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Investigation of Solveat Effects on Temozolomide anticancer drug (TMZ): An ab initio Study

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ABSTRACT

In this work, we have studied the solvent effects on values of Gibbs free energy, enthalpy, entropy and dipole moment in spread of solvents around anticancer drug of temozolomide that is an alkylating agent. For this purpose, the quantum mechanic calculations based on Hartree-Fock theory at the STO-3G/3-21G levels have been done. Moreover, we have compared resulted thermodynamic values in gas phase as well as various solvents when surround the Temozolomide molecule. We obtained the effects of different dielectric constants on Temozalomide with the onsager self-consistent model reaction field (SCRF) by applying Hartree-Fock theory and also we obtained the effects of temperature on thermodynamic values of Temozolomide in gas phase and various solvents.

Keywords: Solvent effect; Quantum mechanic; Dielectric constant; Thermodynamic values; Temozolomide (TMZ)

INTRODUCTION

Temozolomide (TMZ) is an anticancer drug that its brand name is temodar. Early 1980s it was made in a British laboratory and then it was confirmed for use in the United States in 1999[1]. Temozolomide has been approved in the United States for therapy of astrocytoma that is a kind of brain tumor and is entering various phases of clinical estimation against other tumors [2]. A chemotherapy medicine utilized to interfere in development of cancer cells and reduce the size of a cancerous tumor [3]. It belongs to a new sort of oral imidazotetrazines that enter the cerebrospinal fluid and do not need hepaticmetabolism for activation[4-6]. Also it is an alkylating agent of the imidazo [5,1-d]-1,2,3,5- tetrazine series [7]. Temozolomide has outstanding oral bioavailability [8,9], and also has demonstrated important clinical activity against malignant melanomas, astrocytoma and gliomas [10]. Temozolomide is structurally correlated to the antimelanoma drug DTIC; both agents need alteration to MTIC for their clinical activity. In as much as DTIC is metabolically activated to MTIC in the liver, the alteration of temozolomide to MTIC is presumed to be pH dependent [11]. It is stoutly stable under acidic conditions, however the rate of degradation growes speedily on passing through neutral to basic pH [12]. Hence pH-dependent activation of temozolomide may give a significant basis of targeted therapy directed toward tumors (such as gliomas, malignant melanomas and astrocytoma), that are recognized to have a higher pH compared with encircling brain tissue. Temozolomide is chemically classified as an imidazotetrazinone [13]. The defining characteristic of this sort of

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compound is an imidazole ring that is combined with a tetrazinone ring system that includes three adjacently bonded nitrogen atoms [14]. Temozolomide obtaines its cytotoxic effect chiefly by methylating the O^6 position of guanine. This adduct can be eliminated by the DNA repair protein O^6-methylguanine-DNA- methyltransferase (MGMT), that is represented in a subgroup of GBM. Therefore, It shows its highest efficiency against tumors lacking MGMT expression on account of a methylated MGMT promoter [15,16].

However, although temozolomide meaningfully increases the extent of patients surviving for >2 years, long-term survivors are still rare. The biological characteristices of CSC supply a conceivable interpretation for the inattention of chemotherapy in the long term: CSC from several tumor entities overexpress multidrug resistance proteins, that may defend them against cytotoxic drugs that destroy progenitor and discriminated cells[17]. So, in this research, the values of gibbs free energy, enthalpy, entropy and dipole moment have been investigated by quantum mechanic calculations within the onsager self-consistent reaction field (SCRF) model utilizing HF/STO-3G and 3-21G basis sets in various solvens and temperature have been compared.

COMPUTATIONAL METHOD

1-Ab initio method

Ab initio method is available in macromodel program. It is important to choose a level that is well parametrized for the molecular system under study. Accurate geometry coordinates and energy parameters are particularly important in molecular systems since they control conformational interconversions. Low-energy structures found on each surface were selected and subjected to unrestrained quantum mechanical minimization using HF/STO-3G and 3-21G SCRF[18].

The solvent effect in quantum mechanic is gotten a perturbation term in the Hamiltonian of the isolated solute [19],H_0:

$$H = H_0 + H_1 \tag{1}$$

The perturbation term creates from the electric dipole moment operator ($\propto$) and reaction field vector, R :

$$H_1 = -\hat{\propto}.R \tag{2}$$

The reaction field is function of the electric dipole moment $\propto$: $R = -g\propto$ (3)

g is the onsager factor which determines the sterength of the reaction field and depends on the relative permittivity of the medium, ε, and on the radius of the cavity, [19] a_0 :

$$g = \frac{2(\varepsilon - 1)}{(2\varepsilon + 1)a_0^3} \tag{4}$$

The effect of the reaction field by solvent perturbation is united as an additional term in the Fock equation[19]:

$$F = F^0 - g\propto.\langle\propto\rangle \tag{5}$$

The energy is obtained by

$$E = \langle\Psi|H_0|\Psi\rangle - 0.5\propto.R \tag{6}$$

where Ψ is the full wave function of the molecule. These SCRF equation are solved iteratively. A single excited configuration interaction (CI) calculation is acted from the single determinant SCRF ground state [19].The energy correction to the excited state caused by the solvent agitation is obtained by:

$$\Delta E_{CI} = -\frac{n^2-1}{2n^2+1}\frac{1}{a_0}\left(\langle\propto^*\rangle - \langle\propto\rangle\right).\langle\propto\rangle \tag{7}$$

where n denotes the solvent refractive index. $\langle\propto^*\rangle$ the dipole moment of the solute excited state.Thisequation accounts for the fact that only the electronic polarization can respond to the change in the dipole moment during the absorption process.

In a solvent effect calculation cavity radius is the only adjustable parameter and the choice of the radius has been conversed widely. One of method to calculate the radius is to estimate it from the solute molar volume [19].

$$a_0^3 = \frac{3V_m}{4\pi N_A} \tag{8}$$

where N_A is Avogadro's number and V_m is given by experiment. While the experimental molar volume is not attainable, the molecular greatest dimension could be used to estimate the radius[19].

2- Thermochemistry

Calculations in 1 atmosphere pressure and temperatures $298K, 300K, 302\ K, 305K$ and $310\ K$ have been done at STO-3G/3-21G basis sets. Gibbs free energy, enthalpy, energy and entropy obtained by Gaussian 98 program [20]. Four equations will be utilized ta derive the final expressian utilized to calculate the different printed out by Gaussian 98 program.The internal thermal energy E can be gained from the partitian functian [21]:

$$E = Nk_B T^2 \left(\frac{\partial \ln q}{\partial T} \right) \qquad (1)$$

The partitian function from any component can he utilized to calculate the entropy contribution S from which camponent, applying the relatian [21] $n = \frac{N}{N_A}$ and substituting $N_A k_B = R$, the molar entrapy is:

$$S = R \ln(q(V,Y)e) + RT \left(\frac{\partial \ln q}{\partial T} \right)_V \qquad (2)$$

Also molar enthalpy is defined as [21]:

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

Finally, the energy can be utilized to acquire the heat capacity [21]:

$$C_p(T) = \frac{k(T) \Delta H_{VH} \Delta H_{cal}}{(1 + k(T))^2 RT^2} \qquad (4)$$

In this research, Gibbs free energy of the reaction has been appraised by applying expression: $\Delta G(T) = \Delta H(T) - T\Delta S(T)$.

RESULTS AND DISCUSSION

The interaction between the solute and the solvent molecules acts a signification role in comprehending the different malecular processes included in chemistry and biochemistry. Whereas temazalomide (TMZ) is an aral alkylating agent and acts as an inhibitor of DNA mismatch repair and can induee apoptosis[22,23] and Recent clinical studies have demonstrated that TMZ is effective for malignant glioma and accepted as first-line chemotherapy [24,25]. Hence we have investigated values of Temozolomide in gas phase and different solvents. The quantum mechanic calculations is done by the Gaussian 98 program based on the HF/STO-3G and HF/3-21G levels. In the Gaussian program a simple estimation is utilized in which the volume of the salute is utilized to compute the radius of a cavity which farms the hypothetical surface of the molecule [26,27]. Moreover, we surveyed the effects of solvents on PDB form of Temozolamide anticancer drug. Since the solute dipole moment induces a dipole moment in apposite direction in the surrounding medium, polarization of the medium will polarize the charge distribution in the solvent. Also directian of the water molecules at the TMZ-water interface can be influenced the direction of the water dipole mament. The consequences gained from onsager model appeared quite sensitive ta the polarity of the encircling solvent. The dipole moment value af temozolomide drug in various solvents with the same temperature is reported in Table 1.

The diagram of dipole moment is drawn according ta dielectric constant far various salvents in HF/STO-3G and HF/3-21G Levels that exhibited in Fig. 1.

The ather practical approach applies to calculations of the molecular volume as described the contour of Hartree-Fock theory which equal molecular volume ta the radius of a cavity and a constant increasment of the nearest possible approach of salvent molecules. When the volume keyword is osed, the latter approach of Gaussian is applied. Onsager model simply describes the influence of a molecule in solution and its medium, in which we have assumed that the solute is in a spherical cavity inside the salvent. Such case is described as a homogeneous, polarizable medium of dielectric constant. The studies of Temazolomide drug in gas phase and different solvents are performed by the SCRF method at ab initio HF/STO-3G and HF/3-21G levels of theory. The calculated cavity radius, 5.71Å, was used for the geometry optimization in the SCRF method. The results of Onsager model calculations showed that Gibbs free energy, energy, enthalpy and entropy values of Temozolomide is sensitive to polarity of the surrounding solvent. According to this approach, the Gibbs free energy, enthalpy, entropy and energy values, which depend on the dielectric constant ε, are listed in Tables 2,3,4.

Tables(2,4)indicate that with temperature increase from $298K$ to $310K$,thermodynamic values of Gibbs free energy of Temozolomide in gas phase and different solvents decreases which is the lowest amount of Gibbs free energy in temperature of $310K$. Obtained Gibbs free energy values in all examined temperatures decrease according to dielectric constant solvent increase, as the most negative Gibbs free energy value is for the time that Temozolomide remains in water solvent with dielectric constant $\varepsilon = 78.39$. Also Table 2 shows obtained Gibbs free energy, enthalpy and entropy values in different solvents and proves dependency of thermodynamic parameters to temperature Moreover, Tables (2,3,4) indicate changes of energy, enthalpy and entropy of Temozolomide drug in gas phase and different solvents on basis of temperature changes between $298K$ up to $310\ K$. It means temperature increase from $298K$ to $310K$, the most positive values of energy, enthalpy and entropy is for temperature of $310K$. Also calculated values of energy, enthalpy and entropy based on dielectric constant solvent increase in temperature of $298K$ to $310K$ indicate that the values of energy and enthalpy moves toward negative values. As the lowest values of energy and enthalpy occurs when Temozolomide is in water solvent, and the values of entropy is positive and the most positive value of entropy is when temozolomide is in water solvent. Besides in this project the diagram of Gibbs free energy and enthalpy are drawn according to temperature for common solvents in HF/STO-3G and HF/3-21G levels that exhibited in Fig. (2,3)

Table 1. Theoretical dipole moment values in various solvents at several temperatures

Medium	HF	T/K	298	300	302	305	310
Gas phase	STO-3G	Dipole moment /D	22.0994	22.0994	22.0979	22.0988	22.0963
Water			113.9859	113.9855	113.9848	113.9848	113.9851
Acetonitrile			112.9863	112.8963	112.8893	112.9063	112.9540
Methanol			112.6539	112.7960	112.8748	112.7708	112.9537
Acetone			111.4491	114.4399	111.4482	111.4491	111.4487
Tetrahyrofuran			106.0647	106.0602	106.0593	106.0647	106.0630
Aniline			104.8900	104.8651	104.8847	104.8900	102.5497
Chlorobenzene			102.5497	102.5481	102.5475	102.5493	102.5400
Chloroform			84.4535	84.4535	84.4695	84.45452	84.4528
Benzene			83.4293	83.3311	83.4189	83.3311	83.4085
Carbontetrachloride			64.8610	64.7228	64.9079	64.9398	64.8970
Gas phase	3-21G		16.9472	16.8742	16.9079	16.9398	16.8970
Water			1775.1011	1775.1011	1775.1612	1775.1423	1775.1519
Methanol			1572.8440	1572.8333	1572.7640	1572.7949	1572.8151
Chloroform			253.8385	253.8431	253.9002	253.8501	253.8453
Carbontetrachloride			84.4902	84.3678	84.4090	84.4281	84.3283

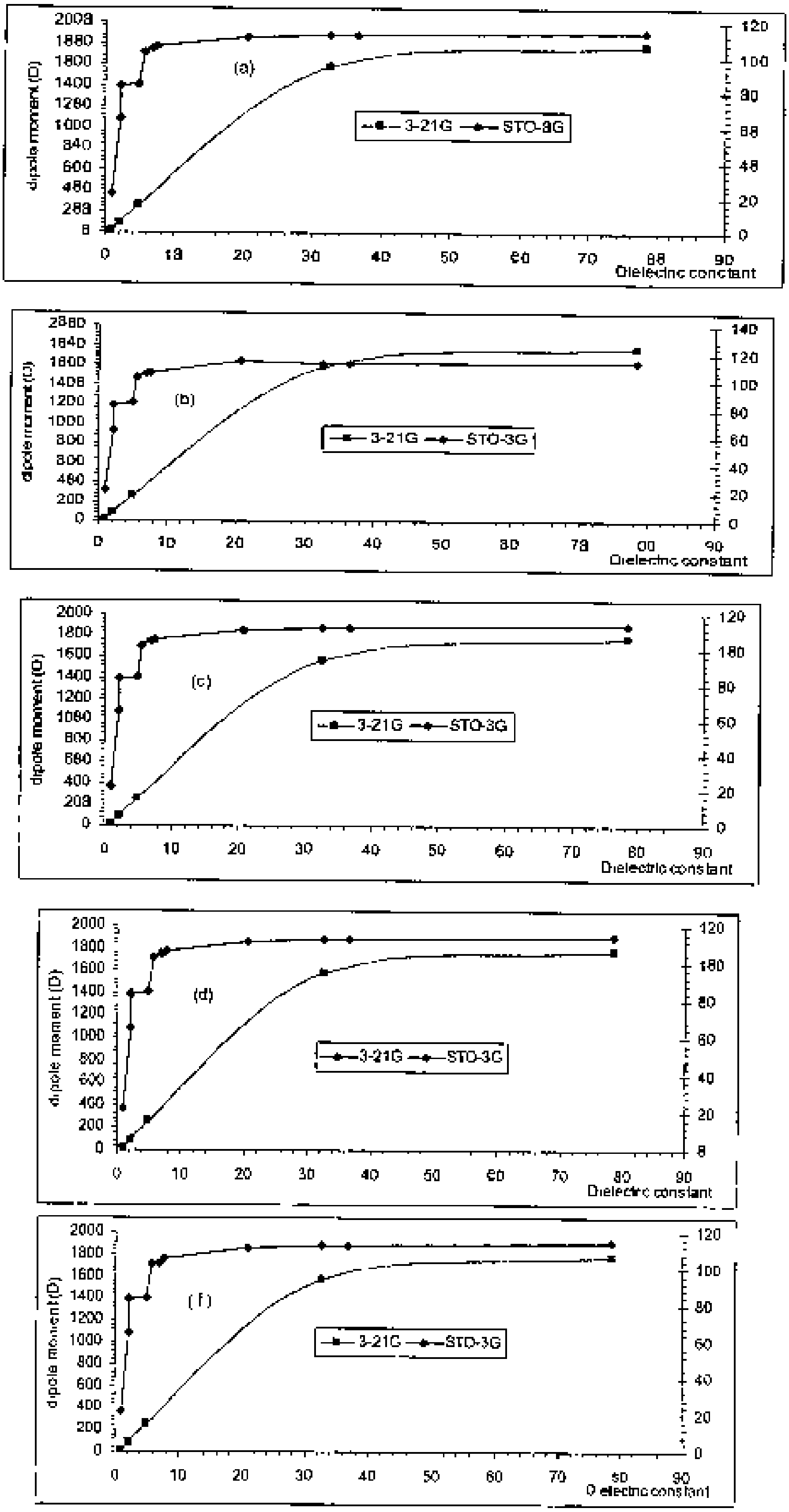

Fig. 1. Dipole moment calculated for TMZ by SCRF model as a function of dielectric constant in (a) 298K. (b) 300K, (c) 302K, (d) 305K, (f) 310K.

Table 2. Theoretical Gibbs free energy and energy values in different salvents at several temperatures HF/STO-3G level

Medium		Temperature(K)				
		298	300	302	305	310
Gas phase	Gibbs free energy(kcal/mol)	-1640283.841	-1640284.038	-1640284.251	-1640284.571	-1640285.106
Water		-1640461.548	-1640461.759	-1640461.988	-1640462.332	-1640462.909
Acetonitrile		-1640452.584	-1640452.796	-1640453.025	-1640453.269	-1640453.541
Methanol		-1640450.469	-1640450.68	-1640450.909	-1640451.254	-1640451.831
Acetone		-1640450.469	-1640450.89	-1640451.309	-1640452.007	-1640452.601
Tetrahyrofuran		-1640389.325	-1640389.528	-1640389.749	-1640390.081	-1640390.637
Aniline		-1640382.519	-1640382.642	-1640382.945	-1640383.278	-1640383.838
Chlorobenzene		-1640368.824	-1640369.041	-1640369.275	-1640369.628	-1640370.219
Chloroform		-1640363.429	-1640363.644	-1640363.876	-1640364.226	-1640364.812
Benzene		-1640310.56	-1640310.754	-1640310.956	-1640311.28	-1640311.809
Carbontetrachloride		-1640309.972	-1640310.166	-1640310.375	-1640310.692	-1640311.22
Gas phase	Energy (kcal/mol)	-1640252.825	-1640252.76	-1640252.69	-1640252.584	-1640252.405
Water		-1640428.128	-1640428.056	-1640427.978	-1640427.86	-1640427.66
Acetonitrile		-1640419.356	-1640419.206	-1640419.084	-1640418.888	-1640418.689
Methanol		-1640417.036	-1640416.963	-1640416.885	-1640416.767	-1640416.568
Acetone		-1640400.471	-1640400.405	-1640400.333	-1640400.225	-1640400.042
Tetrahyrofuran		-1640357.159	-1640357.09	-1640357.016	-1640356.903	-1640356.713
Aniline		-1640350.173	-1640350.102	-1640350.028	-1640349.915	-1640349.723
Chlorobenzene		-1640330.559	-1640330.487	-1640330.409	-1640330.291	-1640330.093
Chloroform		-1640329.433	-1640329.377	-1640329.303	-1640329.192	-1640329.006
Benzene		-1640279.97	-1640279.908	-1640279.84	-1640279.738	-1640279.567
Carbontetrachloride		-1640279.359	-1640279.279	-1640279.229	-1640279.128	-1640278.956

Table 3. Thearetical enthalpy energy and entropy energy values in different solvents at several temperatures HF/STO-3G level

Medium		Temperature(K)				
		298	300	302	305	310
Gas phase	Enthalpy (kcal/mol)	-1640252.232	-1640252.164	-1640252.089	-1640251.978	-1640251.789
Water		-1640427.536	-1640427.46	-1640427.378	-1640427.254	-1640427.045
Acetonitrile		-1640418.564	-1640418.488	-1640418.406	-1640418.282	-1640418.073
Methanol		-1640416.443	-1640416.367	-1640416.285	-1640416.161	-1640415.952
Acetone		-1640399.878	-1640399.809	-1640399.733	-1640399.619	-1640399.426
Tetrahyrofuran		-1640356.566	-1640356.494	-1640356.415	-1640356.297	-1640356.096
Aniline		-1640349.58	-1640349.478	-1640349.386	-1640349.282	-1640349.107
Chlorobenzene		-1640333.966	-1640333.891	-1640333.809	-1640333.685	-1640333.477
Chloroform		-1640328.851	-1640328.703	-1640328.586	-1640328.463	-1640328.29
Benzene		-1640279.377	-1640279.311	-1640279.24	-1640279.132	-1640278.451
Carbontetrachloride		-1640279.359	-1640279.257	-1648278.959	-1640278.721	-1640278.339
Gas phase	Entropy (kcal/mol K^{-1})	0.104591	0.104811	0.105048	0.105403	0.105994
Water		0.116914	0.117166	0.117439	0.117847	0.118524
Acetonitrile		0.115975	0.116213	0.11647	0.116855	0.117494
Methanol		0.114125	0.114359	0.114632	0.115041	0.115721
Acetone		0.114105	0.114333	0.114604	0.115016	0.115696
Tetrahyrofuran		0.114077	0.114331	8.114603	0.115014	0.115696
Aniline		0.110479	0.110736	0.110986	0.111379	0.112034
Chlorobenzene		0.109875	0.110117	0.110379	0.11077	0.11142
Chloroform		0.106020	0.1106248	0.106495	0.106864	8.107477
Benzene		0.105531	0.104884	0.106015	0.106391	8.107017
Carbontetrachloride		0.104664	0.104811	0.105121	0.105477	0.106067

Table 4. Theoretical Gibbs free energy, enthalpy eaergy, energy and entropy energy values in different solvents at several temperatures HF/3-21G level

Medium		Temperature(K)				
		298	300	302	305	310
Gas phase	Gibbs free energy(kcal/mol)	-859152.8049	-859153.0057	-859153.2316	-859153.5641	-859154.1289
Water		-1664892.514	-1664892.698	-1664892.882	-1664893.197	-1664893.698
Methanol		-1664891.225	-1664891.498	-1664891.792	-1664892.254	-1664892.816
Chloroform		-1664738.816	-1664738.897	-1664739.123	-1664739.345	-1664739.916
Carbontetrachloride		-1653335.615	-1653335.829	-1653336.061	-1653336.403	-1653336.992
Gas phase	enthalpy (kcal/mol)	-859119.6979	-859119.6213	-859119.5385	-859119.4136	-859119.2028
Water		-1664857.463	-1664857.325	-1664857.197	-1664856.927	-1664856.511
Methanol		-1664856.932	-1664856.867	-1664856.802	-1664856.691	-1664856.432
Chloroform		-1664708.149	-1664708.106	-1664708.054	-1664707.957	-1664707.804
Carbantetrachloride		-1653305.215	-1653305.134	-1653305.047	-1653304.931	-1653304.693
Gas phase	energy(kcal/mol)	-859120.2903	-859120.1384	-859120.0198	-859119.7190	-859119.2175
Water		-1664857.525	-1664857.463	-1664857.405	-1664857.297	-1664857.127
Methanol		-1664857.463	-1664857.325	-1664a57.197	-1664856.927	-1664856.432
Chlorofarm		-1664708.763	-1664708.72	-1664708.675	-1664708.589	-1664708.439
Carbontetrachloride		-1653305.808	-1653305.731	-1653305.647	-1653305.526	-1653305.308
Gas phase	entropy (kcal/mol K⁻¹)	0.089808	0.089991	0.090172	0.090484	0.090977
Water		0.11538	0.115649	0.11594	0.11642	0.117099
Methanal		0.111036	0.111291	0.111566	0.111978	0.112663
Chloroform		0.099269	0.099438	0.099675	0.100039	0.1000627
Carbontetrachloride		0.099221	0.099395	0.099655	0.100021	0.100023

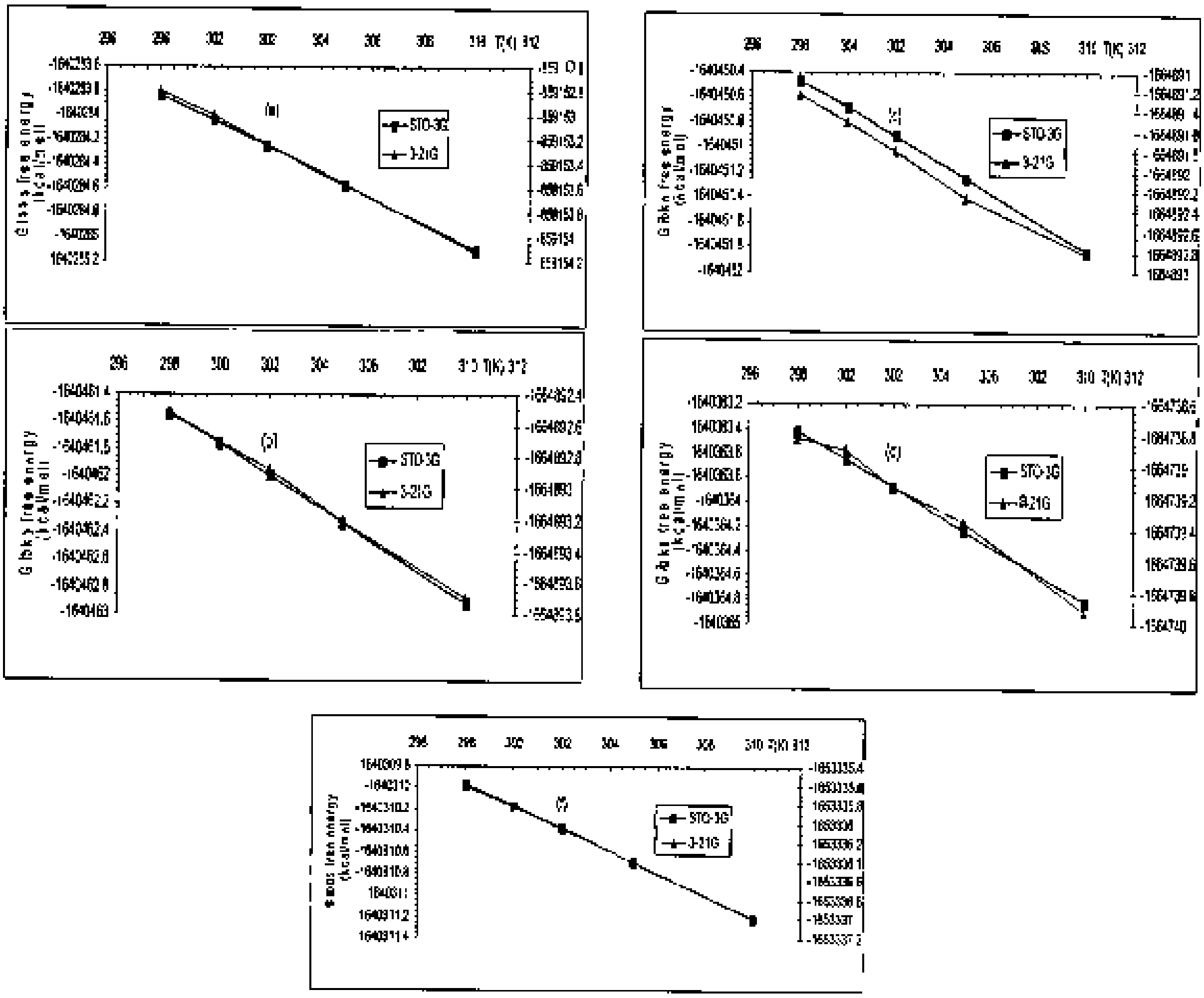

Fig. 2. Gibbs free energies calculated for TMZ by SCRF model as a function of temperature in (a) Gas phase (b) Water (c) Methanol (d) Chloroform (f) Carbon tetrachloride.

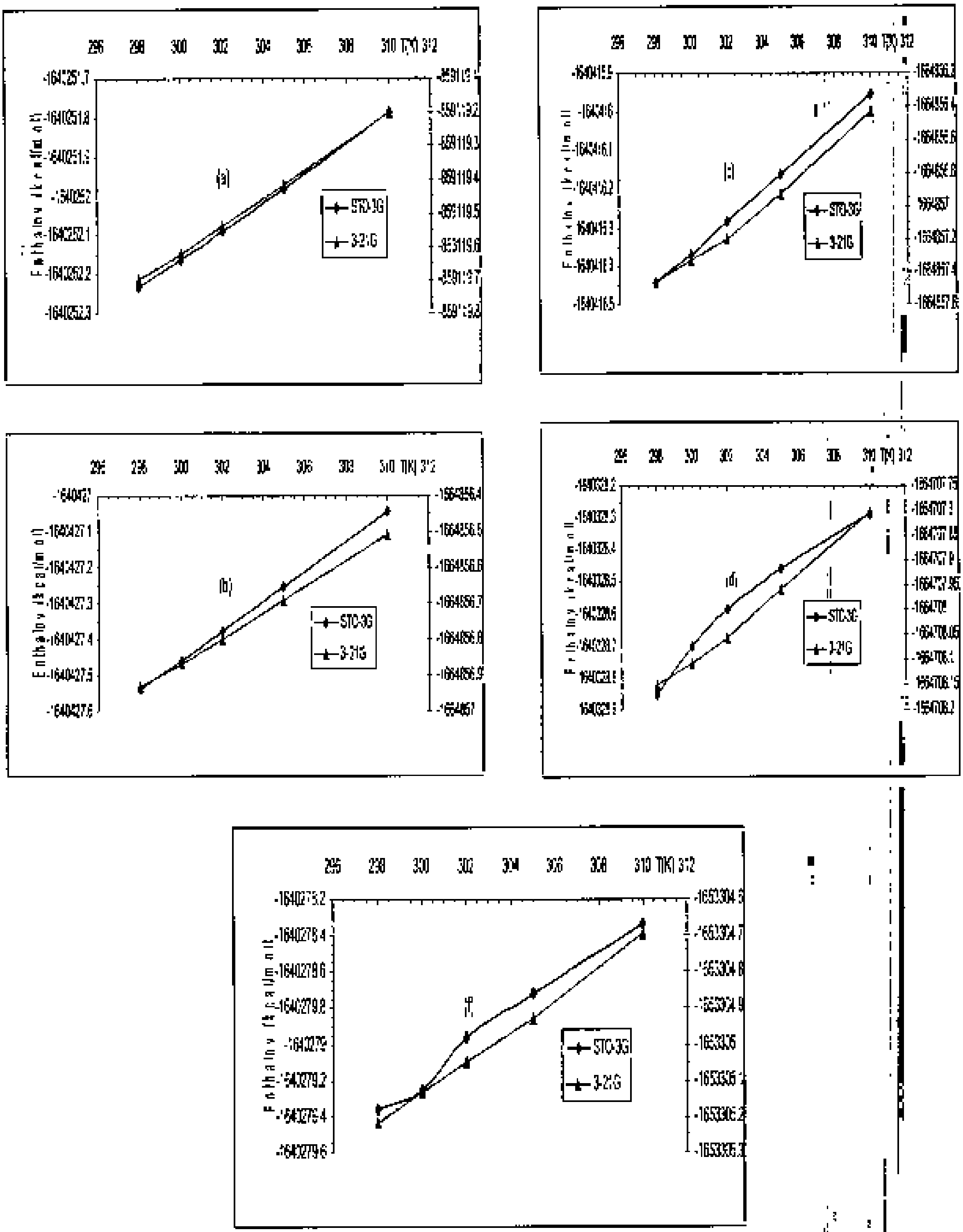

Fig. 3. Enthalpy energies calculated for TMZ by SCRF model as a function of temperature in (a) Gas phase (b) Water (c) Methanol (d) Chloroform (f) Carbon tetrachloride.

CONCLUSION

The most of the prevalent investigation computational chemistry are based on the study of various molecules in different dielectric constants. Thus in this project, we try to study the effects of solvent for the PDB form of temozolomide anticancer drug because Temozolomide is very important drug for cancer cells and is also a common type of anticancer drug that employed to interfere in cancerous tissue growth and reduce the size of cancer cell. In this paper, a dipole in the molecule will induce a dipole in the medium, and the electric field applied by the solvent dipole will in turn in interact with the molecular dipole leading to net stabilization [28]. So we found that dipole moment is a function of dielectric constant and increase of dielectric constant solvent increases the dipole moment. in next stage, we compared obtained Gibbs free energy values based on dielectric constant solvent increase which indicates water solvent is the best enviroment for the anticancer drug of Temozolomide in HF/ STO-3G and HF/3-21G levels becaus it has the most negative Gibbs free energy value.

Our principal results from the point of view of solvent effects can be summarized as follows:

1 - In general, by increasing temperature Gibbs free energy moves toward negative values but energy and enthalpy moves toward positive values.

2 - The thermodynamic values of Gibbs free energy, enthalpy, energy, entropy are functions of dielectric constant solvent. When dielectric constant solvent increases the values of Gibbs free energy, energy and enthalpy decrease, but the values of entropy increase.

3 - Dipole moment is a function of dielectric constant solvent. When dielectric constant solvent increases Tomozolomide dipole moment values surrounded by solvent molecules increase

Finally, we would like to consider the potential energy and kinetic energy of this analysis in further studies of Temozolomide when it places on various solvents.

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