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Thermodynamic study of proton transfer in carbonic anhydrase/activator complex: A quantum mechanical approach

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ABSTRACT

Activation mechanism of human carbonic anhydrase (hCA) isoform II, with L-histidine and histamine has been investigated by using quantum mechanical calculations. Two methods including B3LYP/6-31G* and B3PW91/def2-SVP have been employed to calculate the details of electronic structure and electronic energy of active and inactive forms of carbonic anhydrase enzyme active center, isoform II (CA). Two activators of this enzyme including histamine and L-histidine and complex between these activators and active center of carbonic anhdrase have been investigated. Also thermodynamic functions for the total reaction and for the complexation between activators and CA are evaluated. The calculated results indicate that protonatable moiety of histidine and histamine molecules participate in proton transfer from zinc-bound water molecule and lead to formation of the catalytically active species of CA enzyme, hydroxide coordinated to the zinc ion. In all calculations, solvent effects have been considered in water using PCM method.

1. Introduction

Proton transport is an important event in many biological processes that are influenced by environmental electrostatic charges [1–3]. One class of biological enzymes that facilitate the proton transport is carbonic anhydrase (CA) family. The carbonic anhydrase (CA, EC 4.2.1.1) belong to a family of zinc metalloenzymes that catalyze the reversible conversion of carbon dioxide to bicarbonate, Scheme 1. Bicarbonate is then replaced by a water molecule to generate the catalytically inactive form of this enzyme, EZn^{2+}–OH_2 [4–8].

To regenerate the catalytically active form of this enzyme, a proton transfer from water molecule bounded to Zn^{2+} in the enzyme active center to the external medium must occur, the following equation:

$$EZn^{2+} - OH_2 \leftrightarrow EZn^{2+} - OH^- + H^+ \quad (1)$$

The results of previous studies by Supuran group [9] show that in the presence of activator, the enzyme/activator complex forms and the activator participates in proton transfer process which is the rate determining step in the catalytic cycle, Eq. (2) [10–13].

$$EZn^{2+} - OH_2 + \text{Activator(Ac)} \leftrightarrow [EZn^{2+} - OH_2 \ldots Ac)] \leftrightarrow EZn^{2+} - OH^- + AcH^+ \quad (2)$$

$[EZn^{2+} - OH_2 \ldots Ac)]$: Enzyme/activator complex

Unlike CA inhibitors, which have been studied extensively [14–21], activators of CAs have been less investigated. Previous experimental results indicate that amins, amino acids, their derivatives and oligopeptides act as suitable activators for many isoforms of the human carbonic anhydrase [22–33]. In addition, some pharmacological studies present the potential of activators as compounds to enhance memory or to control the Alzheimer disease [34].

The results of recent studies showed that histamine (hst) and L-histidine (L-his), Fig. 1, act as efficient activators of human carbonic anhydrase (II) [12,13,23,39]. Besides the large amount of experimental work, a few theoretical studies on CA activators have been reported [35–38]. Due to the advances in computational processing power in the last few years, more techniques that are refined 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 complexation of these two activators to the active site of CA enzyme from different positions thermodynamically and compare our results with experimental data to confirm the accuracy of level of calculations. Interaction energies, electronic states and thermodynamic functions such as standard enthalpy of complexation (ΔH°_{com}) and the standard Gibbs free energy of complexation (ΔG°_{com}) for two CA/activator complexes have been determined according to reaction 2. Also all thermodynamic functions, ΔH°_{rxn}, ΔG°_{rxn} and ΔS°_{com}, for the total reaction are evaluated. Determination of the energies and relative orientations

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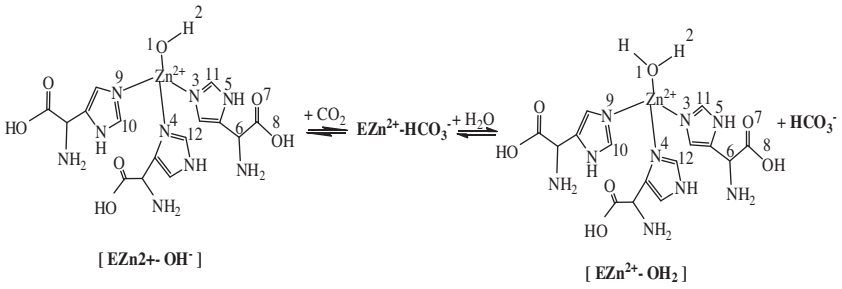

Scheme 1. Schematic representation of the catalytic mechanism for the CA catalyzed CO_2 hydration.

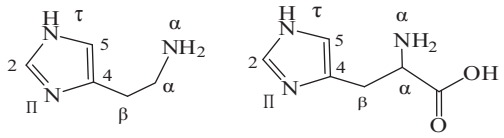

Fig. 1. Chemical structure of histamine and L-histidine with the numbering system shown.

of the active site of CA and activators in CA-activator complex using high-level calculations will contribute to advance our knowledge on the mechanism of activator action. These results may bring novel insights to design new carbonic anhydrase activators (CAAs).

2. Computational details

2.1. Ab initio calculations

All calculations were performed using the Gaussian 98 [40] software. The geometries of active and inactive form of the carbonic anhydrase enzyme active site (CA), activators and their protonated form (AcH^+), the complex between activators and CA from different positions were fully optimized using DFT method [41] with B3LYP and B3PW91 functional [42] with no symmetry constrains. The calculations were performed with standard 6-31G*

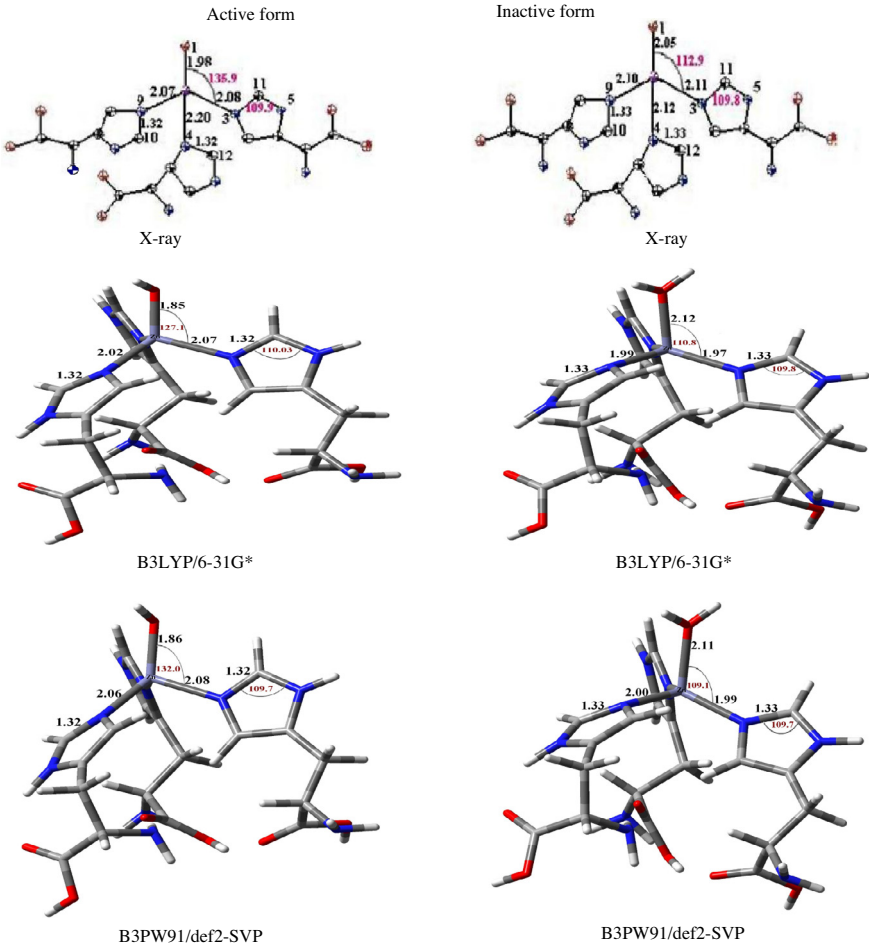

Fig. 2. Comparison between X-ray and optimized structure of the carbonic anhydrase active center enzyme in the water solvent in active form (left) and inactive form (right) by using B3LYP/6-31G* and 3PW91/def2-SVP methods.