(Salen)Mn(III) Compound as a Nonpeptidyl Mimic of Catalase: DFT Study of the Metal Oxidation by a Peroxide Molecule

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Catalase mimics can be used as therapeutic agents against oxidative stress in treatment of many diseases, including Alzheimer's disease, stroke, heart disease, aging, and cancer. (Salen)Mn(III) compounds have been proven to be promising as synthetic antioxidants that, in particular, dismutate H_2O_2, resulting in two water molecules and oxygen. An understanding of the mechanism of the dismutation process is an important basis for rational design and tuning these analogues to yield better therapeutic properties. In addition, the study of the catalytic mechanism of the functional biomimetics of enzymes might contribute to a better understanding of the complex enzymatic activities for the corresponding biological compounds. For the first time, using the density functional theory method, we have performed a quantum chemical investigation of the catalase activity of the (salen)Mn(III) compound. The real compound reacting with a peroxide molecule has been utilized in the calculations to avoid uncertainties connected with using incomplete models. The reaction has been studied on three different spin potential energy surfaces: the singlet, the triplet, and the quintet. The same H_2O_2 dismutation process has been also calculated with participation of an additional water molecule to check the possible explicit involvement of the solvent molecules in the proton-transfer process in the course of the reaction. Our findings suggest that the first part of the dismutation reaction—the metal oxidation by a peroxide molecule—is a one-step process. The concerted breaking of the O−O peroxide bond, oxidation of the Mn, and a water molecule formation occur on the triplet state potential energy surface. This process can be done effectively at the Mn catalytic center with only 3.6 kcal/mol of activation energy needed. No energetic advantages were found for the assisted proton-transfer mechanism with participation of an ancillary water molecule. Although the singlet state is not accessible on the reactant and TS parts of the reaction potential surface, it becomes the ground state in the vicinity of the final geometry and can play an important role in the second part of the dismutation process.

Introduction

Hydrogen peroxide is an undesired metabolic byproduct in living systems. For the degradation of this reactive oxygen species, organisms use catalase enzymes[1,2] which highly effectively dismutate H_2O_2 according to eq 1:

$$2H_2O_2 \rightarrow 2H_2O + O_2 \qquad (1)$$
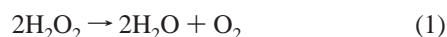
[3] Hydrogen peroxide can be produced at increased levels in a variety of pathological situations. If the production of H_2O_2 overwhelms the activity of catalase enzymes, then H_2O_2 becomes the substrate for the Fenton reaction, resulting in extremely toxic and mutagenic hydroxyl radicals (OH·).[4] To avoid this situation, synthetic antioxidants, which scavenge excess oxidants, can be used as therapeutic agents against oxidative stress. An incomplete list of possible applications of antioxidants include treatment of Alzheimer's disease,[5] stroke,[6] heart disease,[7] aging,[8,9] and cancer. When antioxidants are used in cancer therapy, their main function is to reduce the side effects induced by reactive oxygen species, allowing higher drug doses to be administered.[10]

A number of research groups have been developing low molecular weight catalysts (biomimetics) that mimic natural

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SCHEME 1

1
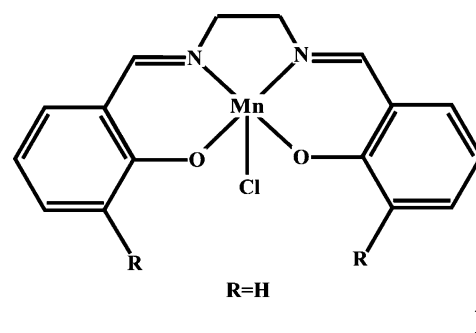
enzyme functions to suppress various reactive oxygen species, including peroxide.[11] Catalase mimics were built around iron(III),[12−14] dinuclear manganese,[15−18] and Mn(III) centers.[19−21] The latter—(salen)Mn(III) compounds (Scheme 1)—have been proven to be especially promising as therapeutics.[8,19] The distinctive feature of the salen−manganese complexes that makes possible their broad pharmacological efficacy is the ability to mimic both catalase and superoxide dismutase enzymatic functions.[20,22]

Though significant therapeutic and chemical information on the salen−manganese catalase mimics have been accumulated from extensive experimental studies,[19−21] the detailed picture of the peroxide dismutation on the molecular level is yet to be

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obtained. An understanding of the mechanism of the dismutation process is an important basis for rational design and tuning these analogues to yield better therapeutic properties. From a fundamental point of view, the study of the catalytic mechanism of the functional biomimetics of enzymes might contribute to a better understanding of the complex enzymatic activities for the corresponding biological compounds. In this paper, for the first time using the density functional theory (DFT) method, we present a quantum chemical investigation of the catalase activity of the (salen)Mn(III) compound **1** (Scheme 1).

We consider a general "ping-pong" mechanism approach[3] to describe the reaction process in which the first molecule of H_2O_2 binds to the metal center (Mn(III)), oxidizes the metal, and releases a molecule of water. The second peroxide molecule approaches the oxomanganese intermediate compound (Mn(V)) and the oxygen atom is transferred back to the peroxide molecule, forming O_2 and H_2O. We concentrate our efforts here on the first part of the dismutation reaction 1, namely, converting H_2O_2 in H_2O with simultaneous oxidation of the Mn atom. Importantly, for our investigation we use not a model but the real compound **1** reacting with a peroxide molecule. Though such an approach makes our calculations computationally challenging, it eliminates uncertainties connected with using oversimplified models that could lead to wrong conclusions, as it was demonstrated by us for the epoxidation reaction with participation of the (salen)Mn catalyst.[24]

Method

All DFT calculations of the different reaction pathways were carried out using the DGauss program[25] as implemented in UniChem 4.0.[26] The calculations were performed using DZVP basis sets; which are (621/41/1) for carbon, oxygen, and nitrogen atoms, (41) for hydrogen atoms, and (6321/411/1) for the manganese atom.[27,28] The nonlocal corrections using the Becke exchange[29] and Perdue correlation[30] potentials have been obtained starting from the Vosko, Wilk, and Nuisar local potential.[31] The choice of the DFT functional for modeling of the reactions with participation of the (salen)Mn compounds was studied by us quite recently in the case of the (salen)Mn-(III)-catalyzed epoxidation reaction.[24] Using high level ab initio calculations (coupled cluster-CCSD(T)), we showed that the BP functional gives a realistic description of the relationship between the different spin channels involved in the reaction and is suitable for the reaction modeling. In contrast, using the B3LYP approach in this particular catalytic system case results in a distorted picture of the spin state order. In addition, the B3LYP approach cannot correctly predict the singlet state as the ground one for the oxomanganese complexes.

The convergence of geometry optimization is less than 0.001 hartree/bohr for the largest Cartesian energy gradient component. For every stationary point, an analytical Hessian matrix[32] was calculated to prove the nature of the optimized structure. All open-shell calculations were performed using unrestricted Hartree−Fock formalism.

Results and Discussion

The investigated reaction has been calculated on the three different spin potential energy surfaces: the singlet, the triplet, and the quintet. The optimized geometries of the reaction critical points are shown in Figure 1. A qualitative similar mechanistic picture of the one-step reaction has been obtained for all spin states. However, the reaction energy profiles appear to be quite quantitatively different (Figure 2). The same H_2O_2 dismutation reaction has also been calculated with participation of an
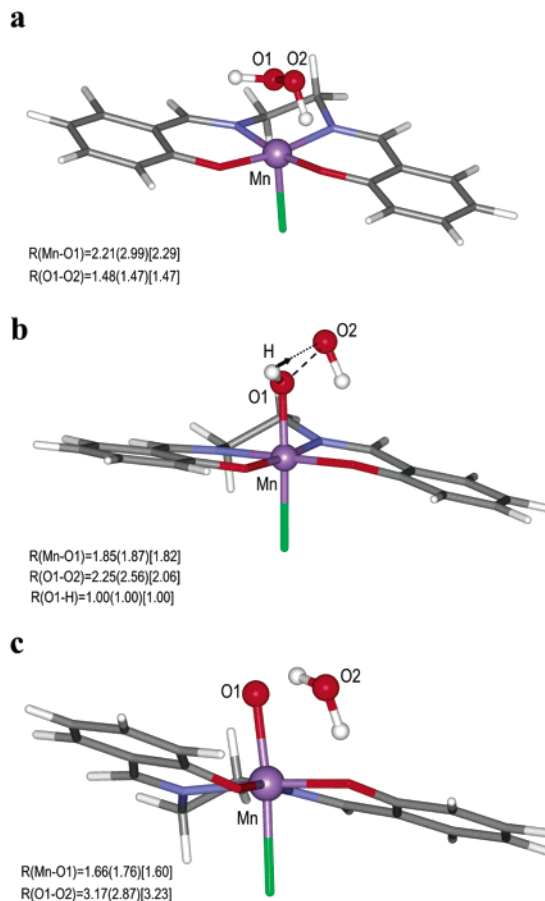

Figure 1. Optimized critical reaction structures for the dismutation reaction: (a) initial catalase mimic−peroxide complex; (b) transition state leading to the final products; (c) final complex. Selected geometrical parameters are shown for the triplet state. The corresponding parameters for the quintet and the singlet states are shown in parentheses ( ) and brackets [ ], correspondingly. Bond lengths are in angstroms.
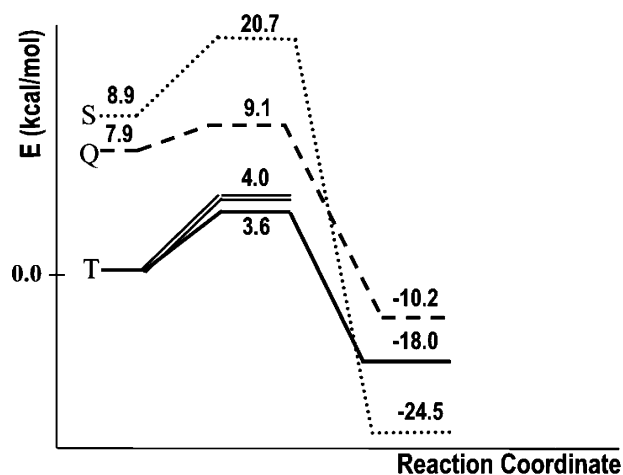

Figure 2. Relative reaction energies of the triplet, quintet, and singlet one-step dismutation pathways. Nonsolid line for the triplet state represents a part of the profile for the reaction with participation of an ancillary water molecule.

additional water molecule to check the possible explicit involvement of the solvent molecules in the proton transfer process in the course of the reaction (Figure 3).The latter calculations were done only for the triplet spin state in which the lowest absolute value of the transition state (TS) barrier is observed.

As can be seen from Figure 1a, in the initial reaction complex, the O1 atom of the peroxide molecule is situated above the Mn,
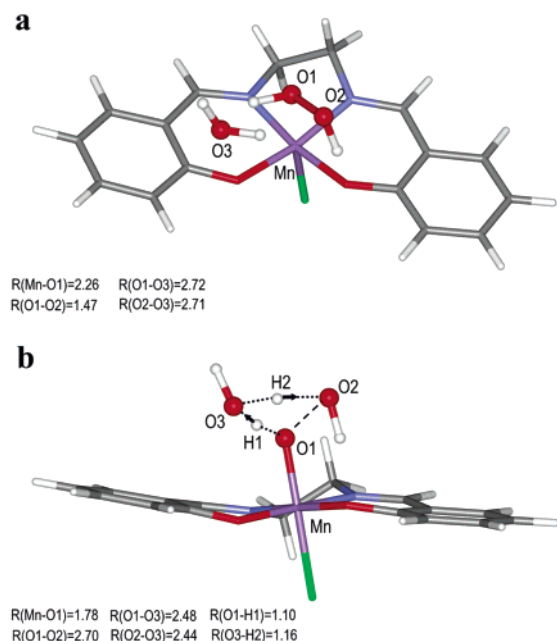
a

R(Mn-O1)=2.26   R(O1-O3)=2.72
R(O1-O2)=1.47   R(O2-O3)=2.71

b

R(Mn-O1)=1.78   R(O1-O3)=2.48   R(O1-H1)=1.10
R(O1-O2)=2.70   R(O2-O3)=2.44   R(O3-H2)=1.16

Figure 3. Optimized initial complex (a) and transition state structure (b) for the dismutation reaction with participation of an ancillary water molecule on the triplet state potential energy surface. Bond lengths are in angstroms.

while O2 forms a hydrogen bond with the O3 atom of the salen moiety. Starting from this conformation, the oxidation of the metal with simultaneous formation of a water molecule can be done via the TS shown in Figure 1b. The TS essentially describes the intramolecular proton transfer from the O1 to the O2 atom of the peroxide, with concerted breaking of the O1–O2 bond followed by coordination of O1 to the metal. The distinctive feature of the TS structure is the practically broken O1–O2 bond ($R = 2.25$ Å versus $R = 1.48$ Å for the initial complex geometry in the triplet state). Note, however, that the transferable proton just starts its movement toward the O2 atom ($R(\text{H}-\text{O1}) = 1.00$ Å versus $R(\text{H}-\text{O1}) = 0.98$ Å of the initial value). The final reaction complex (Figure 1c) represents the oxomanganese salen compound and the formed water molecule that creates the hydrogen bond network with the O1 atom of the metal and O3 atom of the salen moiety.

Analysis of the reaction profiles (Figure 2) shows that the triplet is the lowest spin state during the major part of the reaction and is changed for the singlet only at the vicinity of the final product geometry. At the initial complex geometry, the triplet state is separated from the quintet by 7.9 kcal/mol gap. The singlet state lies higher than the quintet by 1 kcal/mol. Our calculations suggest that only 3.6 kcal/mol activation energy is needed to perform the reaction in the ground triplet state. The quintet channel is even more reactive then the triplet with the relative value of the TS barrier, 1.2 kcal/mol. However, since the quintet is the exited state, the absolute value of the quintet TS barrier—9.1 kcal/mol—is too high to compete with the triplet reaction pathway. Because of a very high absolute value for the singlet TS barrier (20.7 kcal/mol), the singlet channel is irrelevant for the chemical transformations at the first stage of the dismutation reaction.

As we mentioned above, the reaction process involves the intramolecular proton transfer. This transfer can be also done as an intermolecular one with mediation of an additional molecule of water that is used as a proton relay (Figure 3). The corresponding TS structure (Figure 3b) shows the concerted proton transfers from the O1 atom of the peroxide to the oxygen

atom of the water that in turn renders the original proton to the O2 atom. The TS barrier for this process on the triplet surface is 4.0 kcal/mol; that is higher than the corresponding barrier for the intramolecular proton-transfer reaction, 3.6 kcal/mol (Figure 2). Thus, there is not any energetic advantage for the assisted proton-transfer mechanism with participation of an ancillary water molecule.

We finally note that the investigated reaction can be formally described as a spin-forbidden process because of the spin changing for the ground state in the course of the reaction. As it was shown for the (salen)Mn(III)-catalyzed epoxidation reaction, spin-surface crossings can lead to competing reaction channels with different spin states.[24,33−35] This is not the case for the reaction of the H$_2$O$_2$ dismutation by the salen-Mn catalase mimic. The quintet and the singlet states are not accessible on the reactant and TS parts of the reaction potential surface. For this reason the triplet channel is the only one that is essential for the metal oxidation and formation of a water molecule.

Conclusions

We present the first quantum chemical investigation of the mechanism for the (salen)Mn(III) catalase mimic using density functional theory. Our findings suggest that the first part of the dismutation reaction—the metal oxidation by a peroxide molecule—is a one-step process. The concerted breaking of the O–O peroxide bond, oxidation of the Mn and a water molecule formation occur on the triplet state potential energy surface. This process involves the intramolecular proton transfer that can be done effectively at the Mn catalytic center (the reaction TS barrier-3.6 kcal/mol). No energetic advantages were found for the assisted (intermolecular) proton-transfer mechanism with participation of an ancillary water molecule that might represent an explicit solvent involvement in the reaction mechanism. Although the singlet state is not accessible on the reactant and TS parts of the reaction potential surface, it becomes the ground state at the vicinity of the final geometry and it can play an important role in the second part of the dismutation process.

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