. By comparison the orientations of atoms in and out of solvent, it is observed that O25-C24-O26-C27 and C24-O26·····H23-O12 are the most impressed with solvents. The variation of O26·····H23 bond length and C24-O26·····H23 bond angle *vs.* dielectric constant is downward while it is upward in the case of C24-O26·····H23-O12 torsion angle (Fig. 2). The variation of torsion angle has a linear relation with increasing the dielectric constant.

One of the aims of this work is to understand the structure and energies of Vinblastine-Tubulin complex in different conditions. So, the frequency and intensity seem to be helpful to attain this purpose. The results of the calculation demonstrate different frequencies [*F*], intensities [*I*] and dipole moments in different dielectric constants

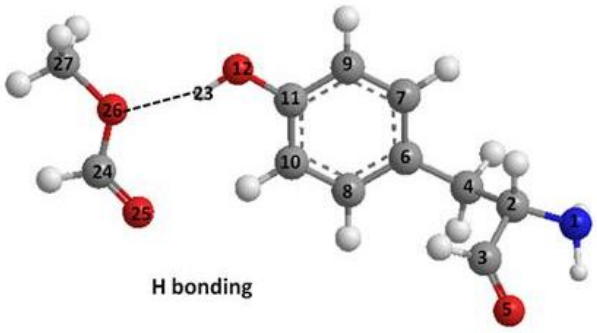

Fig. 1. Atom numbers of vinblastine-tubulin complex.

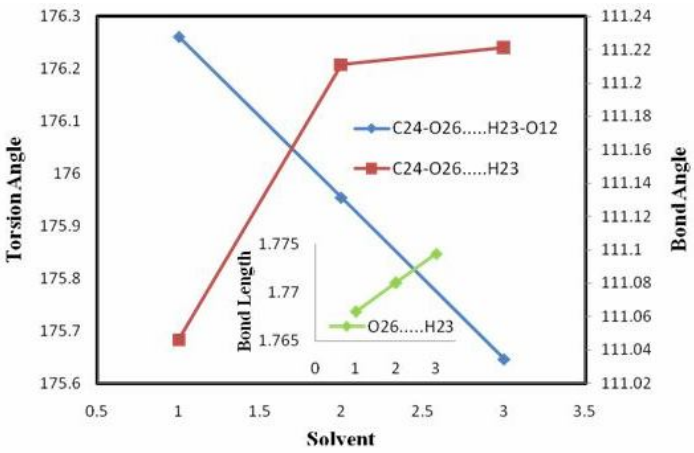

Fig. 2. Plot of bond length (O26·····H23) and bond angle (C24-O26·····H23) and torsion angle (C24-O26·····H23-O12) in vinblastine-tubulin complex *vs.* solvent (1 = water, 2 = methanol and 3 = ethanol).

(Table 1). However, temperature has no influence on mentioned values. The dipole moment (μ) of the vinblastine-tubulin complex is increased by decreasing the dielectric constant. Thus, μ of the complex has the less value in water, and the most in the case of ethanol (Fig. 3a). Polar solvents always weaken the electrostatic interaction between charges. Water is more polar than methanol and ethnanol, so dipole moment of the complex in water is lesser than that in two other ones. By comparison between the atomic charges of the structure in and out of the solvents, O12 is the most impressed atom in each solvent, whereas C6 has no change in its atomic charge. O26 and C24 are also greatly impressed by changing the media. Relationship between frequencies and intensities, obviously indicates that the Ln [*F*] and Ln [*I*] have minimum and maximum values in water, respectively (Fig. 3a). Behavior of thermodynamic parameters demonstrates that free energy and temperature have inverse relationship in all media (Fig. 3b). According to the results of free energy, the structure is more soluble in water than that in the other solvents. The entropy and enthalpy amounts are raised by increasing temperature in different solvents (Figs. 3c and 3d). Enthalpy quantities have negative amounts in different media and temperatures. Comparing the enthalpy in three solvents exhibits that the transfer of vinblastine-tubulin structure from water to methanol has the most exothermic value.

At 25 ºC (298 K) and pH = 7.0, ΔG for vinblastine binding to tubulin is -3.5 kcal mol^{-1}, which was obtained by HF method. At the same temperature and pH, the ΔG of vinblastine interaction with calf brain microtubule protein is -6.0 kcal mol^{-1} [13]. Since the structure of tubulin is changed *in vivo* condition [14,15] due to its interaction with different molecules such as nucleotides [16,17] the affinity of vinblastine to tubulin is increased.

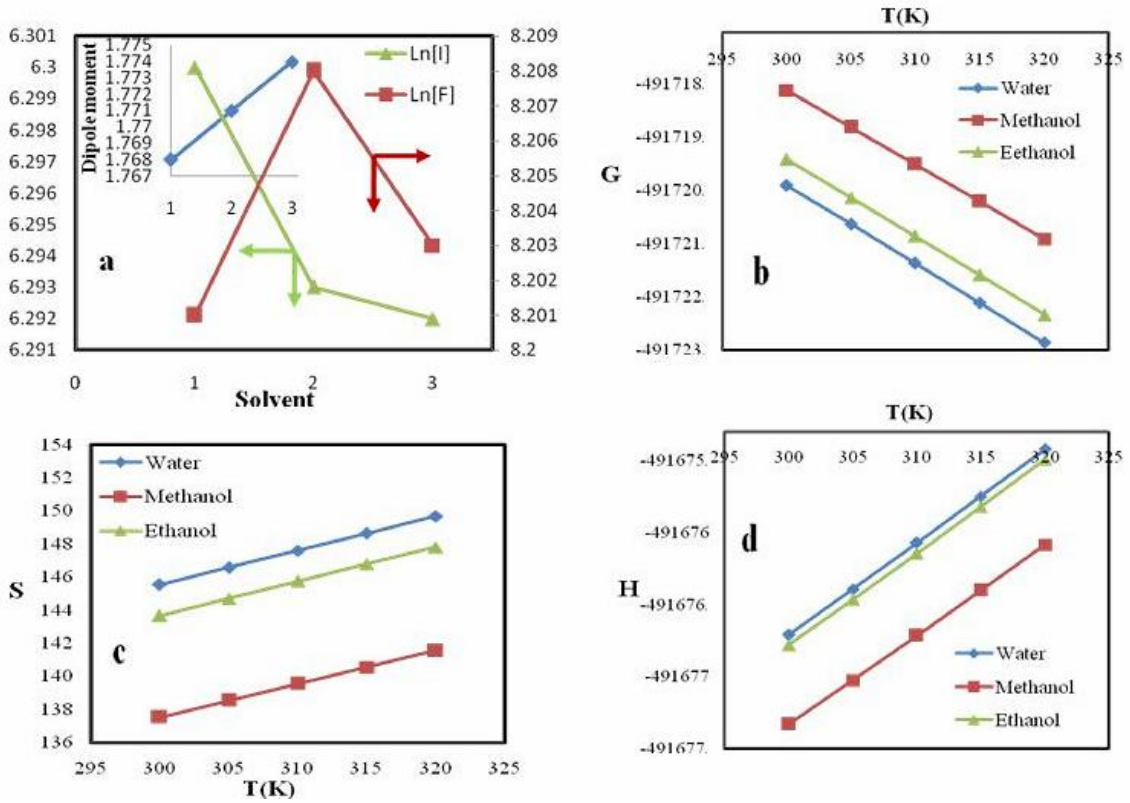

Fig. 3. Plots of (a): dipole moment, vibrational frequency (Ln[*F*]) and intensity (Ln[*I*]) *vs*. solvent (1 = water, 2 = methanol and 3 = ethanol), (b): free energy (G), (c): entropy (S) and (d): enthalpy (H) of the complex *vs.* temperature in different solvents.

CONCLUSIONS

Computational chemistry methods range from highly accurate to very approximate; highly accurate methods are typically feasible only for small systems like the system which have been studied in this paper. This investigation predicts that full geometry optimisation of vinblastine-tubulin complex could be successfully elucidated by the B3LYP and HF methods. Molecular properties are also sensitive to the environment, so we affected different media on the system. The complex is more stable in water than the other solvents. The dielectric constant affects atomic orientations of the structure. Dipole moment of the structure at dielectric constant of 24.55 is larger than that in the other media. The intensity of complex is decreased by decreasing dielectric constant. The enthalpy and entropy energies have direct relationship with temperature. However, the Gibbs free energy and temperature have inverse relationship. While computational results normally complement the information obtained by chemical experiments, it can in some cases predict hitherto unobserved chemical phenomena. In this work, by comparing experimental and theoretical data, we realized that under *in vivo* condition the structure of vinblastine-tubulin complex is changed and therefore the affinity of vinblastine to tubulin is increased.

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