Inorganic Enzyme Mimics
Yihong Zhang,[a, b] Faheem Muhammad,[a, b] and Hui Wei*[a, b]

Enzyme mimics (or artificial enzymes) have emerged as valuable alternatives to natural enzymes since the pioneering work of Ronald Breslow. They have numerous advantages over natural enzymes, such as high stability, low cost, and tailorability. Among varieties of materials explored to mimic enzymes, the inorganic ones, including inorganic complexes and nanomaterials, have attracted increasing interest over the last decade and have the potential to address the current challenges in energy, environment, health, etc.

ChemBioChem and EurJIC, two internationally recognized journals in the field, have now provided us with a unique opportunity to highlight the exciting achievements in the recent years by publishing a joint Special Collection on Inorganic Enzyme Mimics. This Special Collection features 20 contributions including Reviews, Minireviews, Communications, and Full Papers. Sixteen of them are research articles, and the other four are reviews. Among them, 11 are focused on nanomimics, eight on inorganic complexes (mainly transition metal complexes), and one on DNAzymes; this roughly reflects the recent research trend in the field.

Inorganic complexes are promising enzyme mimics because of their rich coordination chemistry, which can imitate the active sites and microenvironments of metalloenzymes. The artificial metalloenzymes might also help us understand the catalytic mechanisms of enzymes at the molecular level. The inorganic complexes reported in this collection mainly mimic hydrogenase and nitrogenase, both of which play important roles in the development of sustainable and renewable energy. There are three types of hydrogenase with distinct active sites (i.e., [NiFe]-H$_2$ase, [FeFe]-H$_2$ase, and [Fe]-H$_2$ase). Inorganic complex models of the latter two are reported in this collection. Song and co-workers synthesized a series of [Fe]-H$_2$ase mimics containing a hydride donor Hantzsch ester HEH moiety. Their synthetic methodology as well as the new complexes could help us to further design better mononiran hydrogenase. [FeFe]-H$_2$ase-mimicking complexes were reported by Hogarth’s group as well as Elleouet and Schollhammer’s group. Electrochemical and other characterizations were carried out to investigate the complexes’ catalytic activity. The limited stability and moderate catalytic activity demand a very fine tuning of these [FeFe]-H$_2$ase mimics in future studies. Although manganese is not used in natural hydrogenases, it is a critical element in photosystem II. Kaur-Ghumaan and co-workers summarized the recent progress in manganese-based complexes for H$_2$ production and oxidation, thus demonstrating that non-native metal hydrogenases based on manganese active sites might be viable.

Nitrogenases are enzymes for nitrogen fixation. A nitrogenase consists of three components: the Fe-protein containing a [Fe$_7$S$_6$] cluster, the electron-transferring P-cluster containing a [Fe$_{12}$S$_{12}$] group, and the cofactor. There are three types of cofactor (FeMo-co, FeV-co, and FeFe-co), which make three corresponding nitrogenases. The FeMo-co with a stoichiometry of Fe$_7$Mo$_7$S$_{14}$C is usually more active than the other two, therefore, the mimics of FeMo-co have been extensively studied. To model FeMo-co, Rauchfuss and co-workers converted [Fe$_5$C$_4$(CO)$_2$S$_2$] into clusters that more closely resemble FeMo-co. Yang and co-workers synthesized a series of diiron complexes with a benzene-1,2-dithiolate (bdt) bridge to mimic nitrogenase. Taking the disproportionation of hydrazine to ammonia as a model reaction, they showed that the substituent modulation of the bdt ligand could tune the reduction potential of the complex and thus its activity. This work provides a strategy to modulate the nitrogenase-mimicking activity of the complex by varying the ligand substituent.

Inorganic complexes can also be used to mimic other enzymes. To this end, Ivanović-Burmazović synthesized various metal complexes to probe their electrochemical behavior and superoxide dismutase (SOD)-mimicking activity. They showed that the redox potential, position of the charged groups, and possible electronic communication with the metal center are all crucial to tune the SOD-like activity. Besides experimental endeavors, the theoretical study has also played an invaluable role in designing new enzyme mimics and deciphering the underlying catalytic mechanisms. In view of this, following their previous experimental study, Hörner and de Visser further carried out a computational study to elucidate the O–O bond-
formation mechanism in m-chloroperbenzoic acid and iron(IV)oxo reaction.

Nanozymes are functional nanomaterials with enzyme-mimicking activities. They are considered to be the next generation of enzyme mimics because of their unique features compared with natural enzymes and conventional enzyme mimics. They are not only more stable and cost-effective, but also have facilely tunable activity and multifunctionality. To this end, several reports in this collection demonstrated various ways to modulate the catalytic activity of nanozymes. Yigit and co-workers demonstrated that the peroxidase-like activity of 2D nanomaterials could be regulated by using metal ions; while Xia and co-workers showed that the peroxidase-like activity of Pd–Ir core-shell nanoparticles could be modulated by their sizes. By taking advantage of the size-dependent activity, they further developed more-sensitive immunoassays with smaller sized nanozymes. Su, Liu and co-workers systematically studied the effects of five representative phosphates on the oxidase-like activity of nanoceria. They showed that the promotion or inhibition effects of phosphates are dependent on the buffer, substrates, and the aggregation states of nanoceria. This study indicated that particular attention should be paid when using nanoceria as enzyme mimic. Rotello and co-workers used a biorthogonal approach to build a coating of monolayer transition metal catalyst to preserve its activity under various pH conditions and in complex biological media conditions under which a free transition metal catalyst is normally deactivated. This active-site-isolation strategy is more or less similar to an isolated active site in a natural enzyme.

The aforementioned studies showed the various strategies used to modulate the nanozyme activity; other articles have demonstrated the wide applications of nanozymes in sensing, diagnosis and therapeutics. Deng, Chen, Hong and co-workers reported copper oxide nanoparticle as an ascorbic acid oxidase–mimicking nanozyme. They further used it to construct a fluorescent assay to selectively detect ascorbic acid. Yin and co-workers reported a lysozyme-mediated exfoliation method to exfoliate MoS₂ and functionalize its surface. The lysozyme-stabilized MoS₂ nanosheets exhibited enhanced bacterial growth inhibition by physical cutting, hydrolyzing cell walls, and producing excessive ROS. Li, Gao and co-workers reported a copper-based bimetallic sulfide nanozyme (CuCo$_2$S$_4$) that displayed an excellent antibacterial performance due to its outstanding peroxidase-like activity under neutral pH conditions. Nitrogenases could also be mimicked by using nanomaterials. Liu, Yao and co-workers found that the bowknot-shaped iron molybdate nanosheet clusters were able to mimic nitrogenase because of the same bimetal-active atoms (i.e., Fe and Mo). They then synthesized ammonia in an electrochemical nitrogen reduction reaction (NRR) with iron molybdate as catalyst.

Three reviews on nanozymes were covered in this collection. Yang et al. summarized recent progress in the detection of virulent microorganisms by using nanozymes. Moreover, they offered many critical points that can be a helpful guide for practical and accurate future applications. In a minireview, Li and Ding highlighted recent developments and biomedical applications of nanozymes. The review of Gu and co-workers is focused on iron-based nanozymes. Taking iron oxide and Prussian Blue as two representative nanozymes, they discussed the synthesis, activity, mechanism and potential applications of iron-based nanozymes.

In their contribution, Wang, Wang, Liu and co-workers carried out a systematic study to understand the links between these two classic and widely used DNAzymes (i.e., GR5 and 17E). They were able to identify key nucleotides for metal specificity.

Even though the above collection represents only a very small fraction of the work in the field, the progress made will encourage the enzyme-mimic community and others to further advance the frontiers of the field. Here, a few potential directions are briefly discussed, solely from our own perspectives. First, although the inorganic complex-based and nano-material-based mimics are discussed separately here, combining...
them could lead to better enzyme mimics and even achieve synergistic properties. Second, traditionally, research into enzyme mimics aims to imitate protein enzymes, now the exploration of (ribo)nucleic acid-based enzyme mimics could be a rewarding adventure given the importance of ribozymes. Third, the combination of experiments (including advanced operando characterizations) with theoretical study is very helpful to understand catalytic mechanisms and design better mimics. Due to the intrinsically interdisciplinary nature of this field, the collaboration among researchers from chemistry, materials science, biology, medicine, etc. will bring more ground-breaking products to fulfill the promise of enzyme mimics and make a big difference in future science.

I am very grateful to all the authors for contributing high-quality papers to this Special Collection, and all the reviewers for their time and efforts in reviewing the recent development in enzyme mimics. I also wish to thank the Editorial Offices of the two journals for their work and help in organizing such a unique collection. Enjoy reading.
EDITORIAL

Making a difference: Inorganic enzyme mimics, mainly consisting of inorganic complexes and nanozymes, have attracted much interest and found widespread applications in healthcare, energy, and environmental fields. Because of their splendid properties, such as high stability, tailorable activity and low cost, these enzyme mimics are making and will continue to make a big difference in future science and technology.

Y. Zhang, Dr. F. Muhammad, Prof. Dr. H. Wei*

1 – 4

Inorganic Enzyme Mimics