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Current Opinion in
Green and Sustainable Chemistry

Remediation of environmentally hazardous organophosphates by artificial metalloenzymes

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Organophosphates constitute environmentally hazardous molecules that are commonly used in agriculture and various industries and as chemical warfare agents. They are extremely stable compounds with a half-life of up to thousands of years. Because of the lack of a protection against their harmful activities in the environment, recently intensive efforts have been made to design synthetic molecules for their hydrolytic degradation. These molecules include both peptidic (short peptides, three-stranded coiled coils, and four-helix bundles) and nonpeptidic (polyoxometalates, metal–organic frameworks, and organometallic complexes) compounds that are often inspired by the catalytic cores of hydrolytic enzymes. However, because of their structural simplicity, the current synthetic analogs are significantly less efficient than natural enzymes. They lack the effective combination of various chemical factors that provides enormous rate acceleration to enzymes. In this review, we discuss the recent progress made in the design of enzymatic mimics with potential applications in the decontamination of organophosphates.

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Current Opinion in Green and Sustainable Chemistry 2021, **32:**100529

This review comes from a themed issue on **Synthetic Enzymes**

Edited by **José M. Palomo**

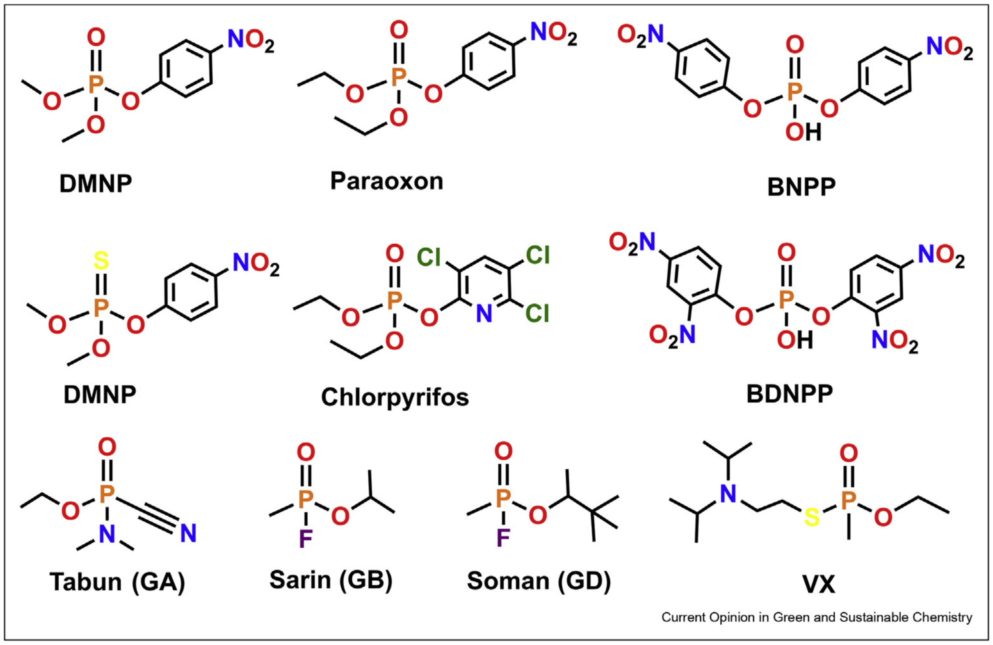
https://doi.org/10.1016/j.cogsc.2021.100529

Introduction

Organophosphates (OPs) are commonly used as insecticides, herbicides, and fungicides in several industries such as food processing, chemical, fertilizer, and textile as well as in agriculture, homes, and gardens [1]. They have also been exploited as chemical warfare agents in the form of nerve agents [2]. OPs have been known as some of the most toxic compounds to the environment and humans (Figure 1) [3–5]. Their toxicity stems from the ability to irreversibly inhibit acetylcholinesterase enzyme. Acetylcholinesterase hydrolyzes the neurotransmitter acetylcholine, which when over accumulated at neuron junctions leads to failure of many physiological functions and consequent death [2]. Among OPs, the insecticide paraoxon and the herbicide dimethyl *p*-nitrophenylphosphate (DMNP) are the most studied substrates in OP decontamination research (Figure 1). Because most OPs contain a non-natural phosphotriester bond and have been synthesized only in the last few decades, barely a couple of human enzymes have been evolved for their degradation. Thus, rigorous efforts have been made to design molecules to either capture or convert OPs into their less toxic forms.

Phosphotriester bonds are extremely stable and resistant to degradation. In the last few decades, because of heavy exposure of OPs, several plant and bacterial enzymes with binuclear metal cores have been evolved to hydrolyze these bonds. The heteronuclear or homonuclear catalytic cores of these enzymes exhibit rich chemical diversity and are formed by different transition metal ions (Zn, Fe, Mn, and Ca) and ligand environments. For instance, phosphotriesterase (PTE) isolated from *Pseudomonas diminuta* and *Flavobacterium* species has been reported to hydrolyze a wide range of OPs (Figure 2a). PTE catalyzes the hydrolysis of two nerve agents, sarin ($k_{cat}/K_m = 9.6 \times 10^3\ s^{-1}\ M^{-1}$) and soman ($k_{cat}/K_m = 8 \times 10^4\ s^{-1}\ M^{-1}$), approximately 10^6–10^7 times faster than their uncatalyzed degradation at pH 7. It also hydrolyzes paraoxon at nearly the diffusion-limited rate ($k_{cat}/K_m = 5 \times 10^7\ s^{-1}\ M^{-1}$) [6]. Its homonuclear (Zn–Zn) catalytic core provides an ideal environment to use a combination of critical chemical factors such as metal ions, ligands, metal cooperativity, noncovalent interactions, and Lewis acidity for its activity (Figure 2a). A detailed mechanism of the degradation of sarin by this enzyme has been proposed using quantum mechanics/molecular mechanics (QM/MM) and MM/molecular dynamics simulations [7]. Because of its remarkable substrate promiscuity, PTE has been one of the most commonly used enzymes for the development of new catalysts for the bioremediation of OPs. In addition, other binuclear enzymes such as glycerophosphodiesterase from *Enterobacter aerogenes* and OP-degrading enzyme from *Agrobacterium radiobacter* have been reported to degrade a variety of OPs [8,9]. Glycerophosphodiesterase exhibits a unique promiscuity by hydrolyzing all three types of

Figure 1



Chemical structures of some common organophosphates (OPs).

phosphoesters (monoesters, diesters, and triesters) as well as several OPs [8–12]. On the other hand, the OP-degrading enzyme from *A. radiobacter* is more efficient in detoxifying chemical warfare agents such as tabun and several pesticides [13,14].

Catalysts for OP degradation

In the last couple of decades, different types of synthetic metallohydrolases including peptidic and nonpeptidic have been developed for the degradation of OPs. However, this review focuses only on advances made in the last 2–3 years.

Peptidic analogs

Among the wide range of synthetic analogs, peptidic mimics are the closest to natural enzymes in terms of their structural complexity. They have even been proposed as precursors to natural enzymes and can adopt diverse structures such as beta-sheet [15], three-stranded coiled coils [16] and four-helix bundles (Figure 2) [17]. These polypeptides serve a twofold purpose by elucidating details of enzymatic functioning and providing templates for the design of their synthetic analogs. In these analogs, functional groups of the amino acid side chains that participate in the reaction provide powerful nucleophiles, activate the substrate by means of noncovalent interactions, stabilize developing charge, and assist the departure of the leaving groups. These self-assembling catalysts require an effective combination of hydrophobic, hydrophilic, and metal-binding residues. The small sequences of short peptides such as Ac-IHIHI$\underline{X}$I-NH_2 (heptapeptide) can self-assemble and catalyze a variety of chemical transformation (Figure 2b) [15]. Their active sites are exposed to solvents, and they can use either a mononuclear (formed by two monomers) or binuclear (generated by three monomers) center for catalysis. Their activities can be tuned by altering a single residue at position 6, and Gln is found to be the most efficient at this location for *p*NPA hydrolysis. For instance, the presence of a Tyr residue in the Ac-IHIHI$\underline{Y}$I-NH_2 sequence accelerates the degradation of paraoxon by more than three orders of magnitude ($k_{cat}/K_m = 1.7 \pm 0.6\ M^{-1}\ min^{-1}$) [18]. Moreover, activities of these small peptides can be further enhanced by mixing two different types of sequences with each other [19]. On the other hand, more structurally complex three-stranded coiled coils [16] and four-helix bundles [17] are formed by connecting α-helical peptides using one or more transition metal-binding sites. Our combined experimental and theoretical (QM/MM) data showed that formation of the heteronuclear three-stranded coiled coils is the most favorable and individual amino acid residues can determine their overall structures and activities (Figure 2c) [20]. In contrast to the previous peptidic analogs, the cavity of four-helix bundles effectively combines both hydrogen bonding and hydrophobic effects for substrate binding and catalysis (Figure 2d). In addition, it allows coordination of different metal ions with distinct ligand geometries. In terms of chemical complexity, these peptidic analogs are simpler than natural enzymes, but more intricate than small metal complexes discussed in the next sections. However, these analogues also lack an optimum ligand environment, second coordination shell residues, and a catalytic acid—base residue.

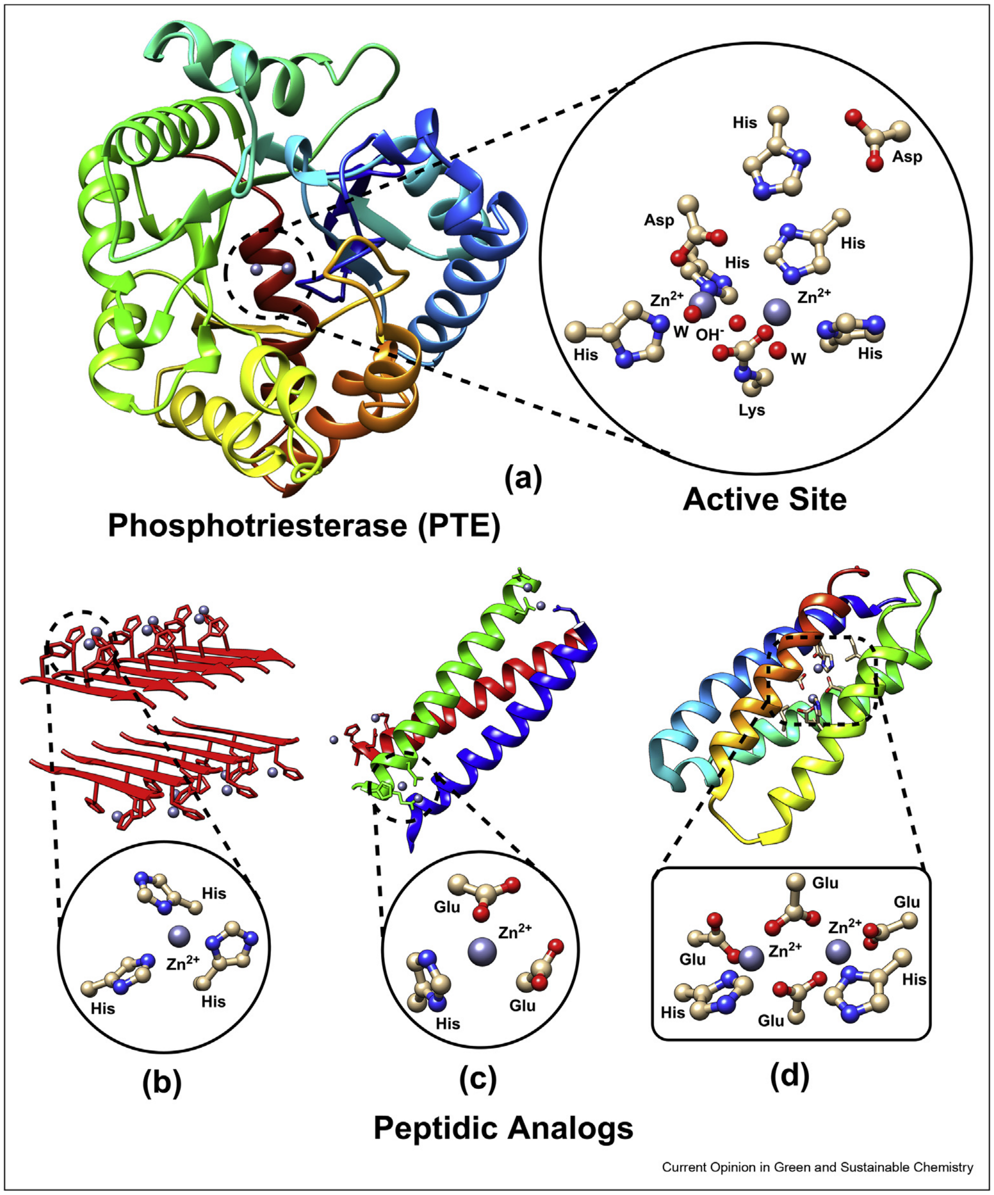
Nonpeptidic analogs

These analogues will require a productive combination of hydrophobic groups, hydrogen bond donating moieties, metal chelates, and the strategically placed organic functional groups on the ligand that are characteristics of enzymes.

Polyoxometalates

Polyoxometalates (POMs) constitute a class of nanosized metal-oxo clusters. Because of their solubility in water, stability, and high negative charge, POMs have been used for the hydrolysis of a wide range of molecules including OPs (Figure 3a). One of the most commonly used POMs is the Keggin-type Zr-containing polyoxotungstate $[PW_{11}O_{39}Zr(OH)(H_2O)_2]^{4-}$ that has been reported to hydrolyze DMNP at near-neutral pH [21]. In this reaction, acetate ions from the buffer were suggested to function as a local base and facilitated the hydrolysis.

Figure 2



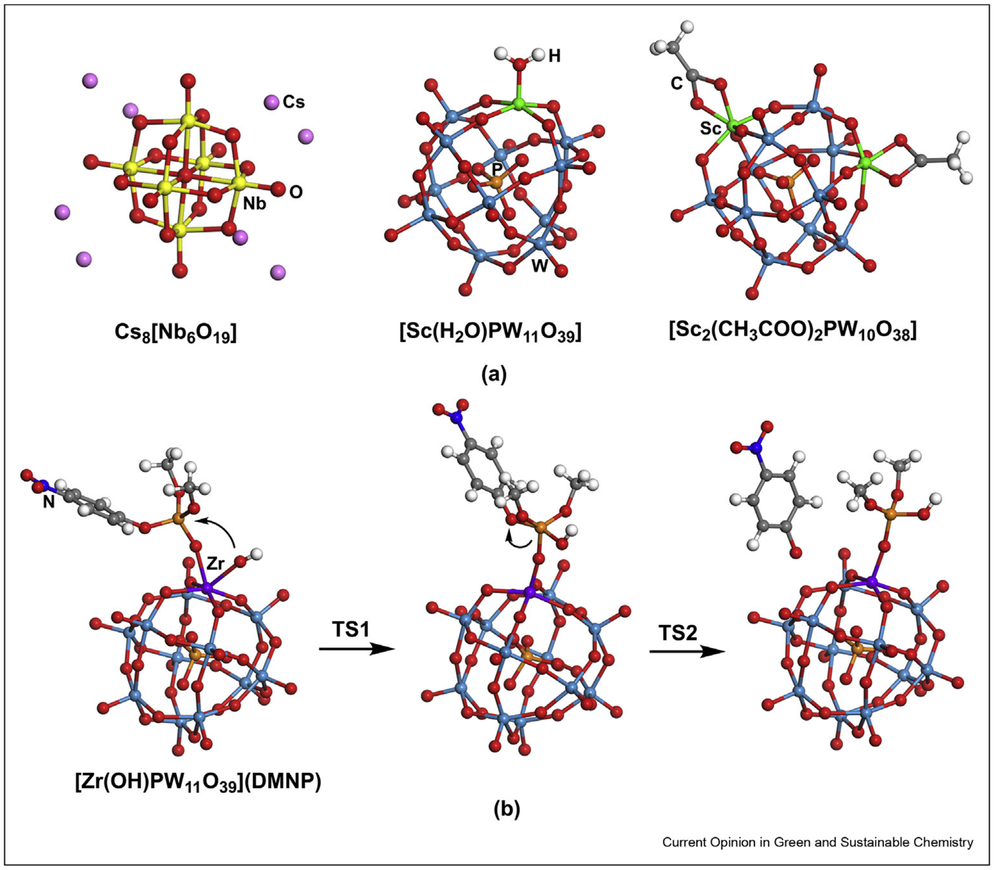
(a) Structure of phosphotriesterase (PTE) from *Pseudomonas diminuta* (PDB ID: 1EZ2), **(b)** structure of β-sheet amyloid (PDB ID: 5UGK), **(c)** three-stranded coiled coils (PDB ID: 2X6P), and **(d)** four-helix bundle (PDB ID: 2HZ8).

Density-functional theory calculations proposed an associative mechanism in which a nucleophilic attack from the Zr-bound hydroxyl ion on the electrophilic phosphorus atom generated a penta-coordinated phosphorane intermediate (Figure 3b) [22]. It then collapsed through the proton transfer from the hydroxyl group to the metal-bound phenoxy group. A $Cs_8[Nb_6O_{19}]$ polyoxoniobate type of POM has also been shown to hydrolyze dimethyl methylphosphonate (DMMP) and adsorb pollutant gases such as NO_2, CO_2, and SO_2 (Figure 3a) [23,24]. A combination of theoretical and experimental techniques (Raman, X-ray absorption fine structure (XAFS), and X-ray powder diffraction (XRD)) suggested that the decomposition of DMMP proceeded via the aforementioned mechanism. A much larger variant of this POM that contained approximately 300 Nb atoms was also synthesized [25]. However, it was concluded using infrared spectroscopic measurements that it can only exist in the solid state and readily dissociates in solution. One of its released fragments $[Nb_{47}O_{128}(OH)_6(CO_3)_2]$ was found to possess modest catalytic activity toward DMNP in the presence of $[Cu(en)_2]^{2+}$. Recently, two novel Keggin-type POMs were synthesized by addition of Sc^{3+} to the lacunary $[\alpha\text{-}PW_9O_{34}]^{-9}$ POM under different pH and buffer conditions (Figure 3a) [26]. Depending on the pH, monosubstituted and disubstituted forms of this complex were generated. The disubstituted form exhibited superior catalytic performance toward the hydrolysis of DMNP (97%) than the monosubstituted variant (28%) after 9 h. The distance between two metal Sc ions in this POM was 5 Å, which is much longer than the corresponding distance (~3.5 Å) in the natural metallohydrolases. This indicates that because of the rigidness of their frames, these synthetic analogs are deprived of metal cooperativity that is so efficiently used by the natural enzymes because of the plasticity of their active sites.

Metal–organic frameworks

In the last few years, a class of highly porous crystalline materials composed of metal nodes connected by organic linkers, termed as metal–organic frameworks (MOFs), has emerged as efficient bioinspired catalysts for the deactivation of OPs (Figure 4) [27,28]. The catalytic moieties in MOFs display lower catalytic rates and turnover frequencies than enzymes. However, they can withstand extreme thermal and pH conditions [29]. In addition, they can be fused in protective equipment

Figure 3



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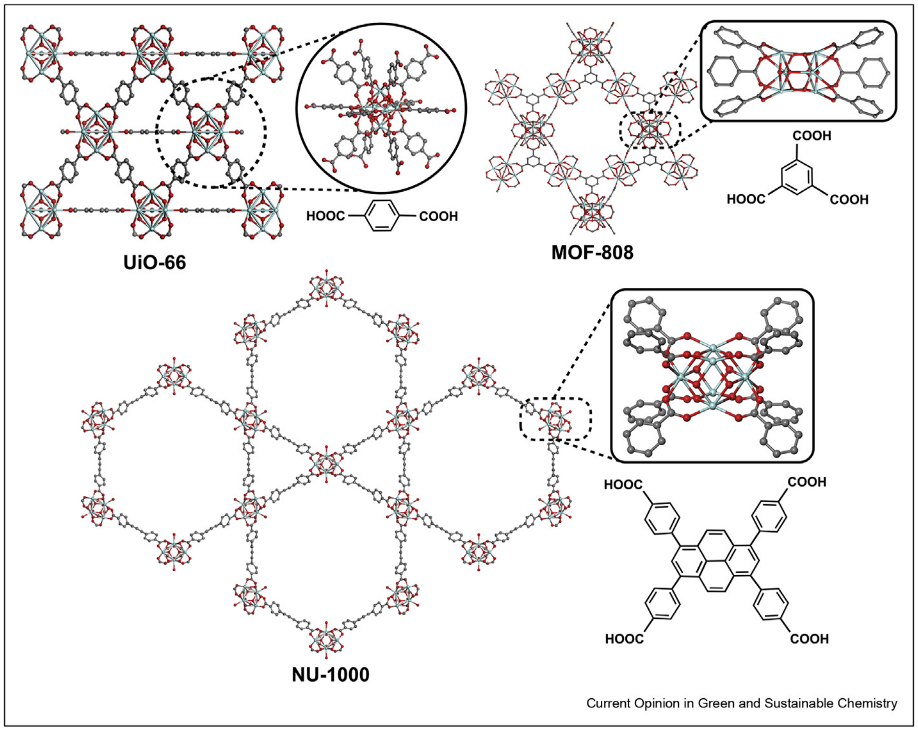
Structure of POMs **(a)** and **(b)** proposed mechanism of DMNP hydrolysis.

Figure 4



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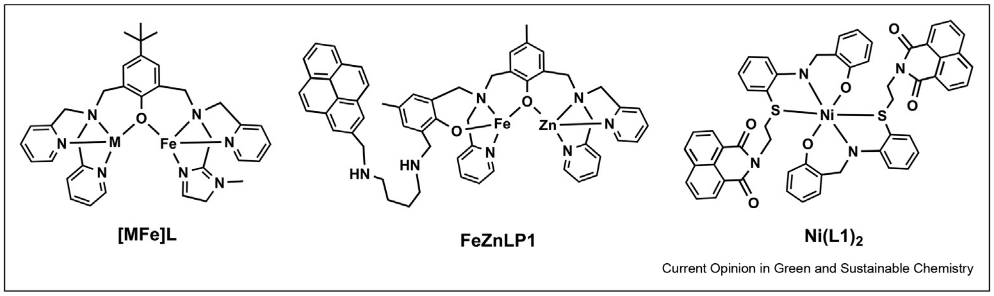
Structure of MOFs. The catalytic unit with different connectivity and organic linkers are highlighted for each MOF (UiO-66 12-connected/benzene-1,4-dicarboxylic acid, NU-1000 8-connected/1,3,6,8-tetrakis(p-benzoic acid)pyrene, and MOF-808 6-connected/benzene-1,3,5-tricarboxylic acid).

such as filters or woven in fabrics of gears to neutralize these toxic chemicals before they reach their biological targets. For instance, Zr(IV)-based MOFs [30] and, more recently, Ce(IV)-based MOFs [31,32] are the most common classes used for the hydrolysis of OPs. The Zr_6 clusters $[Zr_6(\mu_3\text{-}O)_4(\mu_3\text{-}OH)_4]$ of these heterogeneous catalysts mimicked the binuclear M−OH−M catalytic moiety of PTEs. Recently, the catalytic activity of different MOFs called UiO-66, NU-1000, MOF-808, and PCN-777 was analyzed for the hydrolysis of diverse OPs such as VX, soman, tabun, and paraoxon (Figure 4) [33]. Among them, the soman and tabun were hydrolyzed extremely fast by all MOFs in buffer conditions ($t_{1/2} < 1$ min), whereas VX ($t_{1/2} < 0.5$ min for MOF-808 and PCN-777) and paraoxon ($t_{1/2} = 2.6$ min for NU-1000) were hydrolyzed faster by MOFs with more catalytic sites (Figure 4). However, in the absence of a buffer solution, the hydrolysis was found to be slower and incomplete because of the catalyst poisoning.

Inspired by the presence of basic amino acid residues in the active site of PTEs, the organic linkers in MOFs

Figure 5



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Structures of organometallic complexes.

were functionalized with amine groups to enhance their activities. The introduction of the 4-(morpholinomethyl)benzoic linker in the modified NU-901 and MOF-808 reduced the half-life of VX by less than one minute using 12 mol% catalyst loading [34]. The next generation of hybrid composite MOFs capable of simultaneously absorbing and degrading the V-series agent VX and DMNP was developed by incorporating MOF-808 in highly porous styrene HIPE monolith polymer (Figure 4) [35]. The 'swell and destroy' approach used by this complex for the degradation of both compounds showed 95% degradation after 5 h for DMNP and 85% after 24 h for VX by using only 0.68 mol % of the catalyst.

Organometallic complexes

The catalytic performance of these molecules is still far inferior to the previous nonpeptidic analogs. However, these molecules are quite useful to elucidate mechanisms and understand distinct chemical factors such as electronic nature of metal ions, ligand environment, and noncovalent interactions that are responsible for enormous rate accelerations provided by enzymes. A few novel homogeneous and heterogeneous catalysts with both heterodinuclear and homodinuclear metal centers supported over an organic ligand framework have been synthesized (Figure 5) [36–38]. In heterogeneous complexes, catalysts were immobilized on different surfaces such as silica, polymers, and resins [38]. However, spectrometric and kinetic data of homogeneous complexes suggested that a monoaquated and dihydroxo specie $(M_1(H_2O)(\mu\text{-}OH)M_2(OH))^{2+}$ catalyzed the reaction. In another study, two dinuclear Fe—Zn complexes containing one and two pyrene groups, connected to the organic ligand framework by a 1,4-diamino butane linker, were synthesized (Figure 5) [39]. The goal was to investigate the roles of hydrogen bonding, electrostatic, hydrophobic effects, and van der Waals forces that are provided by the second coordination shell residues of enzymes. For instance, the hydrolytic activities of these complexes were significantly increased in comparison with activities of their parent compounds (a ligand without the pyrene group). Spectroscopic measurements unveiled that the pyrene group increased the affinity of the catalyst by π–π stacking interactions with the nucleotides of DNA and the arene groups of bis(2, 4-dinitrophenyl)phosphate. In addition, four novel octahedral nickel complexes with naphthalimide-based organic ligands were prepared by electrochemical methods (Figure 5) [40]. These complexes degraded parathion methyl and chlorpyrifos pesticides. The ^{31}P NMR titration data showed that parathion methyl and chlorpyrifos were completely hydrolyzed in 20 and 50 min, respectively.

Conclusions

In the last few years, tremendous gains have been made in the design of synthetic molecules to match the unprecedented enzymatic hydrolytic activities. However, an analysis of their activities shows that they are still significantly slower than natural enzymes. In contrast to enzymes, most of them combined only one additional effect (hydrogen bonding or hydrophobic effect) to the metal center(s). As a result, the combined effects of the metal ions, ligands, metal cooperativity, noncovalent interactions, Lewis acidity, nucleophile, and allosteric site so efficiently used by enzymes are absent in these complexes. The next generation of enzymatic mimics will require a deeper understanding of the roles of metal ions and ligand (direct and indirect) environment in the functioning of natural and artificial metallohydrolases and chemical modifications in the latter on the basis of those insights.

Funding

The authors declare no competing financial interests. This material is based on work supported by a grant from the National Science Foundation (grant number CHE-1664926) to R.P.

Declaration of competing 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 article.

Acknowledgements

Computational resources from the Institute of Data Science and Computing (IDSC) at the University of Miami are greatly acknowledged.

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