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Regioselectivity of the interaction of temozolomide with borane and boron trifluoride

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Abstract MP2 and B3LYP calculations are used to predict the most favorable site of temozolomide toward BH_3 and BF_3 which are classical Lewis acids. Binding energies, charge transfers, and bond length perturbations of the temozolomide in various complexes indicate that the N_{12} atom is the preferred attack site for BH_3 , while BF_3 prefers the O_{17} atom. The interactions are quite strong, as much as 100 kJ/mol for BH_3 and more than 60 kJ/mol for BF_3 . The molecular electrostatic potential surrounding temozolomide is most negative around the O atoms, which is unable to explain the energetic order of binding of the Lewis acids.

Keywords MP2 · B3LYP · MEP · Noncovalent bond

Introduction

The temozolomide (TMZ) molecule (Fig. 1), characterized by a fused pair of heterocyclic rings containing a total of five N atoms, as well as a carbonyl and one amide group, continues to attract the attention of numerous research groups because of its applications in medicine such as cytotoxic pro-drug for the treatment of astrocytoma,

aggressive brain tumor, glioblastoma multiform, and melanoma [1].

Laboratory studies and clinical trials have investigated whether the anticancer potency of TMZ might be augmented by combining it with other pharmacologic agents. Some clinical trials have indicated that the addition of chloroquine is suspected to be beneficial for the treatment of glioma patients [2, 3]. Likewise, investigations on the effects of TMZ and quercetin on cell death in the human astrocytoma cell line MOGGCCM indicate that quercetin acts in concert with TMZ when used in combination rather than in separate pharmacological applications [4, 5]. Along the same line, in combination, TMZ and irinotecan induced complete responses in four neuroblastomas, two rhabdomyosarcomas, and the glioblastoma line [6]. The activity of the combination was significantly greater than the activity of either agent administered alone in four tumor lines [6]. Nevertheless, the mechanism of the TMZ action remains largely unknown [7].

There are two possible ways for TMZ to act in synergy with chloroquine or quercetin and irinotecan. In one mode, TMZ can act together with one of them simultaneously on different parts of DNA. Alternatively, TMZ can form complexes with the other agents, thus having cooperative effect on the DNA. In this last case, the interactions between TMZ and other pharmacologic agents forming supramolecular complexes are probably noncovalent, consistent with the ubiquitous role of noncovalent interactions in many biological processes [8–18]. The investigation and understanding of these noncovalent interactions has become one of the major goals of modern chemistry. Noncovalent interactions [12–14] form the basis of what is usually called “supramolecular interactions.” However, quantitative elucidation of the thermodynamics solely by means of *ab initio* electronic structure theory remains an

This paper is dedicated to Professor Magdolna Hargittai on the occasion of her 70th birthday.

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Fig. 1 Structure of temozolomide (TMZ)

elusive target, and a phenomenological view of the binding mechanism prevails [15, 16].

As TMZ is a polyfunctional heterocyclic base containing two carbonyl groups and six nitrogen atoms as possible electron donor sites, it would be useful to analyze its potential noncovalent interactions, e.g., hydrogen bond or electrophilic interactions, with other molecules. Our previous study applied computational methods to predict the most favorable site of TMZ toward attack by a water molecule [19]. The outcome of these investigations revealed the terminal amide group of the TMZ as the preferred attack site where water can act as simultaneous proton donor and acceptor (Fig. 2) [19].

However, H-bonds are not the only sorts of interactions in which TMZ can participate. Another important scenario involves more general electrophilic interactions with Lewis acids. As an example, our recent DFT study to determine the stability of the complexes formed between the N and O sites of 3-methyl-4-pyrimidone and 1-methyl-2-pyrimidone found their behavior toward Lewis acids especially intriguing [20]. That study pointed out a strong regioselectivity with borane and its derivatives preferring the nitrogen site in both pyrimidone isomers, while a preference for oxygen is observed for alkali acids in 3-methyl-4-pyrimidone. The complexation of 1-methyl-2-pyrimidone with these hard alkali acids did not show any discrimination between the two sites due to the presence of a continuous delocalized electron density region between the N and O atoms.

Fig. 2 Water–TMZ complex derived from [19]

However, to the best of our knowledge, and despite the biological importance of this molecule, no experimental or theoretical data concerning the regioselectivity of the TMZ molecule in the context of such electrophilic interactions have yet been reported. The interactions between TMZ and BF_3 or BH_3 partners are of the Lewis acid base type, and one is tempted to use Pearson's hard and soft acids/bases principle [21] as a starting point. However, this set of principles represents only a guide, and care should be exercised particularly if both the reactants are not of the hard type (hard–hard interactions), and in intermediate nonmatching cases, predictions are more problematic.

This work considers BH_3 and BF_3 adducts which represent soft and hard Lewis acids, respectively, and thus cover a range. Each boron atom contains an empty $2p$ orbital, perpendicular to the molecular plane. Thus, the main interaction between TMZ and a boron Lewis acid is the electron donation from the oxygen or nitrogen lone pair of the TMZ molecule into the empty orbital on the B atom of the Lewis acid. This work examines all of the potential adducts of TMZ with BH_3 and BF_3 and elucidates the preferred binding sites. As such, one can compare the interaction energies of different N-bound and O-bound isomers, and derive the preferred binding sites, and the energetic advantage of each.

Computational methods

Geometry optimizations were performed using both MP2 and DFT with the hybrid B3LYP functional and a 6-31+G(d,p) set [18, 22]. After consideration of various sites, six BH_3 –TMZ and BF_3 –TMZ conformers were obtained. Vibrational analysis showed each structure to be a true minimum.

The binding energy of each complex was computed as the difference between the energy of each complex and the relaxed structures of the monomers. These binding energies were corrected for the basis set superposition error (BSSE) [23, 24] by the Boys and Bernardi [25] counterpoise correction procedure.

The molecular electrostatic potential (MEP), the interaction of a unit positive charge at a given point $\vec{r}$ with reference to a molecular charge distribution, is evaluated by [26]:

$$v(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d\mathbf{r}'$$

where $\rho(\mathbf{r})$ is the molecular electron density function; the summation over A runs over all nuclei with charge Z_A and distance R_A . All calculations were performed using the Gaussian 09 software package [27, 28]. Atomic charges

and charge transfer energies were assessed by NBO as implemented in Gaussian 09. GaussView and Chemcraft [29] programs were used for visualization [27].

Results

Table 1 reports in the first column the MP2 relative energies of the various optimized dimers combining TMZ with BF_3 , with the N12 complex taken as reference point. (Structures are displayed in Fig. 3.) The O17 site is slightly more attractive than N12, but the other four complexes are much less tightly bound. This conclusion survives the addition of zero-point vibrational energies, as illustrated in the second column of Table 1. The binding energies of each complex are displayed in the succeeding columns of Table 1, both without and with ZPE included. BF_3 is bound to N12 and O17 by 60 kJ/mol, diminishing to nearly 50 kJ/mol upon ZPE correction. Binding energies to the other sites are much smaller in magnitude, <13 kJ/mol, and even positive in one instance. The optimized B...N/O distances in the next column of Table 1 are largely reflective of the energetics. The strongly bound complexes at N12 and O17 are shorter than 1.7 Å, while the others are as long as 2.6 Å.

For purposes of comparison, the same data are reported in Table 2 for DFT calculations using the B3LYP functional, with the same basis set. The main trends are repeated here: O17 provides the strongest binding site, followed by N12, with the others much less potent. However, there are several quantitative differences. In the first place, the difference between O17 and N12 is exaggerated by B3LYP, from <1 to 12 kJ/mol. Another difference is that N2 does not offer a stable binding site; a BF_3 molecule placed here shifts over to the much more stable O17. The very long B...O/N distances predicted by MP2 for N1 and O8 sites are much shorter for B3LYP, well <2 Å.

The corresponding parameters for the binding of BH_3 to TMZ are displayed in Tables 3 and 4, along with Fig. 4. Focusing first on the MP2 data, N12 serves as the preferred site of binding, as opposed to O17 as was the

case for BF_3 . Indeed, there is a wide margin of preference for N12, nearly 20 kJ/mol. Secondly, the binding is considerably stronger for BH_3 , as much as 101 kJ/mol at the N12 site. Indeed, it is not only N12, but all sites bind much more strongly to BH_3 than to BF_3 . The weakest interaction occurs at O8, but even here BH_3 is bound by more than 30 kJ/mol. Consonant with the stronger binding, the intermolecular B...N/O distances are also shorter for BH_3 . B3LYP again reproduces the qualitative trends of MP2 and is even fairly good in a quantitative sense.

As might be expected, there is a good deal of charge that is transferred from TMZ to the Lewis acid. This quantity ΔQ was evaluated as the sum of atomic NBO charges on the Lewis acid and is displayed as the last column of Tables 1, 2, 3 and 4. At the MP2 level, the charge transfer reaches as high as 0.32 e in the complex where BH_3 attacks the N12 atom of TMZ. There is a fair, but by no means precise, correlation between ΔQ and the energetic strength of the binding. For example, the aforementioned BH_3 complex with N12 is the strongest one observed with a binding energy of 101 kJ/mol. The two strongest complexes of BF_3 with TMZ are associated with O17 and N12, which have the largest ΔQ in Table 1. On the other hand, the complex with N18 is very much weaker, yet still has a value of ΔQ very close to those for O17 and N12. In fact, even the weakest complex of BF_3 with N2, barely bound at all, shows a large charge transfer of 0.19 e. On a similar note, the charge transfers for BH_3 in Table 3 are similar to the values for BF_3 , even though the binding energies of the former are generally quite a bit larger. It is finally noted that the B3LYP charge transfers in Tables 2 and 4 are generally quite similar to the corresponding MP2 values.

Despite these very substantial binding energies, there are relatively minor perturbations of the internal geometry of TMZ. Changes in the bond lengths within TMZ caused by each site of complexation are indicated in Figs. 3 and 4, in mÅ. For example, the most strongly bound complex of BF_3 occurs at N12 and O17. This association elongates the two $\text{N}_{12}\text{--C}$ bonds by 4 and 9 mÅ. Association with O17, also a strongly bound complex, causes the C=O17 bond to stretch by 24 mÅ, and the two neighboring CN bonds to contract by some 20 mÅ. It is worth noting the absence of a clear correspondence between the strength of the interaction and the perturbation of the neighboring bond lengths. For example, although the complex with N18 is only moderate in strength, it nonetheless results in the largest bond length perturbation wherein the neighboring NC bond elongates by 89 mÅ. The corresponding bond length changes induced by complexation with BH_3 are displayed in Fig. 4. Again, there is little relation between strength of interaction and internal bond perturbation.

Table 1 Energetics (kJ/mol) of interaction of BF_3 at various sites of the TMZ molecule at MP2/6-31+G(d,p) level

	E_{rel}	$E_{\text{rel}} + \text{ZPE}$	E_{b}	$E_{\text{b}} + \text{ZPE}$	$R, \text{\AA}$	$\Delta Q, e$
O17	−0.79	−1.92	−60.82	−49.94	1.64	0.238
N12	0.00	0.00	−60.04	−48.02	1.69	0.249
N18	36.18	35.62	−23.86	−12.39	1.79	0.225
N1	41.93	37.32	−18.11	−10.69	2.60	0.019
O8	40.12	41.95	−19.92	−6.06	2.54	0.171
N2	53.11	51.74	−6.92	3.72	1.82	0.190

Fig. 3 MP2 equilibrium geometries of complexes of TMZ with BF_3 . Intermolecular distances are in Å. Perturbations of neighboring bond lengths within TMZ are shown in mÅ

Table 2 Energetics (kJ/mol) of interaction of BF_3 at various sites of the TMZ molecule at B3LYP/6-31+G(d,p) level

	E_{rel}	$E_{\text{rel}} + \text{ZPE}$	E_{b}	$E_{\text{b}} + \text{ZPE}$	$R, \text{\AA}$	$\Delta Q, e$
O ₁₇	-12.08	-11.20	-65.03	-57.40	1.61	0.266
N ₁₂	0.00	0	-52.95	-46.21	1.67	0.267
N ₁₈	41.03	41.56	-11.93	-4.65	1.79	0.059
N ₁	45.01	42.87	-7.95	-3.34	1.90	0.012
O ₈	40.51	36.65	-12.44	-9.56	1.74	0.213
N ₂	-	-	-	-	-	-

BF_3 shifts to O₁₇ when placed on N₂

Although the complex with N₁₂ is the strongest, the bond length changes are <10 mÅ, some of the smallest perturbations of all.

Table 3 Energetics (kJ/mol) of interaction of BH_3 at various sites of the TMZ molecule at MP2/6-31+G(d,p) level

	E_{rel}	$E_{\text{rel}} + \text{ZPE}$	E_{b}	$E_{\text{b}} + \text{ZPE}$	$R, \text{\AA}$	$\Delta Q, e$
N ₁₂	0.00	0	-101.05	-78.59	1.62	0.320
O ₁₇	22.36	19.72	-78.69	-58.67	1.61	0.265
N ₁	30.90	30.71	-70.15	-47.68	1.61	0.180
N ₁₈	39.17	39.10	-61.88	-39.29	1.73	0.275
N ₂	43.52	42.48	-57.53	-35.41	1.63	0.255
O ₈	69.91	65.04	-31.14	-13.35	1.68	0.199

In a number of cases in the literature, the strength of the interaction has been directly related to the MEP of the molecules of interest. Figure 5 illustrates the MEP

Table 4 Energetics (kJ/mol) of interaction of BH₃ at various sites of the TMZ molecule at B3LYP/6-31+G(d,p) level

	E_{rel}	$E_{\text{rel}} + \text{ZPE}$	E_{b}	$E_{\text{b}} + \text{ZPE}$	$R, \text{\AA}$	$\Delta Q, e$
N ₁₂	0.00	0	-95.68	-79.06	1.65	0.315
O ₁₇	7.69	7.22	-87.99	-71.84	1.65	0.261
N ₁	22.35	22.43	-73.33	-56.62	1.66	0.250
N ₁₈	42.58	44.42	-53.09	-34.63	1.74	0.303
N ₂	43.98	43.07	-51.69	-35.98	1.67	0.247
O ₈	57.62	55.06	-38.05	-23.99	1.76	0.250

surrounding the TMZ molecule; the MEPs of BF₃ and BH₃ are displayed in Fig. 6. The negative regions are red, and the positive areas are blue. The most negative region surrounds O17, followed by O8, and then N2 and N1 and N12. Purely electrostatic attraction to the positive potential above the B atom of BF₃ would thus follow this same

order. However, even though the negative region around N12 is rather weak, this atom still serves as one of the two strongest binding sites for BF₃. And even though there is no negative potential in the vicinity of N18, this atom nevertheless serves as a reasonably strong binding site, surpassed only by O17 and N12. Another example arises with O8; despite a very negative potential surrounding it, O8 offers only weak binding to BF₃. The situation with BH₃ is similarly poorly correlated. N12 is the strongest binding site, but has only a weak negative region around it. And again, despite the absence of a negative potential, N18 represents a strong binding site. It is thus clear that the binding forces are not controlled by electrostatics.

One can thus attempt to rationalize the energetic ordering as a composite of electrostatic attraction and charge transfer effects. This importance of the latter is perhaps best illustrated by comparison of O17 and N12 as binding sites. O17 represents the area with the most

Fig. 4 MP2 equilibrium geometries of complexes of TMZ with BH₃. Intermolecular distances are in $\text{\AA}$. Perturbations of neighboring bond lengths within TMZ are shown in m $\text{\AA}$

Fig. 5 Molecular electrostatic potential surrounding TMZ on surface representing 1.5 times the van der Waals radius of each atom. Blue color indicates a potential of +0.05 au, and red corresponds to -0.05 (Color figure online)

Fig. 6 Molecular electrostatic potential surrounding **a** BF₃ and **b** BH₃ on surface representing 1.5 times the van der Waals radius of each atom. Blue and red colors represent ±0.02 au, respectively, for BF₃ and ±0.01 au for BH₃ (Color figure online)

negative potential surrounding TMZ, whereas N12 lies in a much less negative area. Nonetheless, the similar charge transfer to these two sites of TMZ from BF₃ overrides the MEP effect, and this Lewis acid binds to the two sites with roughly equal binding energy. In the case of BH₃, the charge transfer from the N12 site is larger than that for O17, and the binding energy is similarly greater as well. On the other hand, electrostatics dominate other pairs of binding sites. The more negative MEP around O17 versus O8, N2, N1, or N18 cannot be surpassed by charge transfer considerations. For example, O17 is preferred by BH₃ to N18, even though the charge transfer in the latter case surpasses that of the former.

These results can be placed in the context of similar interactions studied earlier. The stronger BH₃ complexes compared to BF₃ mirrors previous studies [20] on the interaction of these same molecules with pyrimidones. One can

also compare the interactions [19] of TMZ with water. At the same MP2/6-31+G* level, the relevant binding energies span a range from 11 to 40 kJ/mol, weaker than those of the two Lewis acids. Water prefers association with O17, but the OH...O17 H-bond is supplemented by a N₁₈H...O_w HB, so the 40 kJ/mol can be considered a composite of both HBs. Even so, the total binding energy of 40 kJ/mol is smaller than the maximum value for either BH₃ or even BF₃. Indeed, most of the complexes of water with TMZ involve a pair of HBs, which underscores the weakness of each individual HB when compared to BH₃ or BF₃, each of which has only a single N/O...B interaction. The exceptions to this rule concern the interactions of BF₃ at the O17 site where there is a possible auxiliary NH...FHB. Although the $R(\text{H}\cdots\text{F})$ distance is only 1.96 Å, the bond is highly bent, with $\theta(\text{NH}\cdots\text{F}) = 127^\circ$. Another weak NH...F HB occurs in the complex with N12, with $R(\text{H}\cdots\text{F}) = 1.90$ Å and $\theta(\text{NH}\cdots\text{F}) = 154^\circ$. Water's first choice of O17 as a binding site does mirror the two Lewis acids where this site is clearly one of the preferred locations. Lastly, very recent work [30] confirms the considerably stronger interactions of BH₃ as compared to BF₃ when interacting with a Lewis base.

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