

## QM/MM Study on the Mechanism of Aminophenol Oxidation by Functionalized $\beta$ -Cyclodextrin as Oxidase Nanomimic

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*(Received 1 February 2016, Accepted 14 May 2016)*

In this study, functionalized  $\beta$ -cyclodextrin ( $\beta$ -CD) by aldehyde group was investigated as an oxidase enzyme mimic for the amino phenol oxidation. All calculations were performed by GAUSSIAN 09 package using two layers ONIOM method at the ONIOM (MPW1PW91/6-311++G(d,p)/UFF) level. In the first step,  $H_2O_2$  is encapsulated in the hydrophobic cavity. In the second step,  $H_2O_2$  molecule oxidized the aldehyde group of the functionalized  $\beta$ -CD, through the wide edge of  $\beta$ -CD. This step is the *Rate Determining Step* (RDS) with the activation energy of  $54.4 \text{ kcal mol}^{-1}$ . Natural population analysis has been performed for calculation of the global electron density transfer of the atoms involved at the center of the reaction. In order to have a knowledge of the intermolecular interactions, HOMO-LUMO analysis has been done and showed a reduction in the chemical hardness during the reaction. Topological analysis of the structures at the RDS confirmed that the ratio of the potential to the kinetic energy density for the O-O bond at the transition state is covalent in nature.

**Keywords:**  $\beta$ -Cyclodextrin, Aminophenol, Oxidase enzyme, Nanomimic, Hydrogen peroxide, Quinine imine, Biocatalyst

### INTRODUCTION

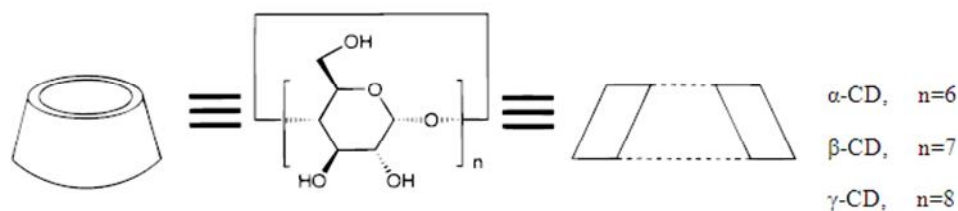
Cyclodextrins with nano dimensions are a set of the oligosaccharides which are produced in the industrial scale and high purity by enzyme modification (cyclodextrin glycosyltransferase) of starch (corn, potato, rice and the other resources) [1-3]. Cyclodextrins have a conical structure, including glucose units by  $\alpha$ -1,4-glucoopyranose-linked. Generally, there are 3-16 glucose units in the cyclodextrin structures [4-8].  $\alpha$ -Cyclodextrin (cyclohexaamylose),  $\beta$ -cyclodextrin (cycloheptaamylose) and  $\gamma$ -cyclodextrin (cyclooctaamylose) are three main types of cyclodextrins which are reported as the mostly applied cyclodextrins [9].

Cyclodextrins have two rims of hydroxyl groups (Fig. 1.) in which hydrogen atoms of the hydroxyl groups are replaced by different functional groups. Also cyclodextrins have a narrow and a wide entrance, therefore they include

internal and external cavity. Internal cavity is hydrophobic while the external cavity is hydrophilic. Due to the existence of the hydrophobic cavity in the cyclodextrins, they are able to form the inclusion complex. This ability in the presence of the organic host molecules makes it possible to form supramolecular threads. In this way molecular architectures such as catenanes, rotaxanes, polyrotaxanes, and tubes, can be constructed [10-14].  $\beta$ -Cyclodextrins have been considered by researchers more than  $\alpha$  and  $\gamma$  structures, because of a lower price, more fitness with human body and easier reactions.

Cyclodextrins have been studied widely as the biomimetic catalysts, and several superior reviews have been published [15-23]. For example, the aerobic oxidation of alcohols was presented in a one-pot biomimetic approach using recyclable ruthenium on charcoal and randomly methylated  $\beta$ -cyclodextrin in the water under the neutral conditions without loss of activity [15]. Singleton and coworkers reported that  $\beta$ -CD is able to provide a first generation of the artificial protein environment for a small

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**Fig. 1.** Various representations of the cyclodextrins, including  $\alpha$ ,  $\beta$  and  $\gamma$ -CD.

molecule model of the [FeFe]-hydrogenase enzyme active site. Through the synthetic modification of the host and guest parts of the system, they concluded that  $H^+$  reduction or  $H_2$  oxidation is possible [16]. In an experimental work by S. Manuel *et al.*, the complexation properties of three novel cyclodextrin tripods bearing three ureido-bipyridyl tethers on the cyclodextrin upper rim, towards the Eu(III), Tb(III) cations and Cu(II), Co(II) cations were studied in solution [24]. Based on the obtained results, they proposed that by using the new CD derivative with adjusted chelating and amphiphilic properties, new nano-surfaces designing with specific applications such as the actuator or sensor are possible. There are also computational studies on the CDs in the literature. In a molecular dynamic simulation and QM/MM study by Larget group, the guest molecule of *p*-nitrochlorobenzene has been chosen for investigation of the significant polarization effects in  $\beta$ -CD substrate. They found that the polarization effects are consistent with an effective dielectric constant in the range of 3-8 which was consistent with some experiments [25]. Finally, they predicted that the role of specific host-guest and water-guest interactions is important.

Based on the published researches on the CDs, there are famous methods for modifying the hydroxyl groups and hydrophobic guest molecules which interact with the hydrophobic cavity of the cyclodextrin [26].

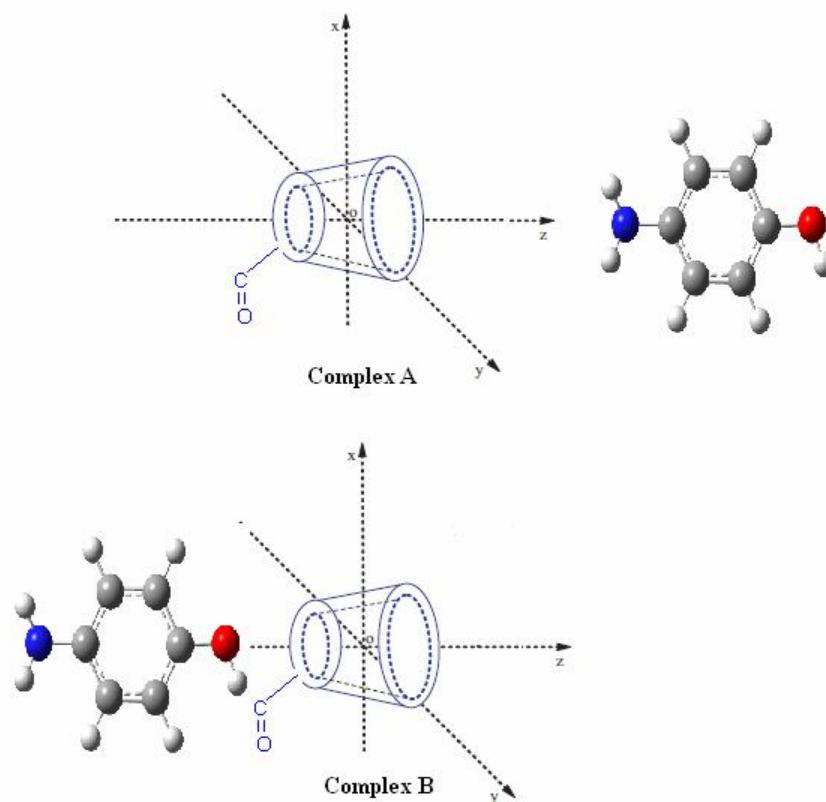
Nowadays, kinetics and mechanism of the cyclodextrin reactions, especially from the industrial application viewpoint, is of interest. Also, the designing of the enzyme mimics is very important, because of the ability to tolerate different functional groups on the carbon skeleton. We know that some functional groups such as aldehyde can convert the cyclodextrin to an oxidase enzyme nano-mimic which increases the rate of the chemical reactions similar to

enzymatic reactions. Therefore functionalized  $\beta$ -cyclodextrin as oxidase enzyme mimic in the aminophenol oxidation has been chosen as the biocatalyst due to its importance from the electrochemical aspects. Phenols such as aminophenol are important because they are involved in the biological and industrial reactions. These compounds are the members of a large group of vitamins, food antioxidants and hormones [27]. Hence, in this project, the mechanism and the kinetics of the aminophenol conversion to quinine imine have been investigated by using both of the quantum mechanics and the classical mechanics calculations.

The purpose of this research was to simplify the study of the enzyme kinetics by using Our own N-layered Integrated molecular Orbital and molecular Mechanics (ONIOM) methods [28-29]. In this study, the catalytic studies of the  $\beta$ -cyclodextrin with one aldehyde group attached to the primary face has been reported. Cyclodextrin aldehyde is able to catalyze the oxidation of aminophenol to quinine imine in a process that follows Michaelis-Menten kinetics in most cases. Quinine imine subsequently leaves the cyclodextrin and undergoes further reactions (oxidation and/or condensations). Therefore, the changed  $\beta$ -CD can be used as an oxidase mimic in electrochemical processes.

## COMPUTATIONAL METHODS

The starting geometry of the  $\beta$ -cyclodextrin was taken from Chemoffice 3D ultra (version 10, Cambridge software), and functionalized by aldehyde group. The structure of the  $H_2O_2$  and aminophenol were constructed using Gaussview 05 [30]. Density functional theory (DFT) and ONIOM2 calculations have been carried out at the MPW1PW91/6 -311++G(d,p)/UFF level using the Gaussian

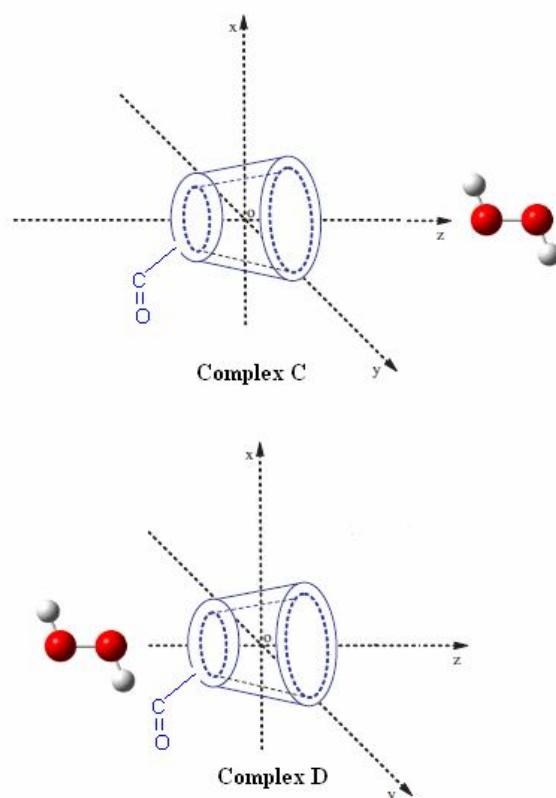


**Fig. 2.** The positions of amino phenol relative to the functionalized  $\beta$ -CD, wider rim of the  $\beta$ -CD “A complex”, and smaller rim of the  $\beta$ -CD “B complex”.

09 package. QM/MM procedure is applied when a full quantum chemistry description of the system is not possible, mainly because of the numerous atoms and computational costs. In QM/MM method, the large system of interest is divided into two or three parts. The larger part, which is not directly involved with the chemical reaction, is treated at a low cost level of the theory, such as MM. The smaller part where the chemical reaction occurs is treated with a more accurate level of the theory, such as QM, with a higher computational cost. In three-layer ONIOM models, middle model system affects the first layer by important electronic effects which were not important in our model, because of the equality of the molecular structure of the  $\beta$ -CD. Therefore 2-layer model has been considered in this project. Quantum mechanics regions of the reactants, transition states (TSs) and products were fully optimized with the 6-311++G(d,p) basis set. Frequency calculations were used to

confirm the nature of the stationary points. Thermodynamic and kinetic parameters such as the activation Gibbs free energy and entropy were calculated in the gas phase at 298.15 K. The synchronous transit-guided quasi-Newton (STQN) method as implemented by Schlegel et al. was used to locate the TSs [31]. Intrinsic reaction coordinate analysis was done to confirm that the transition structures connect the reactants and products, properly.

The following initial steric conditions were applied for docking of amino phenol into the  $\beta$ -CD cavity. The glycoside oxygen atoms of the cyclodextrin molecule were placed onto the XY plane and their center was defined as the center of the coordinates system. Two possible orientations of the guest molecule in the complex were considered. For simplicity, the orientation in which amino phenol molecule points toward wider rim of  $\beta$ -CD was called “A complex”, and the other orientation, in which

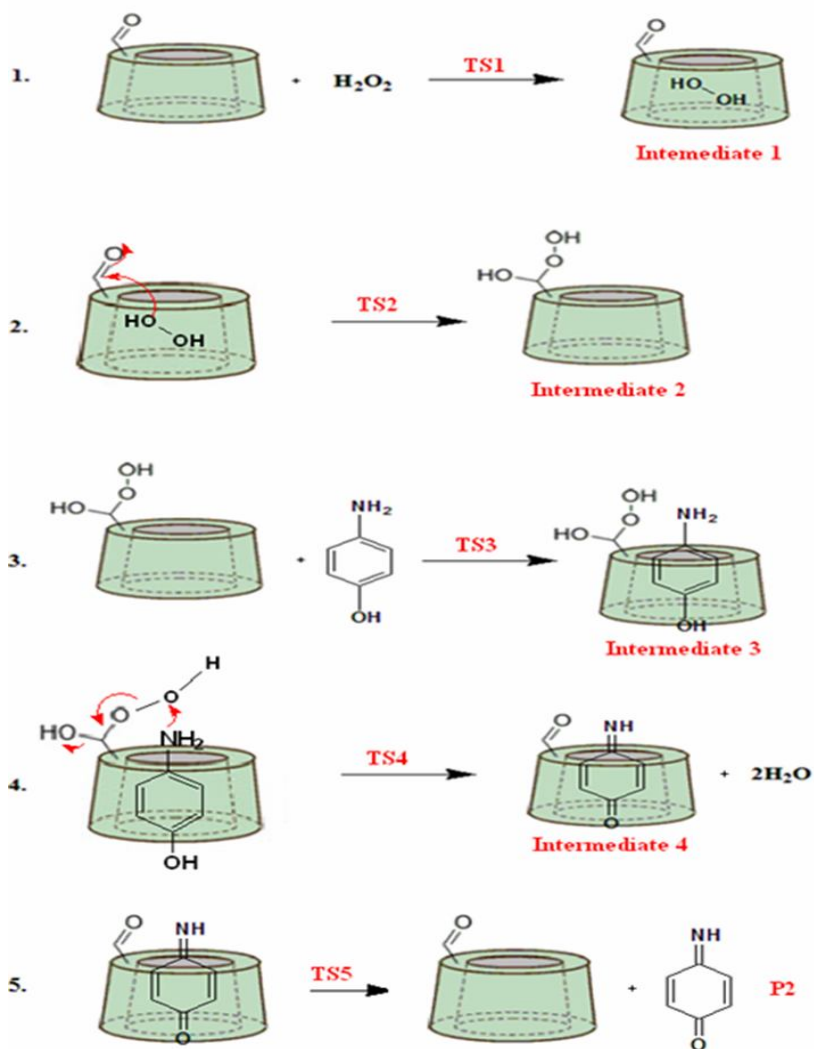


**Fig. 3.** The position of  $\text{H}_2\text{O}_2$  molecule relative to the functionalized  $\beta$ -CD through the wider and smaller rim.

amino phenol molecule points toward the smaller rim of the  $\beta$ -CD was called ‘‘B complex’’, (see Fig. 2). Also, two possible orientations of  $\text{H}_2\text{O}_2$  molecule in the complex were considered, the orientation in which  $\text{H}_2\text{O}_2$  molecule points toward the wider rim of the  $\beta$ -CD was called ‘‘C complex’’, and the other orientation, in which  $\text{H}_2\text{O}_2$  molecule points toward the smaller rim of the  $\beta$ -CD was called ‘‘D complex’’, (see Fig. 3). The guest molecule was moved into the  $\beta$ -CD cavity along the Z-axis from  $-8 \text{ \AA}$  to  $+8 \text{ \AA}$  with a step of  $1 \text{ \AA}$ . The generated structures at each step were optimized by using the ONIOM methods at the MPW1PW91/6-311++G(d,p)/UFF level.

Electronic population, global electron density transfer (GEDT), electronic charge distribution on the atoms at the center of the reaction were investigated using the natural bond orbital analysis (NBO) in the gas phase [32-34]. Topological properties of the hydrogen bonds (HBs) in the studied complexes of the reactants and transition states (TS)

were characterized by using the quantum theory of atoms in molecules (QTAIM) with the AIM 2000 package [35]. The points lying between the bonded atoms are named bond critical points (BCPs). The BCP is a minimum of  $\rho(r)$  along the bond path and a maximum in the interatomic surface. Local properties at the BCPs provide valuable information about the molecular structure. The important element in this regard is the Laplacian of the density  $\nabla^2\rho(r)$ . Commonly, the  $\nabla^2\rho$  identifies whether the charge of the region is locally depleted ( $\nabla^2\rho > 0$ ) or concentrated ( $\nabla^2\rho < 0$ ). The former is typically associated with interactions between the closed-shell systems (ionic bonds, hydrogen bonds ...), whereas the latter characterizes the covalent bonds, where the electron density concentrates on the internuclear region. The corresponding wave functions have been generated from the ONIOM (MPW1PW91/6-311++G(d,p):UFF) calculations in Gaussian 09.



Scheme 1. Probable mechanism of *para*-aminophenol oxidation by oxidase nanomimic ( $\beta$ -CD)

## RESULTS AND DISCUSSION

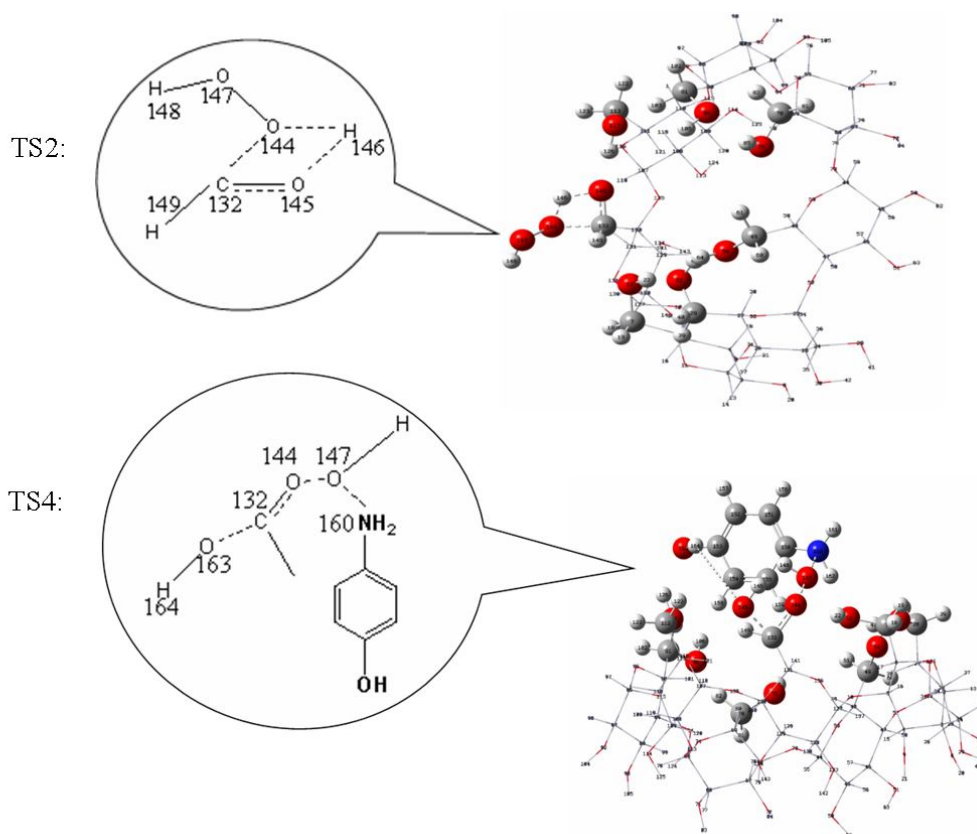
### Reaction Mechanism

The oxidation of *para*-aminophenol inside the cavity of the functionalized  $\beta$ -CD has been shown in Scheme 1, in the presence of hydrogen peroxide. This proposed mechanism is composed of five continuous steps in which different bond making and breaking have been taken place. In the first step,  $\text{H}_2\text{O}_2$  is encapsulated in the hydrophobic cavity through the wide entrance of the  $\beta$ -CD. The oxidation of the aldehyde group of the functionalized  $\beta$ -CD by  $\text{H}_2\text{O}_2$  occurred in the second step. The third step is initiated by

encapsulation of the aminophenol in the hydrophobic cavity of the changed  $\beta$ -CD through the wide edge of the  $\beta$ -CD. In the next step, aminophenol molecule reacts with the peroxide group on the  $\beta$ -CD, yielding quinine imine as the final product along with two water molecules. Finally, the quinine imine comes out the cavity and the  $\beta$ -CD is obtained.

### Structural Analysis

After optimization of the reactants and the products in each step, the corresponding transition states were obtained and reoptimized to the saddle points. TS structures of the



**Fig. 4.** Optimized structures of the transition states in steps 2 and 4 of the proposed mechanism. (See Fig. S1 for clearer atom numbering)

steps 2 and 4 of the proposed mechanism with atoms numbering were depicted in Fig. 4. During the TS2, O145-H146, C132-O144 and O144-H146 bonds are formed, yielding the intermediate 2. Analyzing the bond lengths for the broken and forming bonds at the TS2, it is confirmed that O145-H146 bond formation is faster than O144-H146 bond cleavage. This behavior is according to the asynchronous concerted mechanism.

At the TS4, H164-O145, C132-O144 and O147-N160 bonds are formed, yielding the intermediate 4, followed by the final product formation. According to Table 1, H164-O145 bond formation is faster than C132-O145 bond cleavage, confirming that this step of the reaction proceeds through the asynchronous concerted path.

### Energy Analysis

Computed activation parameters such as the Gibbs free

energy and entropy for each step of the proposed mechanism were reported in Table 2. In the first step, H<sub>2</sub>O<sub>2</sub> molecule is encapsulated in the hydrophobic cavity. Two paths were considered for H<sub>2</sub>O<sub>2</sub> entering into the  $\beta$ -CD. These paths are possible through the narrow or the wide entrance of the  $\beta$ -CD. Calculated activation Gibbs free energy ( $\Delta G^\ddagger$ ) were 5.8 and 4.2 kcal mol<sup>-1</sup> through the narrow and the wide entrance of the  $\beta$ -CD, respectively. Accordingly, H<sub>2</sub>O<sub>2</sub> passing through the wide entrance is more favorable than the narrow one. In the second step, the aldehyde group on the  $\beta$ -CD is oxidized by H<sub>2</sub>O<sub>2</sub> molecule. This step is the RDS of the overall reaction which has an activation energy of 54.4 kcal mol<sup>-1</sup>, which is greater than the corresponding systems studied by the experimental methods. This discrepancy is mainly related to the applied QM/MM procedure and solvent effects on the reaction.

Also, two routes, wide and narrow entrance, were

**Table 1.** Geometrical Parameters of the Reactant, TS2, TS4 and the Product in the Gas Phase (Bond Length are in Å)

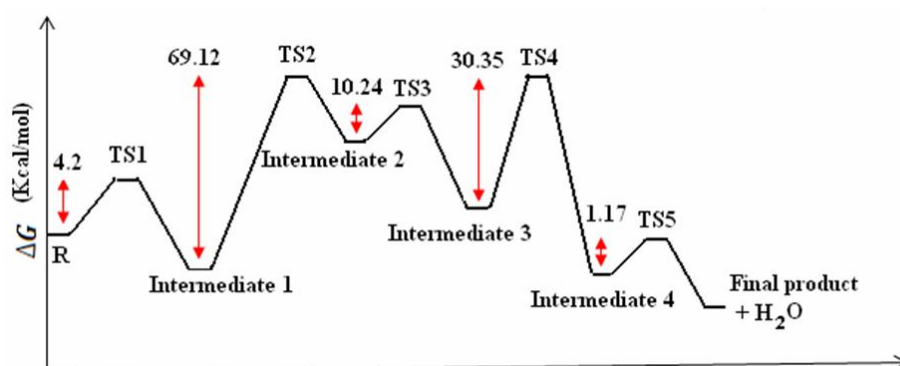
	Reactant	TS2	TS4	Product
C132-O145	1.20	1.34	-	1.39
O145-H146	6.68	1.34	-	0.96
C132-O144	5.28	1.81	-	1.44
O144-H146	0.96	1.19	-	2.49
O147-O144	1.43	1.49	-	1.43
O147-H148	0.98	1.00	-	0.96
O163-H164	0.96	-	3.22	7.27
H164-O145	8.68	-	1.29	0.97
O145-C132	1.38	-	5.85	3.37
C132-O144	1.44	-	1.21	1.44
O144-O147	1.42	-	5.46	4.82
O147-N160	5.17	-	1.41	1.14

**Table 2.** Activation Parameters for the Reaction at 298.15 K in the Gas Phase

	Entrance	$\Delta G^\ddagger$ (kcal mol <sup>-1</sup> )	$\Delta S^\ddagger$ (cal mol <sup>-1</sup> K <sup>-1</sup> )
Step1	Narrow	5.8	-26.2
	Wide	4.2	-18.3
Step2	-	69.1	-41.4
Step3	Narrow	49.5	-
	Wide	10.2	-
Step4	-	30.3	-18.9
Step5	Narrow	7.7	17.3
	Wide	1.2	11.4

considered for the encapsulation of the aminophenol in the  $\beta$ -CD. Analyzing the activation Gibbs free energy through the studied routes shows that the amino phenol passing through the wide entrance is more favorable than the narrow

one. In the next step, the encapsulated aminophenol reacts with the  $\beta$ -CD, yielding quinine imine as the final product (P). Scheme 2 shows the potential energy diagram in which TS2 is on the highest saddle point through which the overall



Scheme 2. The potential energy diagram for the proposed oxidation reaction of aminophenol by the  $\beta$ -CD as the oxidase enzyme mimic

**Table 3.** Atomic Natural Charges (in e) of the Atoms Involved in the Center of the Reaction

	O145	C132	H146	O144
Reactants	-0.505	0.435	0.457	-0.440
TS	-0.824	0.403	0.526	-0.409

**Table 4.** Significant Natural Bond Orbital Interactions of the Reactant and the TS in the Gas Phase and their Second-order Perturbation Stabilization Energies E(2) (kcal mol<sup>-1</sup>)

R	E(2)	TS	E(2)
Lp O 145 $\rightarrow$ RY* C 132	13.7	Lp O 145 $\rightarrow$ $\sigma^*$ O 144 - H 146	86
Lp O 145 $\rightarrow$ $\sigma^*$ C 131- C 132	19.8	Lp O 145 $\rightarrow$ $\sigma^*$ C 132 - O 144	52.1
Lp O 145 $\rightarrow$ $\sigma^*$ C 132 - H 149	23.3	Lp O 145 $\rightarrow$ $\sigma^*$ O 144 - H 146	12.7
Total	56.8	Total	150.8

reaction rate is controlled.

### NBO and QTAIM Analysis

Atomic charge distribution on the reactants and the TSs were calculated by NBO method and reported in Table 3.

The electronic charge of H146 is reduced about 0.03 e and the electronic charge of O145 is increased, 0.32 e, at the TS2, which shows electronic charge transfer from the H146 to O145 during the TS formation. There is a similar behavior for O144 and C132 atoms confirming the global



**Table 5.** Electron Density,  $\rho$ , Laplacian,  $\nabla^2\rho$ , and  $-V/G$  Ratio at the Bond Critical Points for the TS2

(BCP)		Reactant	TS
C132-O144	$\rho$	0	0.104
	$\nabla^2\rho$	0	0.121
	$-V/G$	0	1.561
O145-H146	$\rho$	0	0.246
	$\nabla^2\rho$	0	0.116
	$-V/G$	0	1.831
O144-H146	$\rho$	0.372	0.182
	$\nabla^2\rho$	-2.645	-0.470
	$-V/G$	11.75	3.490

**Table 6.** Calculated Quantum Reactivity Indices in the Gas Phase

Structure	Chemical hardness $\eta$ (a.u.)	Electronic chemical potential $\mu$ (a.u.)	Electrophilicity $\omega$ (a.u.)
Reactant	0.15	-0.25	0.20
TS	1.99	0.99	-0.24

electron density transfer (GEDT) from O144 to C132.

The effective interaction at the TS2, by considering the Table 4, is related to the interaction of  $H_2O_2$  molecule with the  $\beta$ -CD. The difference in total stabilization energies of the reactants and TS2 is 94 kcal mol<sup>-1</sup>, showing an increment in the stabilization interactions at the TS2.

Electron densities ( $\rho$ ), Laplacian and the potential energy density to the kinetic energy density ratios for the bonds at the center of the reaction, were calculated by the QTAIM. According to Table 5, the electron densities of the C132-O144 and O145-H146 bonds were increased at the TS2 while O144-H146 bond was weakened. These changes in the electron density confirm the C132-O144 and O145-H146 bond formation and O144-H146 bond cleavage.

In order to have an estimation of the bonds nature at the TS2, the electron density of the fluctuated bonds have been analyzed. Calculated  $-V/G$  ratios of 1.56, 1.83 and 3.49 for the critical bonds of C132-O144, O145-H146, O144-H146, respectively, confirm the covalent nature of these bonds at the TS2.

### HOMO-LUMO Analysis

One of the important parameters for investigation of the chemical reactivity is chemical hardness. A hard molecule has a wide band gap and a soft molecule has a small one. HOMO and LUMO represent the electron donation and the electron's reception ability of a molecule, respectively.

HOMO and LUMO graphs of the reactants in the gas phase have been shown in Fig. S2. Calculated band gap of the  $\beta$ -CD, TS2 and intermediate 2 were 1.5, 1.99 and 1.84 eV, respectively, which shows that the band gap was increased after the reaction. Quantum reactivity indices such as the electronic chemical hardness, electronic chemical potential, electrophilicity and charge transfer have been computed and reported in Table 6. According to Table 6, electronic chemical hardness has been increased after the reaction which corresponds to the band gap increment. Electronic chemical potential and the electrophilicity of the  $\beta$ -CD have been reduced at the TS2.

Considering all of the calculated quantum chemistry descriptors, it can be concluded that using the functionalized  $\beta$ -CD with an aldehyde group as a nano-enzyme mimic, enables us to simulate the mechanism of the unknown bioorganic reactions without any computational constraints.

## CONCLUSIONS

According to the theoretical data, the encapsulation of para amino phenol inside the cyclodextrin cavity in the presence of  $H_2O_2$  molecule through the wide opening is more favorable than the narrow edge. The proposed mechanism is composed of five continuous steps in which different bonds, making and breaking have been taking place. In the first step,  $H_2O_2$  is encapsulated in the hydrophobic cavity, through the wide edge of the  $\beta$ -CD. In the second step, the aldehyde group is oxidized by  $H_2O_2$  molecule. This step is the RDS which has an activation energy of  $54.4 \text{ kcal mol}^{-1}$ . In the next steps, the encapsulated aminophenol is converted to quinine imine as the final product.

HOMO-LUMO analysis has been done and showed that band gap is reduced during the reaction. Quantum chemistry reactivity indices such as the electronic chemical hardness, electronic chemical potential, electrophilicity and charge transfer have been computed. These parameters showed that the electronic chemical hardness has been increased after the reaction which corresponds to the HOMO-LUMO gap extension. Electronic chemical potential has been elevated while the electrophilicity of the  $\beta$ -CD has been reduced after the reaction. These parameters predict that the  $\beta$ -CD can be used as an oxidase mimic in electrochemical processes.

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