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Carbonic anhydrase inhibitors: A quantum mechanical study of interaction between some antiepileptic drugs with active center of carbonic anhydrase enzyme

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ABSTRACT

Density functional theory (DFT) using B3LYP and split-valance 6-31G* basis set have been employed to calculate the details of electronic structure and electronic energy of carbonic anhydrase enzyme active center (CA), six inhibitors of this enzyme including topiramate and its derivatives and its analogue, and complex between these inhibitors and active center of carbonic anhydrase. Also thermodynamic functions such as deprotonation enthalpy of inhibitors, standard enthalpies of formation (ΔH_f°), standard entropy of formation (ΔS_f°) and standard Gibbs free energy of formation (ΔG_f°) for six CA–inhibitor complexes are evaluated. The calculated results indicate that deprotonated inhibitors are coordinated to the Zn^{2+} ion and all the complexes have tetrahedral geometry. According to the calculated thermodynamic functions substitution of sulfonamide group with hydroxyl reduces the tendency of inhibitor to bind to the active center of carbonic anhydrase. In all calculations solvent effects have been considered in water using SCRF method.

1. Introduction

The carbonic anhydrase (CAs, EC 4.2.1.1) comprise a family of ubiquitous zinc metalloenzymes widespread in the bacterial, plants, animal and man [1–3]. These enzymes catalyze a very simple physiological reaction, the interconversion between carbon dioxide and the bicarbonate ion, and are thus involved in crucial physiological processes connected with respiration and transport of CO_2/bicarbonate between metabolizing tissues and lungs [4–8]. All known isozymes of carbonic anhydrase contain a single Zn^{2+} ion which is essential for catalytic activity. The zinc ion is located at the bottom of a deep, conical cavity, tetrahedrally coordinated to three histidine residues via their imidazole nitrogens. The fourth position occupied by a water molecule at an acidic pH (<7), which is catalytically inactive, and by a hydroxyl ion at the higher pH, via proton-transfer reaction from water bound to Zn(II) within the enzyme active site to the external medium [4–8], Fig. 1. One main class of CA inhibitors (CAIs) is known as the metal complexing anions which bind to the Zn(II) ion of the enzyme by substituting the non-protein zinc ligand, Eq. (1), generating tetrahedral geometry of the Zn(II) ion. Thus, the CA–inhibitor interaction constitutes the initial stage of the mechanism of inhibitors action.

$$[\mathrm{E{-}Zn{-}OH_2}]^{+2} + \mathrm{I}^-(\text{inhibitor anion}) \leftrightarrow [\mathrm{E{-}Zn{-}I}]^+ + \mathrm{H_2O} \quad (\text{substitution, tetrahedral adduct}) \tag{1}$$

The most potent inhibitors used in applications still present a primary sulfonamide group on a benzenoic or heterocyclic structure with anticonvulsant, antiurolithic, antiglaucoma, and anticancer properties [9,10] that binds to the zinc ion through the deprotonated nitrogen atom [7–10]. However, despite the availability of several drugs, only 75% of the epileptic population significantly benefits from current pharmacotherapy. Thus, the search for less toxic, more efficacious agents for the treatment of seizure disorders has been a continuing end over. In the present study we use the quantum mechanical calculations to investigate on the binding of six inhibitors with anticonvulsant activity to active site of CA enzyme, Fig. 2. These compounds are a monosaccharide derivative and contain sulfonamide, carboxamide and hydroxide functionality. The antiepileptic drug topiramate [11–14], compound **1**, and its derivatives, compounds 2 and **3**, and its sulfamide analogue, compound **4** are sulfamate substituted monosaccharide, marketed worldwide for the treatment of epilepsy [15] and prophylaxis of migraine [16]. These results may bring novel insights to design of carbonic anhydrase inhibitors (CAIs).

Previous calculations for the interaction between inhibitors and the active site of CA have been performed employing molecular dynamics simulations [17–23]. Due to the advances in computational processing power in the last few years, more refined techniques have become available, and DFT methods have been established as one of the main methods for calculation on different compounds. With this goal, we study the interaction between the active site of CA enzyme and the six inhibitors by means of density functional theory calculations thermodynamically. Interaction

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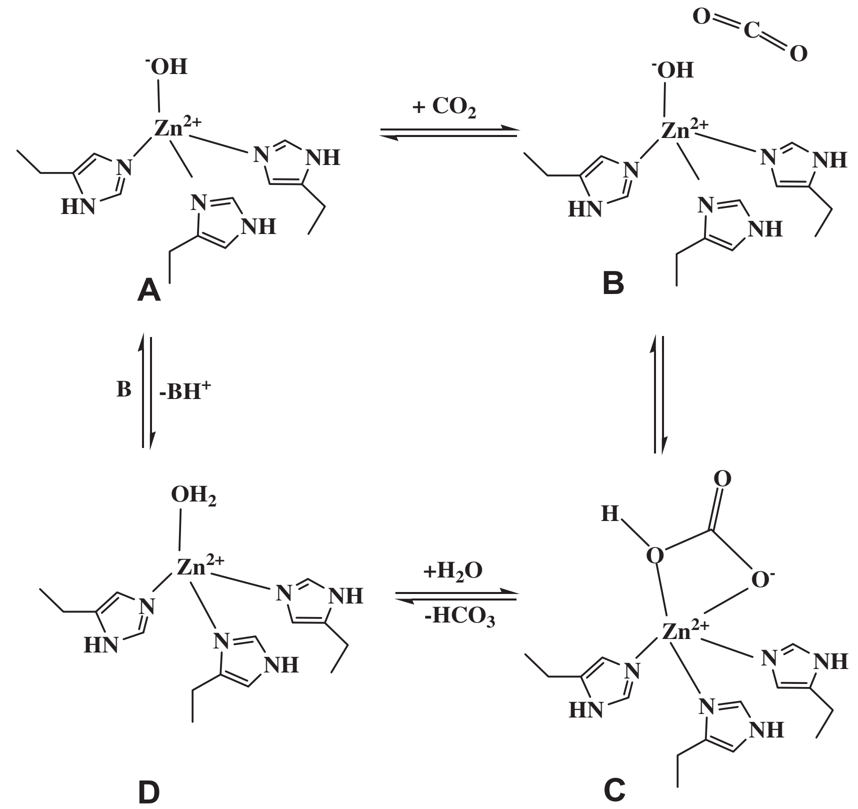

Fig. 1. Schematic representation of the catalytic mechanism for the CA active center catalyzed CO_2 hydration.

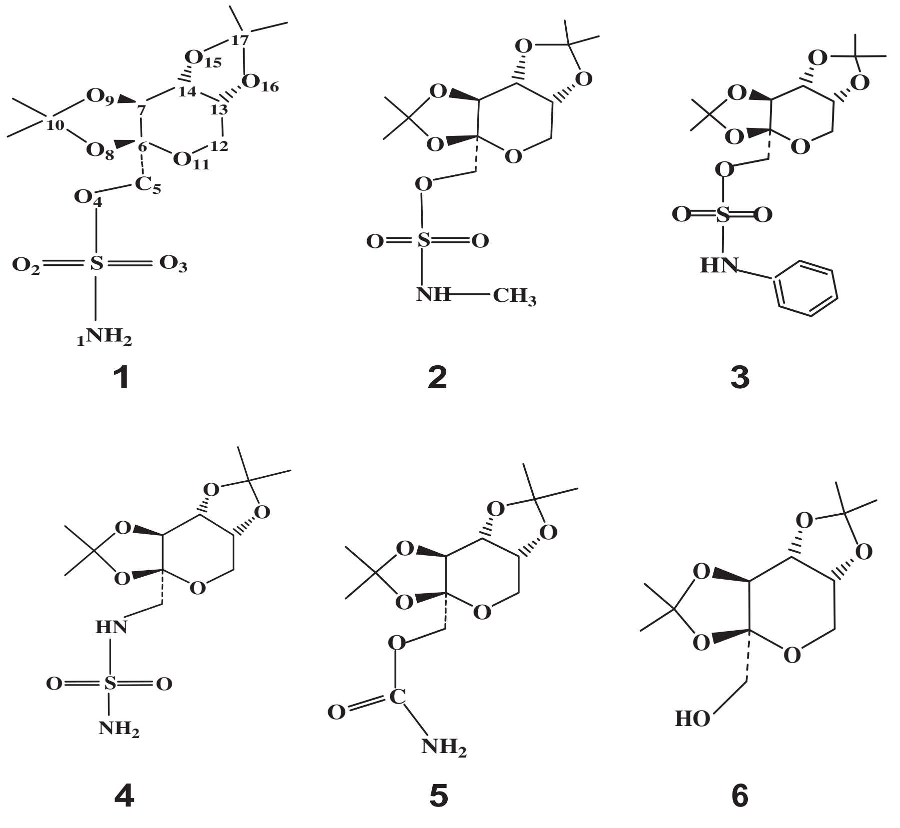

Fig. 2. Chemical structure of compounds **1**–**6**.