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Tautomeric transformation of temozolomide, their proton affinities and chemical reactivities: A theoretical approach

Wichien Sang-aroon [a,b,*], Vithaya Ruangpornvisuti [c], Vittaya Amornkitbamrung [b,d,**]

[a] Department of Chemistry, Faculty of Engineering, Rajamangala University of Technology Isan, KhonKaen Campus, KhonKaen 40000, Thailand
[b] Integrated Nanotechnology Research Center, Department of Physics, Faculty of Science, KhonKaen University, KhonKaen 40002, Thailand
[c] Supramolecular Chemistry Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University, Pathumwan, Bangkok 10320, Thailand
[d] Thailand Center of Excellence in Physics, CHE, Ministry of Education, Bangkok 10400, Thailand

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ABSTRACT

The gas-phase geometry optimizations of bare, mono- and dihydrated complexes of temozolomide isomers were carried out using density functional calculation at the M06 – 2X/6 – 31 + G(d,p) level of the theory. The structures and protonation energies of protonated species of temozolomide are reported. Chemical indices of all isomers and protonated species are also reported. Energies, thermodynamic quantities, rate constants and equilibrium constants of tautomeric and rotameric transformations of all isomers **I1** ↔ **TZM** ↔ **HIa** ↔ **HIb** ↔ **I2** ↔ **I3** in bare and hydrated systems were obtained.

1. Introduction

Glioblastoma is one of the most severe forms of human cancer, which is a primary brain tumor [1]. Malignant gliomas including glioblastoma multiforme and anaplastic astrocytoma occur more frequently than other types of primary central nervous system tumours. Even if these cancers are treated with surgery, chemotherapy and radiation, survival is less than 1 year [2]. Additionally, the average lifespan for a MG patient postdiagnosis is 14.6 months with most patients experiencing tumor relapse and outgrowth within 7 months of initial radiation therapy [3–5]. Nowadays, temozolomide is one of the most widely used and effective chemotherapeutic drug for glioblastoma patients. Temozolomide is a prodrug of the alkylating agent 5-(3 methyltriazen-1-yl) imidazole-4-carboximide (MTIC) [6]. Temozolomide is an oral chemotherapy drug. Temozolomide readily crosses the blood-brain barrier and has a broad spectrum of antineoplastic activity [7–9]. However, although radiotherapy followed by accompanying and auxiliary temozolomide therapy showed encouraging results in patient survival [3], recent studies indicate a rather discomfiting result. Over 40% of patients undergoing chemotherapy and 55% of newly diagnosed cases do not benefit at all from temozolomide therapy [10,11]. Upon administration, temozolomide hydrolyzes spontaneously at physiological pH to the active metabolite (MTIC). MTIC is therefore hydrolyzed to methylhydrazine [12,13].

There are still a little amount of work has been done on temozolomide. The anticancer, antitumor activity and skin delivery potency of temozolomide ester prodrugs have been reported [14,15]. TiO_2 nanostructured reservoir with temozolomide has been synthesized and structural evaluated [16]. The quantitative determination of temozolomide in bulk and capsule has been determined by UV spectrophotometric method [17]. XRD, FTIR and FT-Raman analysis have been used to characterize some cocrystals of temozolomide [18]. The possibilities of encapsulating temozolomide into polybutylcyanoacrylate nanoparticles by polymerisation was studied [19]. The physiochemical properties of temozolomide process related impurities and their structure were investigated [20]. Interaction of temozolomide in water has been investigated by means of theoretical approach [21]. The structure, vibrational and electronic spectra of temozolomide molecule has been elucidated by combined experimental and theoretical methods [22].

* Corresponding author at: Department of Chemistry, Faculty of Engineering, Rajamangala University of Technology Isan, KhonKaen Campus, KhonKaen 40000, Thailand.
** Corresponding author at: Integrated Nanotechnology Research Center, Department of Physics, Faculty of Science, KhonKaen University, KhonKaen 40002, Thailand.
E-mail addresses: wichien.sa@rmuti.ac.th (W. Sang-aroon), vittaya@kku.ac.th (V. Amornkitbamrung).

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According to the vast pharmaceutical importance, an investigation has been made in this study to investigate transformation of temozolomide. The compound should be extensively investigated for their isomers, energetic, thermodynamic properties for their equilibria and kinetics. In the present work, the optimized molecular geometries of temozolomide isomers have been calculated using DFT method with M06 – 2X/6 – 31 + G(d,p) basis function. The tautomerization due to direct (bare system) and water – assisted proton transfers (hydrated system) were investigated. Protonation energies and stabilities of various protonated temozolomide species were also investigated. Energies of all temozolomide isomers, thermodynamic quantities, rate constants and equilibrium constants of their tautomeric reactions were reported. Relative stabilities and reactivities based on frontier molecular orbital energies (E_{HOMO} and E_{LUMO}) of all isomers were also computed and discussed.

2. Computational methodology

The dispersion-corrected functional M06–2X was used to perform calculation in this work. Even B3LYP is one of the most popular functional used in the calculation based on its reliable result and computational cost, however, it has been reported that B3LYP activation barriers overestimate experimental activation energy by 3 – 4 kcal/mol while M06-2X activation barrier underestimate the experimental value by 2.8–3.7 kcal/mol [23]. To understand the effect of basis set on the relative energy of temozolomide before selecting the suitable one, so, geometry optimization of the six isomers carried out at various basis sets were shown in Table 1. The zero – point corrected relative energies based on the M06 – 2X/6 – 31 + G(d,p), M06 – 2X/6 – 311 + +G(d,p) and M06 – 2X/aug – cc – pVQZ are in the same increasing order and the obtained values from the three basis sets are very close. The result is in agreement to the previous work [24] which the effect of basis function on relative energies of nitrosamine were computed based on B3LYP/6 – 31G(d), B3LYP/6 – 311 + +G(d,p) and B3LYP/aug-cc-pVQZ levels and the obtained values from these three levels were not much different (~2 kcal/mol). Thus, in this work, the gas – phase structure of isomers of the temozolomide and the transition states of all transformation reactions were optimized using the hybrid functional of Truhlar and Zhao M06 – 2X [25] with 6 – 31 + G(d,p) basis function. The solvent effect was investigated by single–point calculations on the M06 – 2X/6 – 31 + G(d,p)-optimized gas-phase structures using the conductor–like polarizable continuum model (CPCM) and integrated-equation formalism polarizable continuum model (IEFPCM) [26–28]. All calculations were performed with the Gaussian 09 program [29]. The molecular graphics of all related species were generated with the MOLEKEL 4.3 program [30].

The reactivity indices including Mulliken electronegativity (χ), chemical hardness (η), and electronic chemical potential (μ) for all isomers of the temozolomide were computed using orbital energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) at the M06 – 2X/6 – 31 + G(d,p) level of theory. The chemical indices were derived from the first ionization potential (I) and electron affinity (A) of the N – electron molecular system with a total energy (E) and external potential ($v(\vec{r})$) using the relations: $\chi = -(\partial E/\partial N)_{v\vec{r}} = -\mu \cong 1/2(I + A)$, $\eta = -(\partial^2 E/\partial N^2)_{v\vec{r}} \cong 1/2(I - A)$ and the first ionization potential is $I = E(N-1) - E(N)$and electron affinity is $A = E(N) - E(N+1)$[31]. I and A were computed from the E_{HOMO} and E_{LUMO} using the relationship $I = -E_{HOMO}$ and $A = -E_{LUMO}$ according to the Koopmans theorem [32]. The rate constant at the standard temperature 298.15 K (k_{298}), was computed based on transition state theory (TST). The rate constant derived from the Gibbs free energy of activation ($\Delta^{\dagger}G$) computed based on Eq. (1) [33,34], and derived from activation energy ($\Delta^{\dagger}E$) computed based on Eq. (2) [23].

$$k(T) = \frac{k_B T}{hc^{o}} \exp(-\Delta^{\dagger}G/RT) \quad (1)$$

$$k(T) = \kappa \frac{k_B T}{h} \frac{Q_{TS}}{Q_{REA}} \exp(-\Delta^{\dagger}E/RT) \quad (2)$$

$$= \kappa A \exp(-\Delta^{\dagger}E/RT)$$

where k_B is the Boltzmann's constant, h is Plank's constant, T is the absolute temperature, c° is the concentration factor, and R is the gas constant. Q_{TS} and Q_{REA} are the total partition functions of the transition states and reactants which composed of electronic, translational, rotational, and vibrational partition functions. The standard thermodynamic quantities including reaction enthalpy (ΔH^{o}_{298}) and Gibbs free energy changes (ΔG^{o}_{298}) for all reaction pathways were derived from the frequency calculations at the M06 – 2X/6 – 31 + G(d,p) level of theory. The equilibrium constant at standard temperature and pressure (K_{298}) is computed based on Gibbs free energy changes (ΔG^{o}_{298}) using a thermodynamic Eq. (3):

$$K_{298} = \exp(-\Delta G^{o}/RT) \quad (3)$$

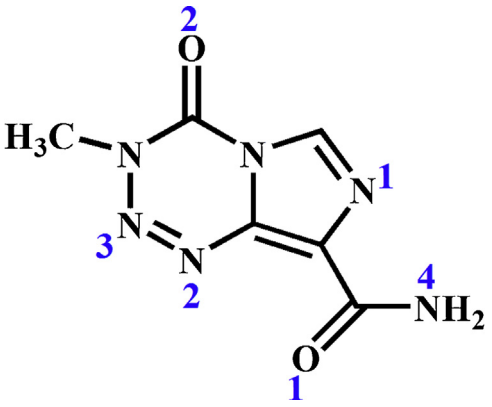

Fig. 1. Chemical structure and atomic labeling of temozolomide molecule.

3. Results and discussion

3.1. Energetics and thermodynamics of transformational reaction of temozolomide

The molecular structure and atomic labeling of temozolomide is shown in Fig. 1. For tautomeric isomers, the original temozolomide is named **TZM**. Imide isomers corresponding to the amide proton transfer to the three aromatic nitrogen atoms N1, N2 and N3 are defined as **I1**, **I2** and **I3** while two rotameric hydroxy imide isomers are called **HIa** and **HIb**, respectively. The M06 – 2X/6 – 31 + G(d,p) – optimized gas – phase structures of temozolomide isomers, their transformation reactions in bare, monohydrated and dihydrated systems are depicted in Fig. 2. The zero – point corrected relative energies derived from the M06 – 2X/6 – 31 + G(d,p), M06 – 2X/6 – 311 + +G(d,p) and M06 – 2X/aug – cc – pVQZ are in the same decreasing order. The relative stabilities based on the total energies derived from M06 – 2X/6 – 31 + G(d,p) level of the six isomers are in decreasing order: **TZM** (0.00) > **HIa** (12.15) > **HIb** (15.33) > **I1** (45.36) > **I2** (59.19) > **I3** (67.76) kcal/mol. The relative energies due to single – point calculation using CPCM and IEFPCM at M06 – 2X/6 – 31 + G(d,p) level are very close. However, the relative stabilities of gas-phase optimized structures and single-point calculations in both solvation models