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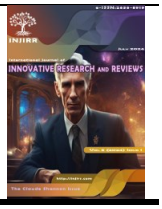

REVIEW ARTICLE

The Role of Some Transition Metals in Enzymatic Reactions in Context of Eco-Friendly Oxidative Halogenation

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ABSTRACT

Catalysts are a fundamental part of the chemical industry and today they are involved in the manufacture of approximately 90% of chemical-based products. Among the many types of catalysis, metal transfer catalysis is particularly important due to their ability of to form various oxidation stages. Therefore, it opens up protocols that demonstrate unprecedented complexity, efficiency and selectivity compared to classical reactions. In nature, catalytic processes are mediated by enzymes. Many of all known enzymes require one or more metal ions for catalytic activity. The natural enzymes constitute the state of the art in catalysis and can perform a wide range of transformations with efficiency and selectivity that often exceed man-made systems. In recent years, with the discovery of naturally occurring metal-containing enzymes in various organisms, numerous studies have been conducted on the role of these enzymes in enzymatic reactions. As a result of these studies, researchers have focused on investigating the active roles of these metals in halogenation reactions and developing environmentally friendly metal-catalyzed halogenation reactions based on the presence of iron, vanadium, molybdenum, and tungsten in the structure of various haloperoxidases. This review summarizes the roles of some transition metals in biological systems, as well as their functions of natural haloperoxidases and oxidative halogenation reactions.

Contents

1. Introduction

Enzymes found in living organisms play a vital role in sustaining life by enabling the formation of metabolic processes under moderate conditions [1]. One-third of all known enzymes require one or more metal ions for catalytic activity. Metals can participate in catalysis in many ways if they are tightly bound to the enzyme or if they are present in the solution together with the substrate. Metals are usually found either directly bound to proteins or in clusters bound to cofactors such as porphyrins or cobalamins, with ligands generally being O, N, S, or C [2, 3].

In nature, electrophilic halogenation primarily occurs through the catalyzed oxidation of the halide ion to produce a halogenating reagent. In the laboratory, halogenation is performed using hazardous, toxic, and corrosive molecular halogens in general, and is often carried out in chlorinated solvents. Ecological awareness among chemists has

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increasingly grown, leading to increased research in the field of understanding of oxidative halogenation in biological systems, which has boosted research in this field. The interest of researchers has focused mainly on the development of biomimetic systems because this reaction is usually performed by heme dependent or vanadium dependent haloperoxidases in biological systems. Therefore, the researchers have mainly directed their attention toward the use of vanadium(V), molybdenum(VI) and tungsten(VI) complexes.

1.1. The role of transition metals in metalloenzymes

In multicellular organisms composed of various specialized cells, the storage of transition metals and the synthesis of carrier molecules are not carried out by every type of cell, but by specialized cells specialized in these tasks. The metals are always in ionic form, but their oxidation state can change depending on biological needs. Transition metals that are important for biological storage and transport include iron, zinc, copper, molybdenum, cobalt, chromium, vanadium, and nickel (Table 1). Transition metals and zinc are most commonly associated with proteins that catalyze the arrangement of electrons within or between molecules. Although zinc is not a typical transition metal, it shares many bioinorganic properties with transition metals [2, 4].

Table 1 The biological functions of the metal ions found in some metalloenzymes [5, 6]

Metals	Biological functions
Magnesium	Hydrolase, Phosphate transfer
Manganese	Hydrolase, O_2 production, isomerase
Vanadium	Oxidase Nitrogen fixation, haloperoxidase
Tungsten	Dehydrogenase, oxidase, oxygene transfer, haloperoxidase
Molibdenium	Oxygen transfer, nitrogen fixation, oxidase, haloperoxidase
Iron	Electron transfer, oxidation, oxygen transfer
Cobalt	Oxidase, group transfer, haloperoxidase
Copper	Oxidase, electron transfer
Nickel	Hydrolase, H transfer,
Zinc	Hydrolase, peptidase, phosphatase, H transfer

In addition to cobalt found in the structure of vitamin B-12, cobalt is also found in the structure of eight enzymes (methionine aminopeptidase, prolidase, nitrile hydratase, glucose isomerase, methylmalonyl-CoA carboxy transferase, aldehyde decarbonylase, lysine-2,3-aminomutase and bromoperoxidase) that do not contain corrin rings, the isolation and characterization of which have been completed to date [7]. The bromoperoxidase obtained from *Pseudomonas putida* catalyzes the formation of a carbon-bromine bond in the presence of peroxides, but it is activated not by other transition metals such as iron, nickel, zinc, and vanadate, but only by the incubation with cobalt ions. [7, 8]. Iron is primarily found in enzymes involved in oxidation-reduction reactions and also plays an important role in oxygen transport [9, 10]. Copper is found in numerous enzymes that catalyze redox reactions such as tyrosinase, lysine oxidase and cytochrome oxidase [11, 12]. Manganese constitutes a component of pyruvate carboxylase in chicken liver and is found in *Escherichia coli* superoxide dismutase [13]. Although it also serves as an activator for many metal-dependent enzymes, in most of these cases, magnesium and other divalent cations can perform the same function [10]. Nickel containing enzymes such as glyoxalase I, urease, superoxide dismutase, nickel-iron hydrogenase, carbon monoxide dehydrogenase, acetyl-coenzyme A synthetase/decarbonylase, methyl-coenzyme M reductase, and lactate racemase, play critical roles in bacteria, archaea, fungi, algae, and higher plants [14]. Zinc enzymes are involved in the synthesis or breakdown of carbohydrates, lipids, proteins, and nucleic acids [10]. Hundreds of known zinc-containing enzymes catalyze reactions such as hydrolases, dehydrogenases, phosphatases, and peptidases. The largest group of zinc-containing enzymes is hydrolases. Carbonic anhydrase (CA), carboxypeptidase (CP), alkaline phosphatase (AP), phospholipase C (PLC), aminopeptidases are some of the zinc-containing enzymes [2, 9, 10]. In addition to vanadium interacts with small molecules in biological systems, binds transporting and binding proteins, serving as an electron transfer agent in fungi [15]. Vanabins isolated from *Asidia sydneinsis samea* naturally bind vanadium, and amavadin obtained from the *Aminitamuscaria fungus* is a natural vanadium complex. Particularly, there are nitrogenases and haloperoxidases that contain vanadium as a structural metal [15]. Aldehyde ferredoxin oxidoreductase (**1**) from *Paracoccus furiosus* and acetylene hydratase (**2**) from *Pelobacter acetylenicus* are natural tungsten-containing enzymes [16].

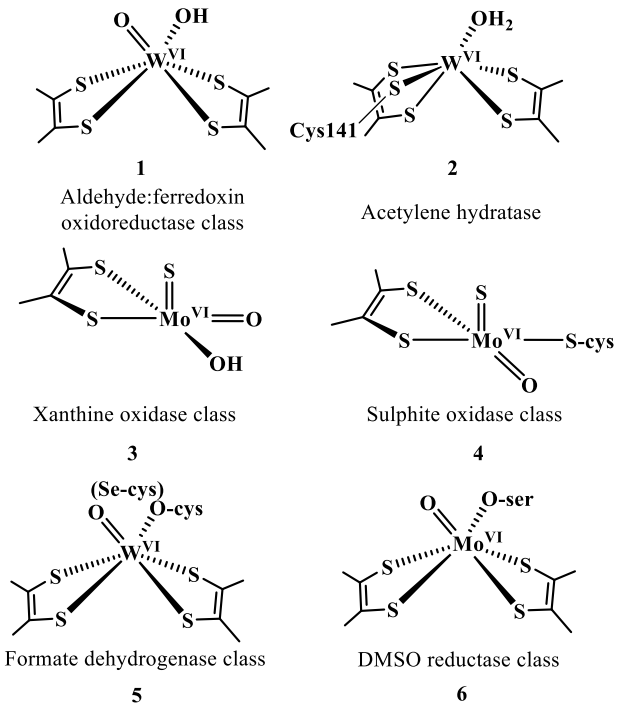

Figure 1 Some enzymes containing molybdenum and tungsten metals [9, 16]

Molybdenum proteins catalyze the reduction of nitrogen and nitrate, as well as the oxidation of aldehydes, purines, and sulfites. Xanthine oxidase (**3**) that found in cow's milk, sulfite oxidase (**4**) and aldehyde oxidase obtained from bird or mammal liver are molybdenum-containing enzymes [16]. Biotin-*S*-oxide reductase, trimethylamine-*N*-oxide reductase, dissimilatory nitrate reductase, and formate dehydrogenase (**5**) belong to DMSO reductase family (**6**) that is extremely large enzymes family and contain

molybdenum or tungsten as structural metals. The enzymes such as formate dehydrogenase and nitrate reductase have ligands such as oxygen (aspartic acid, serine, water, oxo, hydroxo), sulfur (cysteine) and selenium atoms (selenocysteine) [17]. The structure of several enzymes are given in Figure 1.

2. Oxidative Halogenation and Haloperoxidases

Naturally occurring electrophilic halogenation occurs primarily through oxidative halogenation catalyzed by the oxidation of halogen ions to form a halogen reagent [18]. Various oxidative halogenation methods using different oxidants such as metals, persulfates, mineral acids, and hypervalent iodine for the generation of electrophilic bromine have been mentioned in the literature. For example, in the preparation of isocyanate, vinyl chloride, which is widely used in industry, is obtained by passing oxygen and ethylene gases over waste HCl at temperatures above 200°C in the presence of Cu^{II} catalyst, and the resulting harmful by-product HX is regenerated with H_2O_2 or O_2, yielding only water as a side product (Figure 2) [19].

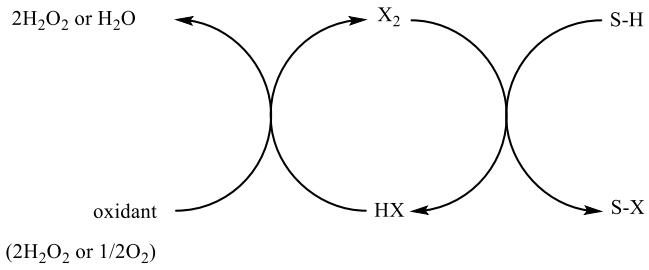

Figure 2 Oxidative halogenation with H_2O_2 or O_2 [19]

In the regeneration of HX, oxidants such as peroxides, oxygen, hypervalent iodine compounds, persulfates, and metals are also used [20]. Gunten and Oliveras [21] proposed a mechanism given in Figure 3 for the formation of brominated organic compounds and bromate in advanced oxidation processes [21].

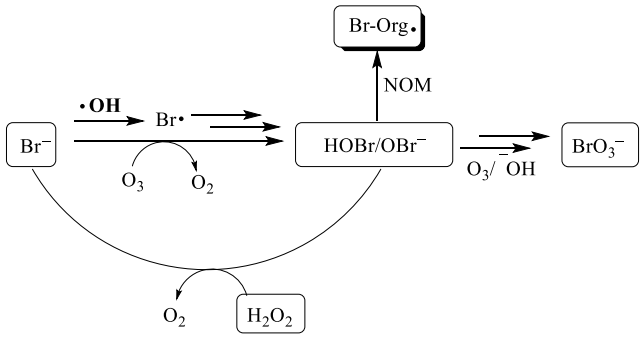

Figure 3 Formation of brominated organic compounds and bromate in advanced oxidation processes [21]

Based on these naturally occurring reactions, researchers have focused on environmentally friendly metal oxide-catalyzed oxidative halogenation reactions. The oxidative halogenation of 1,3-dimethoxybenzene (**7**), has shown in Figure 4, has been achieved with ammonium metavanadate (NH_4VO_3) and vanadium (V) oxide catalysis [22].

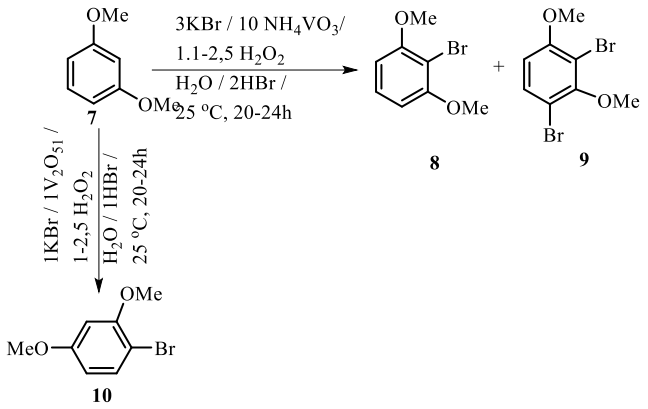

Figure 4 Oxidative bromination of 1,3-dimethoxybenzene (**7**) [22]

Another class of complexes catalyzing oxidative halogenation with H_2O_2 is Mo (VI) complexes. The oxidative bromination of anisole (**11**) is given in Figure 5.

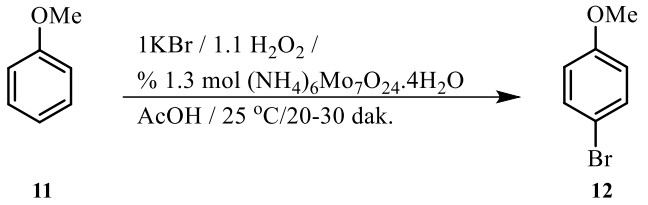

Figure 5 Oxidative bromination of anisole (11) [22, 23]

Haloperoxidases catalyze the chlorination, bromination, and iodination reactions of a wide range of organic molecules [24] and can be classified based on which halide ions they can use in halogenation reactions. Chloroperoxidases can use chloride, bromide, and iodide, while bromoperoxidases can use bromide and iodide in halogenation reactions, and iodoperoxidases can only use iodide [25]. Additionally, haloperoxidases catalyze sulfoxidation, epoxidation, and oxidation reactions [26].

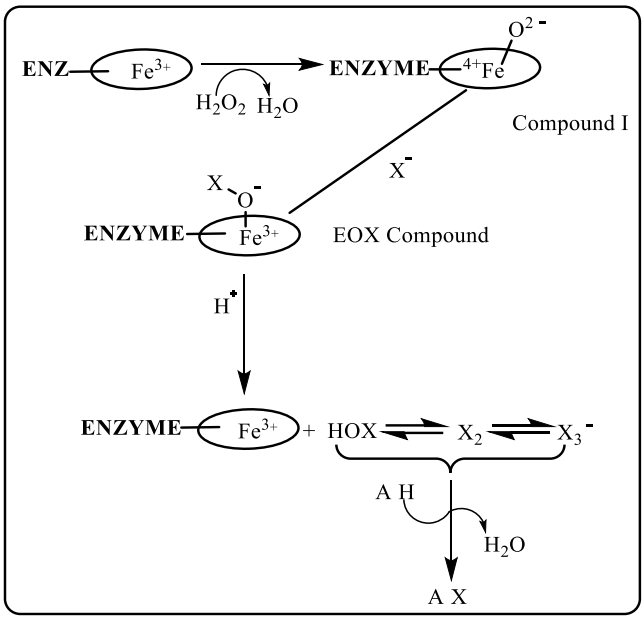

Figure 6 Halogenation mechanism of heme-containing haloperoxidases [27]

The discovery of enzymes containing various cofactors (including heme group and vanadium, and those without metal ions) has led to changes in our understanding of

biological halogenation [28, 29]. Although the use of enzymes in oxidative halogenation is not yet suitable for large-scale processes, researchers are mainly focused on the use of biomimetic systems. Heme or vanadium-dependent haloperoxidases constitute a significant group of halogenation enzymes. Therefore, the effects of these enzymes are intensively investigated in enzymatic reactions and biomimetic studies [30]. Franssen [27] summarized the halogenation reaction mechanism of heme group-containing haloperoxidases as shown in Figure 6.

In the study conducted by Duhalta et al. [31] was given in Figure 7, the electrophilic chlorination reactions of polycyclic aromatic hydrocarbons containing aromatic hydrocarbons were carried out with the heme-bound first chloroperoxidase enzyme isolated from the fungus *Caldariomyces fumago*, along with hydrogen peroxide and chloride anion [31].

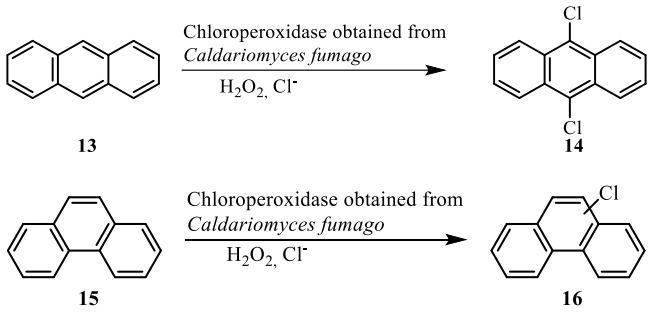

Figure 7 Oxidative chlorination of anthracene (**7**) and phenanthrene (**9**) [31]

The chloroperoxidase obtained from *Curvularia inaequalis* (a mold fungus), and the bromoperoxidase enzymes obtained from *Ascophyllum nodosum* (brown algae) and *Corallina pilulifera* (red algae) contain vanadium as a prosthetic group [32–34]. These vanadium-containing enzymes are more stable than the variable heme group-containing enzymes (the chloroperoxidase obtained from *Caldariomyces fumago*) [35] and functional in neutral or slightly acidic environments [27]. Vanadium haloperoxidases are still the most effective oxidants of halides among the vanadium catalysts studied so far, and this activity is influenced by the role of specific amino acids in the activation of the vanadium (V) peroxide bond for halogen oxidation and also in the potential halogen selectivity [36].

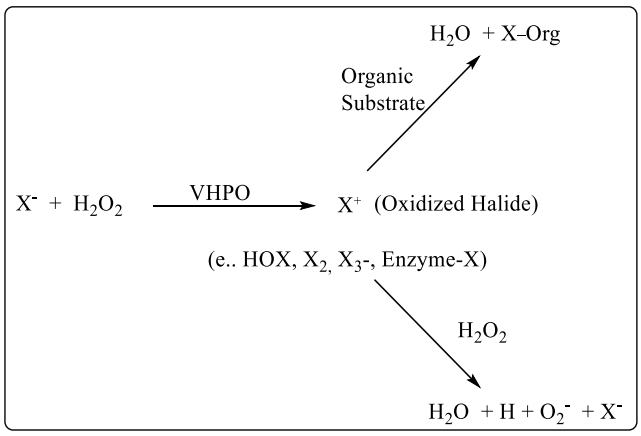

Figure 8 Mechanism of oxidative halogenation reaction of haloperoxidases containing vanadium [37–39]

Vanadium haloperoxidases are still the most effective oxidants among the vanadium catalysts studied so far, and this activity is influenced by the activation of the vanadium (V) peroxide bond for halogen oxidation and also the possible role of specific amino acids in the selective halogenation [36]. We can summarize the mechanism of oxidative halogenation reaction of vanadium-containing haloperoxidases as shown in Figure 8.

The synthesis reaction of natural bromopyrrole derivative (**18**) found in the *Agelas oroides sponge* [40] is catalyzed by vanadium-dependent bromoperoxidase (VBrPO) and the reaction was given in Figure 9.

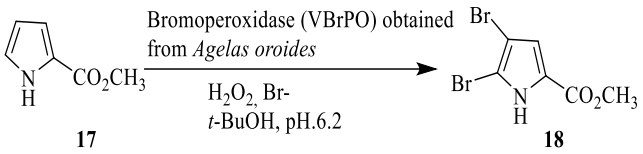

Figure 9 Oxidative bromination of pyrrole-2-carboxylic acid (**17**) [41]

The oxidative bromination reaction of 4,8-dimethylazulene (**19**) catalyzed by another natural VBrPO is obtained from Ascophyllum nodosum (knotted wrack) is given in Figure 10.

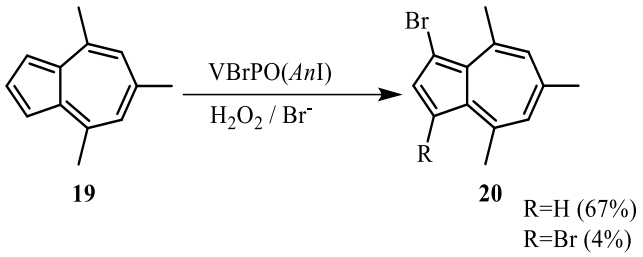

Figure 10 Oxidative bromination of 4,8-dimethylazulene (**19**) [42, 43]

The oxidative bromination of the molecule 4-tert-butyl-cyclohexene (**21**) is catalyzed by another VBrPO as shown in Figure 11.

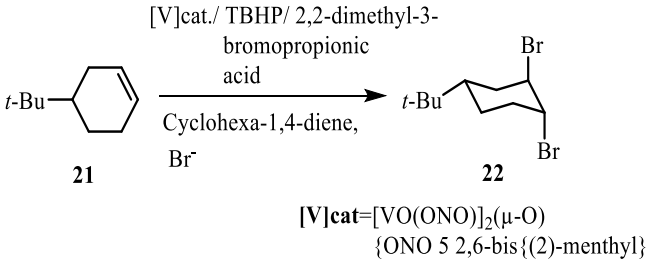

Figure 11 Oxidative bromination of 4-tert-butylcyclohexene (21) [42]

3. Sulfoxidation and Oxidation Reactions of Haloperoxidases

In addition to oxidative halogenation, vanadium haloperoxidases also catalyze sulfoxidation, epoxidation, and oxidation reactions. The oxygen transfer of bromide and sulfide occurs via a hydroperoxo intermediate under the catalysis of an oxovanadium complex in Figure 12.

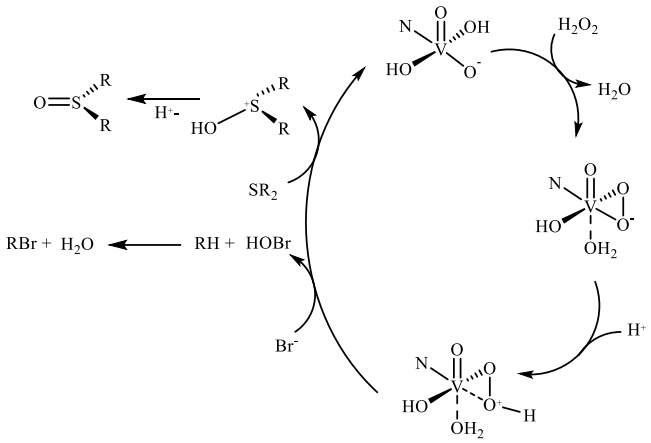

Figure 12 Haloperoxidation and sulfoxidation of oxovanadium complexes [36, 44]

Natural haloperoxidases obtained from *Ascophyllum nodosum* and *C. Officinalis* catalyze the sulfoxidation of methyl-phenyl sulfide (**23**) and 1,3-dihydrobenzothiophene (**25**) in Figure 13.

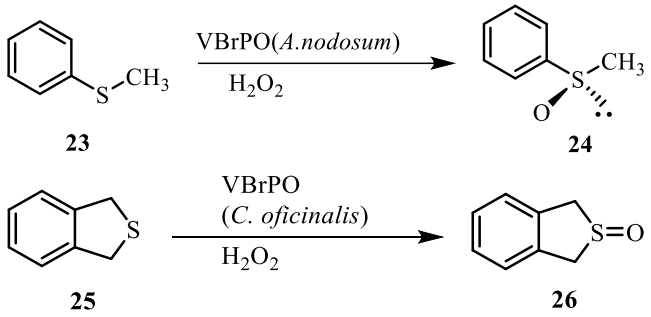

Figure 13 Sulfoxidation of phenylmethyl sulfide (**23**) and 1,3-dihydrobenzothiophene (**25**) [26]

Enzymes containing molybdenum and tungsten play an important role in nitrogen uptake in green plants, microbial respiration, and human health [45]. Despite molybdenum being only a small component of the Earth's crust, it can easily access biological systems due to the solubility of molybdate salts in water. Indeed, molybdenum is the most abundant transition metal in seawater, and its widespread involvement in biological systems is not surprising [16]. The enzyme *xanthine oxidase*, found in cow's milk and containing molybdenum, catalyzes the conversion of xanthine (**27**) to uric acid (**28**) as shown in Figure 14 [46–48].

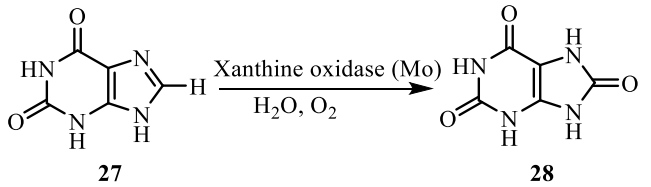

Figure 14 Oxidation of xanthine (**27**) to uric acid (**28**) [47, 48]

Enzymes containing molybdenum and tungsten can catalyze a wide range of oxygen transfer reactions (such as sulfoxidation, epoxidation, and phosphorylation) as well as haloperoxidation reactions [49–51]. However, the formation of the MoO-X bond is endothermic [52] making the use of molybdenum-containing natural enzymes in haloperoxidation reactions rare [52]. The dimethylsulfoxide (DMSO) reductases are obtained from *Rhodobacter sphaeroides* and *Rhodobacter capsulatus* [53, 54] and also DMSO reductases are unprecedented among molybdenum enzymes reviewed to date due to posessing the molybdenum cofactor as the sole prosthetic group and as the sole redox-center [48, 55]. The double oxo transfer experiment (Figure 15) is performed with DMSO reductase showed that the oxidation of 1,3,5-triaza-7-phosphoadamantane to 1,3,5-triaza-7-phosphoadamantane-7-oxide is catalyzed by DMSO reductase while the reduction of dimethyl sulfoxide to dimethyl sulfide is achieved [56]. The $Mo^{VI}O$ group acts as an oxo donor, and the non-oxo Mo^{IV} center acts as an oxo acceptor, which is the natural function of the enzyme [9, 56–58].

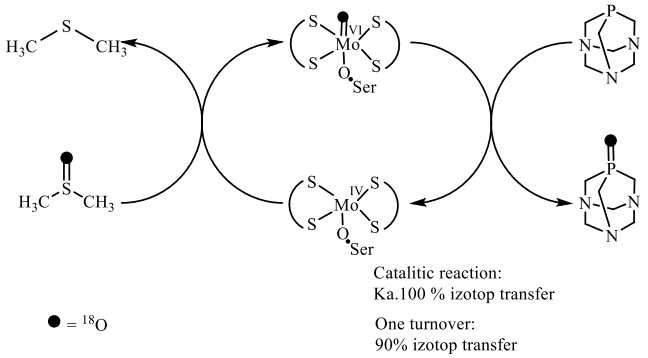

Figure 15 Sulfoxidation and phosphoroxidation of molybdenum complex (The double oxo transfer reaction demonstrated for a DMSO reductase) [9, 57]

Molybdenum and tungsten, both belonging to the same group, are the only second and third row transition metals required by most living organisms. They exhibit common structural features and catalyze various oxygen transferase reactions by providing two-electron redox chemistry in the metal cycles between +6 and +4 oxidation states (Figure 16), generally with water as the product or substrate for oxygen supply [9, 45, 55, 59].

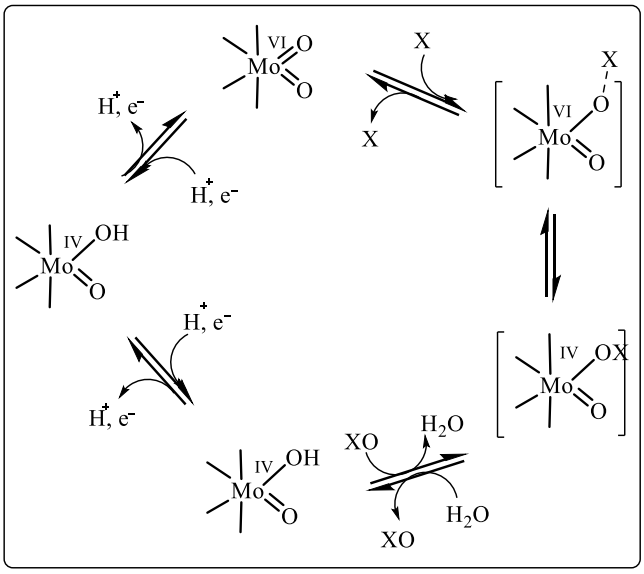

Figure 16 Oxygen transfer in oxomolybdenum complex [9, 55]

For instance, aldehyde ferredoxin oxidoreductase (AOR) is an enzyme obtained from *Paracoccus furiosus* and containing tungsten, facilitates the conversion of phenylacetaldehyde (**29**) to phenylacetate (**30**) in Figure 17.

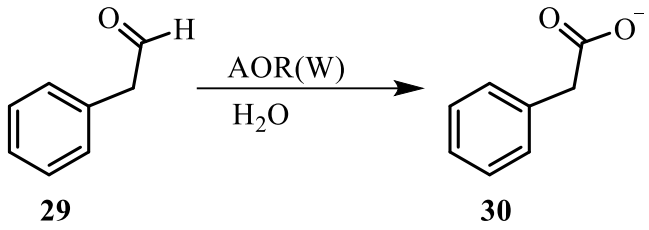

Figure 17 Oxidation of phenylalanine (**29**) to phenylacetate (**30**) [60]

Similarly, the tungsten-containing acetylene hydratase (AH) obtained from *Pelobacter acetylenicus* catalyzes the conversion of acetylene (**31**) to acetaldehyde (**32**) in Figure 18.

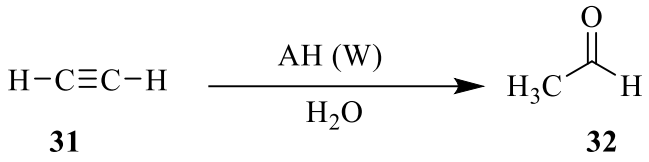

Figure 18 Conversion of acetylene (**31**) to acetaldehyde (**32**) [61]

4. Conclusion

Catalysts enable high efficiency in chemical reactions by reducing the raw material and energy requirements, thanks to their high selectivity, impurity reduction, time savings, and reusability. Determining environmentally friendly transition metal catalysts for haloperoxidation, sulfoxidation, and oxidation reactions requires a broad investigation of enzymatic reactions based on enzymes containing transition metals. Inspired by enzymatic reactions, it is crucial for the reagents used in catalytic reactions to have very low toxic effects, especially using hydrogen peroxide as an oxidizing reagent, which also forms only water as a waste product, making it highly important for green chemistry.

Since catalysts are generally specific to each reaction, a catalyst that catalyzes one reaction very well may not be a good catalyst for another reaction containing similar reactants. Therefore, this review article is important in drawing the attention of researchers to the development of new transition metal catalysts and the application of known catalysts in new areas. Additionally, it is also important to promote the widespread use of known haloperoxidase enzymes in organic syntheses.

Recent years the interest of researchers has focused mainly on the development of biomimetic systems. The development of transition metal catalysts that are able to perform at low catalyst loading would be of great impact in the development of this research area. Moreover, the development of active catalysts will have important an outcome in the industrial application of sulfoxidation, oxidation and oxidative halogenation and in future, the usage of enzymes will be suitable for the development of large scale processes.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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