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Investigation of proton and sodium Ion affinities of topiramate (anticonvulsant drug) by DFT calculations

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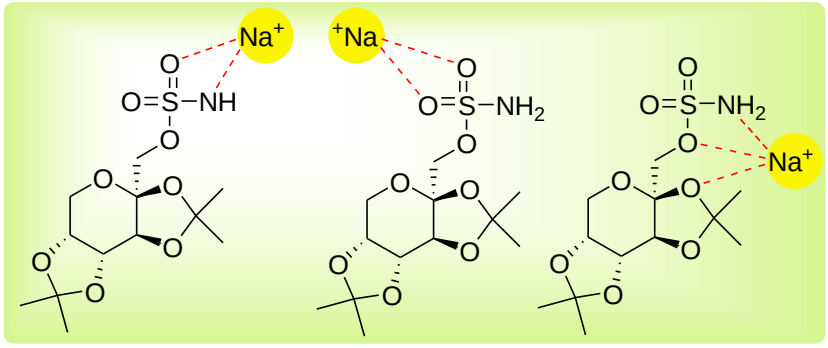
Abstract: In this present study, the proton and sodium ion affinities of topiramate has been investigated by density functional theory calculations. The most basic site for protonation on topiramate is nitrogen atom of sulfamate group. It is interesting that sodium ion affinity of topiramate was determined as 670 kJ mol-1 is less than its proton ion affinity. It was found that during sodiation, topiramate conformation is changed. Because of the limited understanding of the biological molecular mechanism of topiramate, these results might devise a clear understanding of the role of topiramate in blockade of voltage-dependent sodium channels in biological systems.

Keywords: *Topiramate, anticonvulsant drug, DFT calculation, sodium ion affinity, Theoretical chemistry, Sulfamate esters.*

Graphical Abstract



The proton and sodium ion affinities of Topiramate has been investigated by DFT approach. The most basic site for protonation on Topiramate is nitrogen atom of sulfamate group. It is also interesting that sodium ion affinity of Topiramate was determined as 670 kJ mol^{-1} is less than its proton ion affinity. Because of the limited understanding of the biological molecular mechanism of Topiramate, these results might devise a clear understanding of the role of Topiramate in blockade of voltage-dependent sodium channels in biological systems.

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1. Introduction

Epilepsy has been recognized as a neurological disorder, affecting of people. Every year, approximately 0.25 million new cases are added to this population [1, 2]. Anticonvulsant drugs are useful in treating 90% of the epileptic patients [3]. Compounds bearing sulfamate moiety are an important group of compounds in chemistry and biology. They are widely used in the production of pharmaceuticals and sweeteners [4–6]. Topiramate, namely 2,3:4,5-bis-*O*-(1-methylethylidene)-*β*-D-fructopyranose sulfamate (Figure 1), has emerged as newer and promising anticonvulsant drug marketed worldwide for the treatment of epilepsy [7].

Topiramate is structurally unrelated to other antiepileptic drugs and its biological molecular mechanism of action is still unknown [8-11]. This drug acts by multiple neurostabilizing mechanisms. One of them is blockade of voltage-dependent sodium channels [12, 13].

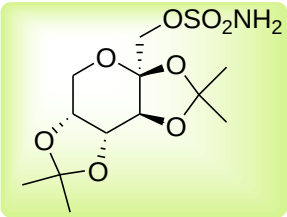


Figure 1. Chemical structure of topiramate.

Topiramate is structurally unrelated to other antiepileptic drugs and its biological molecular mechanism of action is still unknown [8-11]. This drug acts by multiple neurostabilizing mechanisms. One of them is blockade of voltage-dependent sodium channels [12, 13]. Sodium ion, the most important electrolyte, is one of the most abundant metal ions in biological systems. It is involved in a variety of biological processes, including osmotic balance, the stabilization of biomolecular conformations and information transfer *via* ion pumps and ion channels [14-16]. Understanding of topiramate interactions with Na^+ and H^+, and to obtain some information about the intrinsic binding modes of these ions to topiramate, is necessary. The present study addresses this subject by using density functional theory calculations (DFT) calculations.

2. Computational Details

Geometry optimizations and frequency calculations of all species were carried out using the Gaussian 03 program [17]. Density Functional Theory with the Becke three parameters hybrid functional (DFT-B3LYP) calculations were performed with a 6-31G (d) basis set for all atoms. Vibrational frequencies were calculated at the same level to ensure that each stationary point is a real minimum. Harmonic-oscillator approximation was also used for the thermodynamic partition functions. After geometry optimization and frequency calculations, zero-point energies (ZPEs) and thermal corrections are obtained at 298.15 K.

3. Results and discussion

Topiramate structure, was fully optimized in the B3LYP method using 6-31G(d) basis set [18, 19] and then, the most stable conformer is used for proton and sodium ion affinities (see supporting information, Figure 1S). Proton ion affinity for topiramate [PIA (T)] in the gas phase can be defined as the negative value of the enthalpy variation (ΔH) for the process:

$$\text{Topiramate} + H^+ \longrightarrow [\text{TopiramateH}]^+$$

$$\begin{aligned}\mathbf{PIA(T)} &= -\Delta\mathbf{H} = -\Delta\mathbf{E} - \Delta(\mathbf{pv}) = \\ &-\Delta\mathbf{E} - \Delta\mathbf{n}_g\mathbf{RT} = -\Delta\mathbf{E} + \mathbf{RT} = \\ &-\mathbf{E(T{-}H^+)} + \mathbf{E(T)} \\ &+ \mathrm{E(H^+)} + \mathrm{RT} = \\ &-\mathrm{E(T{-}H^+)} + \mathrm{E(T)} + 3/2\mathrm{RT} + \mathrm{RT} = \\ &-\mathrm{E(T{-}H^+)} + \mathrm{E(T)} + 5/2\mathrm{RT}\end{aligned} \quad (1)$$

Like proton ion affinity, sodium ion affinity for topiramate [NaIA (T)] in the gas phase can be assumed:

$$\begin{aligned}\mathrm{NaIA(T)} &= -\Delta\mathrm{H} = -\Delta\mathrm{E} - \Delta(\mathrm{pv}) = \\ &-\mathrm{E(T{-}Na^+)} + \mathrm{E(T)} + \mathrm{E(Na^+)} + \mathrm{RT}\end{aligned} \quad (2)$$

In equations (1) and (2) E is the total energy calculated for the optimized structures of topiramate, protonated and sodiated topiramate at 298.15 K. The 5/2RT term includes the translation energy of proton [20]. Zero point vibrational energies were computed in order to correct all the calculations to 298.15 K.

Three basic sites for protonation were assumed on topiramate structure: the nitrogen atom of amino group (A), the oxygen atom of sugar ring (B, C—O—C) and the oxygen atom of O=S moiety (C). The most stable corresponding protonic structures of protonated topiramate are shown in Figure 2. The isomer A is stabilized by two intramolecular hydrogen bonds between amino group and oxygen atoms of sugar unit. Due to positive charge of nitrogen atom on amino group, these intramolecular hydrogen bonds in A, are more strong than the others. The proton ion affinity (P*IA*) and the proton ion affinity difference (ΔP*IA*) between these species are given in Table 1. The results show that among the three basic sites, the amino group has the greatest P*IA*. The proton ion affinity of the NH_2 group is estimated to be 27 kJ mol^{-1} and 57 kJ mol^{-1} higher than of oxygen atoms of sugar ring and O=S, respectively at the B3LYP/6-31G(d) level.

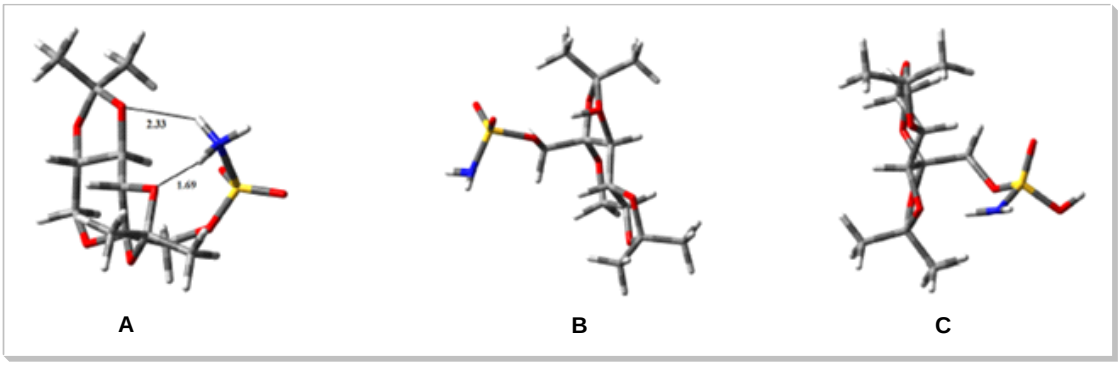
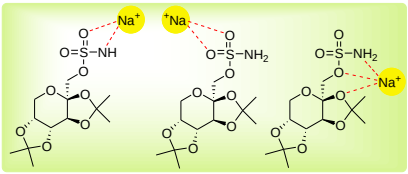


Figure 2. Optimized protonated isomers of topiramate at B3LYP/6-31G(d) level (distances are in Å).

Table 1. *PIA* and ΔP*IA* of optimized protonated isomers of topiramate determined in kJ mol^{-1}.

P*IA*(**A**)	P*IA*(**B**)	P*IA*(**C**)	ΔP*IA*(**A-B**))	ΔP*IA*(**A-C**)
919	892	862	27	57

In the next step, calculations were performed for topiramate complexes corresponding to the position known as the active sites for the interaction of sodium ion. As seen in Scheme 1, in principle, sodium ion can interact with topiramate at different positions: (1) on a nitrogen of amine, oxygen atom of O=S, oxygen atoms of sugar ring; (2) on combination of 1, 2 and 3 situations as a tri-coordinated or bi-coordinated ligand (see supporting information, Figure 3S). The optimized structures of some sodiated conformers of topiramate are given in Figure 4S of supporting information.

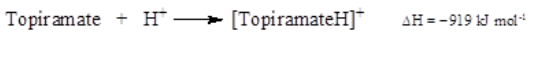


Scheme 1. Some of the initial structures used for complexation of topiramate with sodium ion.

The results of calculations show that during metalation, the topiramate conformation is changed significantly. As can be seen from Figure 3, the tri-coordinated complex, is the most stable sodiated conformer of topiramate, in which the sodium has attractive electrostatic interactions with the oxygen atoms of sugar ring and O=S group. Sodium ion affinity for topiramate [Na*IA* (T)] in the gas phase using the equation (2) for the most stable conformer was calculated to be 249 kJ mol^{-1} at the B3LYP/6-31G(d).

4. Conclusion

The amino group has been confirmed to be the most favorable protonation site of topiramate in the gas phase. On the other hand, comparing the calculated ΔH of the reactions:



Indicating that the protonation of topiramate is more exothermic than the sodinization (670 kJ mol^{-1}).

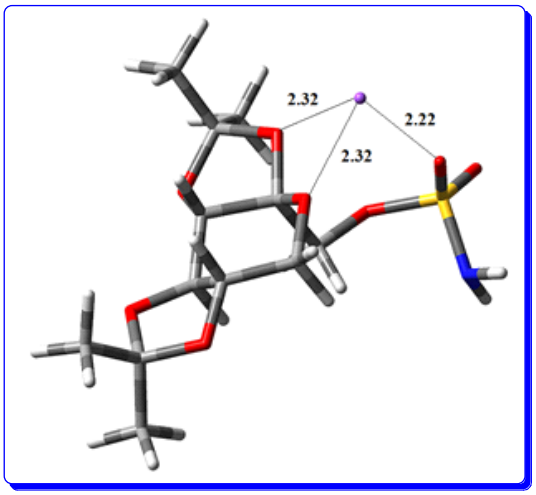


Figure 3. Optimized structure and main geometrical parameters of the most stable conformer of sodiated topiramate at the B3LYP/6-31G(d) level (distances are in Å).

Difference in energies between H^+ and Na^+ reflect the fact that the sodium ion has electrons and hence its positive charge is spread over space while H^+ is a point charge and the positive charge is not spread out at all. These two, therefore, bind with very different energies. DFT calculation results, for the gas phase, can be used as a guideline for the condensed phase and it might devise a clear understanding of the role of topiramate in blockade of voltage-dependent sodium channels in biological systems.

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