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Cleaving DNA-model Phosphodiester with Lewis Acid-Base Catalytic Sites in Bifunctional Zr-MOFs

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COMMUNICATION

Cleaving DNA-model Phosphodiester with Lewis Acid-Base Catalytic Sites in Bifunctional Zr-MOFs

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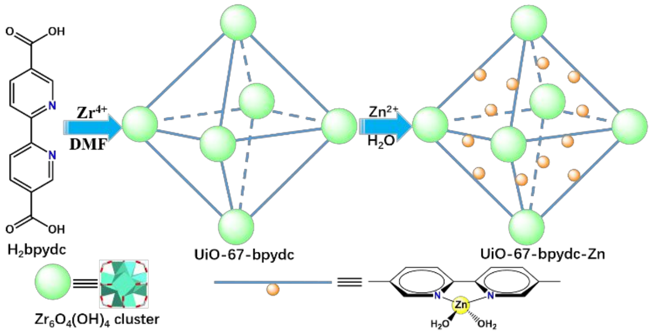
Abstract: Organophosphates exist in many biomolecules. The design of artificial nucleases for efficient P-O bond cleavage is essential for the fields of genetic engineering and molecular biology. Herein, metal-organic frameworks (MOFs) with cooperatively isolated multi-catalytic active sites were utilized as heterogeneous catalysts for the hydrolytic cleavage of bis(p-nitrophenyl) phosphate (BNPP).

Phosphodiester linkages in DNA are extremely resistant to hydrolysis, with a half-life of approximately two hundred million years under neutral conditions (pH 7.0 and 298 K).[1-3] However, the hydrolytic scission of DNA is an essential process in probing the structures and functions of nucleic acids in molecular biology and genetic therapy.[4] In contrast to DNA cleavage enzymes, low molecular weight artificial nucleases usually exhibit higher stability and less dependence on reaction conditions.[5]Therefore, it is of great desire to exploit artificial metallohydrolase to the increase cleaving ability of P-O bonds. Zinc complexes act as an ideal Lewis acid at its zinc ion coordination site, and are generally identified as an active site of hydrolase. An ideal Lewis acid may undergo rapid ligand-exchange and facile deprotonation of its coordinated water, which in turn induces effective hydrolysis cleavage.[6-8] Although the zinc hydroxide Lewis base species is known to be highly active for breaking the P-O bond, homogeneous molecular catalysts often undergo a polymerization process bridged by the hydroxide group, resulting in deactivation of its catalytic performance.[9,10] Heterogeneous catalysts, with the merit of homogeneous catalytic sites and multi-site-isolation, may overcome the above decomposition process.[11,12] At present, some CeO_2-based nanomaterials and porous organic polymers have been designed as heterogeneous catalysts for cleaving the P-O bond of organophosphate reagents.[13-15] Alternatively, metal-organic frameworks (MOFs) constructed by metal nodes and organic linkers have attracted tremendous attention in the development of heterogeneous catalysis due to the benefits of precise pore size control, large surface areas, and tunable structures.[16-19] Recently, Zr^{IV}-based MOFs, such as MOF-808, NU-1000 and UiO-66 with Zr_6-cluster nodes, have demonstrated their capabilities to degrade organophosphorate via Zr^{IV} cations serving as strong Lewis acids to activate and cleave the P-O bond.[20-22] UiO-67-bpydc has a similar structure to UiO-66, which can be further functionalized by metalation, where the linkers with open coordination sites could further coordinate with other active metal ions. The main hypothesis of this work is that the catalytic performance of MOFs can be further improved by coupling the Lewis acid catalytic site at the node with the Lewis base catalytic site via the zinc center at the linker.



Scheme 1. Schematic illustration depicting synthesis of UiO-67-bpydc-Zn for BNPP hydrolysis.

Herein, Zr-MOFs of UiO-67-bpydc and UiO-67-bpydc-Zn were synthesized as heterogeneous catalysts for the cleavage of bis(*p*-nitrophenyl) phosphate (BNPP) as the DNA model. The observed first-order rate constants were determined to be 2.23×10^{-4} and 4.31×10^{-4} s^{-1} at pH 7.8 and 308 K by the initial rate method. This catalytic activity is almost 100-fold higher than most dinuclear molecular zinc complexes. pH effect on BNPP hydrolysis was further investigated under various pH conditions at 308 K (Figure 4).

As shown in Scheme 1, UiO-67-bpydc was prepared by a solvothermal reaction of $ZrCl_4$, 2,2'-bipyridine-5,5'-dicarboxylic acid (H_2bpydc), and benzoic acid as a modulator in DMF. UiO-67-bpydc-Zn was obtained via postsynthetic modification of UiO-67-bpydc nanocrystals by reacting with zinc perchlorate salts in aqueous solution. As illustrated in Figure 1a, the MOF structure is assembled by bridging linkers of $bpydc^{2-}$ with the 12-connected second building unit (SBU), consisting of six zirconium atoms with eight μ_3-OH and μ_3-O groups from twelve carboxylate groups. Scanning electron microscopy (SEM) images reveal that UiO-67-bpydc and UiO-67-bpydc-Zn crystallize with a well-defined octahedron morphology and an average size of 3.2 μm (Figure 1b-e). Moreover, energy-dispersive X-ray spectroscopy (EDX) analysis in a scanning transmission electron microscope revealed the coexistence of zicorium, zinc, carbon, oxygen, and nitrogen (Figure S1). These results indicate that the zinc atoms are homogeneously dispersed over the entire MOF architecture (Figure 1f). The Zn content in UiO-67-bpydc-Zn was determined to be 1.42 wt%, by inductively coupled plasma atomic emission spectroscopy (ICP-AES).

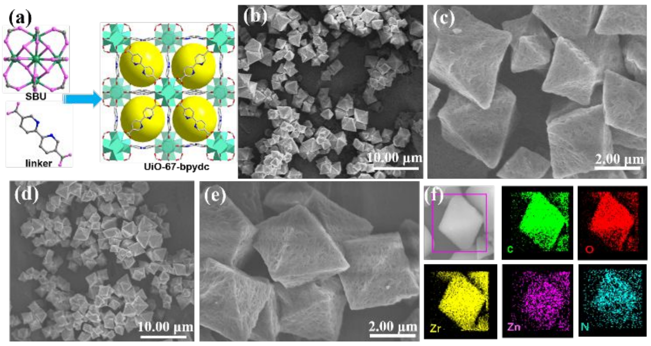


Figure 1. (a) Representation of UiO-67-bpydc. SEM images with different magnification of UiO-67-bpydc (b, c) and UiO-67-bpydc-Zn (d, e). Corresponding EDS maps of UiO-67-bpydc-Zn (f).

Additionally, UiO-67-bpydc and UiO-67-bpydc-Zn were characterized by powder X-ray diffraction patterns (PXRD) (Figure 2a), which match well with the simulated pattern of single crystal UiO-67.[23] Enlarged partial FT-IR spectra of UiO-67-bpydc and UiO-67-bpydc-Zn are shown in Figure 2b. For all samples, the observed vibration bands between 1350-1800 cm^{-1} were assigned to the carboxylate stretch, which differentiated the MOF compounds from the precursor ligand (H_2bpydc). FT-IR results indicate that the COO^- groups were ligated to metal ions with the 1700 cm^{-1} peak decreasing in intensity after coordinating,[24] while the 663 cm^{-1} peak corresponds to the formation of a Zr-O bond in the MOF node.[25] In the case of UiO-67-bpydc-Zn, a sharp peak at 1085 cm^{-1} can be attributed to the unique stretching vibration of the ClO_4^- anion.[26] This suggests that the zinc ions ligated to the linker through the Zn-N bonds, and the perchlorate anions may be utilized to maintain the charge equilibrium. Moreover, XPS measurements had been performed to investigate the interaction between the nitrogen atom of the bipyridine linker and the zinc ion in UiO-67-bpydc-Zn, and compared with the mixture of UiO-67-bpydc and zinc perchlorate (denoted UiO-67-bpydc/Zn). As shown in Figure S2, C1s peak position of UiO-67-bpydc-Zn (284.78 eV) and UiO-67-bpydc/Zn (284.73 eV) was almost identical. However, the zinc $2p_{1/2}$ (1022.23 eV) and $2p_{3/2}$ (1045.18 eV) peaks in UiO-67-bpydc-Zn (Figure 2c) exhibited a slight shift toward lower binding energy compared to UiO-67-bpydc/Zn. The N 1s peak at 399.53 eV (Figure 2d) also demonstrated similar binding energy shifts, indicating the formation of Zn-N coordination bond.[27-29] Additionally, thermogravimetric analysis (TGA) of UiO-67-bpydc-Zn was performed (Figure S3). Two weight-loss steps were observed in the TGA profiles, indicating decomposition of the organic moieties and collapse of the framework at about 410 °C.

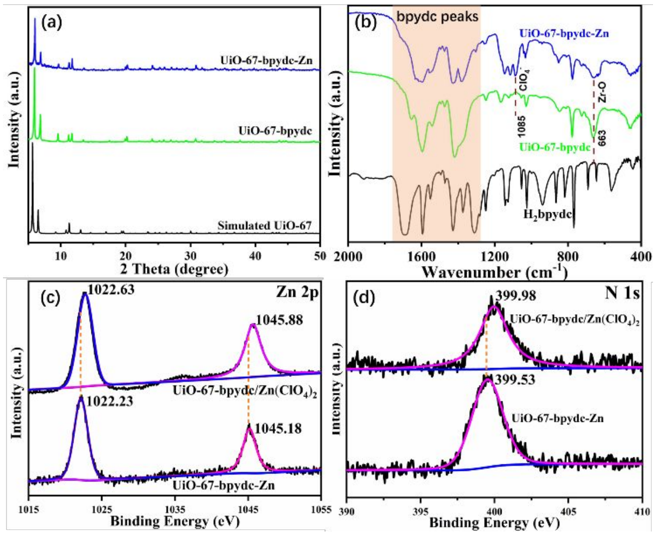


Figure 2. PXRD patterns (a) and FT-IR spectra (b) of UiO-67-bpydc and UiO-67-bpydc-Zn; XPS spectra (c) of Zn 2p and (d) N 1s in UiO-67-bpydc-Zn compared with the mixture of UiO-67-bpydc and $Zn(ClO_4)_2{\cdot}6H_2O$.

To investigate catalytic activity for the hydrolysis of BNPP, the initial reaction rates were obtained by the appearance of the *p*-nitrophenolate peak at 400 nm in aqueous solution. [30,31] Absorbance versus reaction time during hydrolysis of BNPP catalyzed by UiO-67-bpydc and UiO-67-bpydc-Zn (at pH 7.8 and 308 K) was plotted during the 150-min reaction (Figure 3a). The 2,2'-bipyridine zinc complex (bpy-Zn), $Zn(ClO_4)_2{\cdot}6H_2O$, and sodium perchlorate were employed as control experiments, respectively. All three exhibited negligible activity for hydrolytic cleavage of BNPP. In the case of the bpy-Zn complex (Figure S4),[32] each zinc ion is hexa-coordinated by three bipyridine ligands and thus has no unsaturated coordination site, unlike the MOF UiO-67-bpydc-Zn structure. The observed first-order rate constants (k_{obs}, min^{-1}), were obtained from plotting $\log[A_\infty/(A_\infty - A_t)]$ versus time ($R^2 \geq 0.98$) (Figure 3b),[33] in which A_t is the observed absorbance at 400 nm at time t, and A_∞ is the final absorbance at the end of the reaction. The k_{obs} values of UiO-67-bpydc and UiO-67-bpydc-Zn were found to be 2.23×10^{-4} and4.31×10^{-4} s^{-1} at pH 7.8, respectively (Figure S5). The catalytic activity of UiO-67-bpydc-Zn is 1.94-fold higher than that of the pristine UiO-67-bpydc. The enhancement may be due to the formation of zinc hydroxide by deprotonation of coordinated water in the bipyridine-based zinc complex under slightly basic conditions,[34] thereby acting as a Lewis base for nucleophilic attack on the P-O bond.[8,10] The BNPP hydrolysis rate clearly increased when altering the UiO-67-bpydc-Zn amounts from 2.5 to 5.0 mg (Figure S6), while the reaction rate only slightly increased when more catalyst is added (10.0 to 15.0 mg). This might be explained by a saturation effect between catalyst and substrate at higher catalyst concentration. The k_{obs} value of UiO-67-bpydc-Zn is much larger than other reported heterogeneous catalyst containing zinc complexes (Table 1).[35,36]

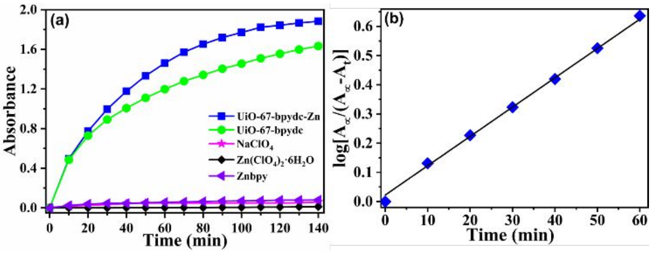


Figure 3. (a) Absorption at 400 nm of 0.75 mM BNPP hydrolysis at 308 K catalyzed by the materials (5.0 mg of UiO-67-bpydc-Zn, UiO-67-bpydc, $Zn(ClO_4)_2{\cdot}$ $6H_2O$, $NaClO_4$ and bpy-Zn complex) at pH 7.8 with the buffer solution as a reference. (b) Plots of log $[A_\infty/(A_\infty - A_t)]$ *versus* time for 60 min during BNPP hydrolysis catalyzed by UiO-67-bpydc-Zn.

Table 1. The observed rate constant (k_{obs}) for BNPP hydrolysis over zinc compounds.

Catalyst amount	Reaction conditions	k_{obs} (s^{-1})	Ref.
UiO-67-bpydc 0.25 mg/mL	H_2O, 308 K pH 7.8	2.23×10^{-4}	this work
UiO-67-bpydc-Zn 0.25 mg/mL	H_2O, 308 K pH 7.8	4.31×10^{-4}	this work
$\{Zn_3(dpdo)_7\}[PW_{12}O_{40}]_2{\cdot}3H_2O$ [a] 81.35 mg/mL	H_2O, 323 K pH 8.2	8.80×10^{-7}	[35]
[MPGN-Zn] [b] 72.63 mg/mL	H_2O/MeOH, 313 K pH 7.0	3.60×10^{-5}	[36]

[a] dpdo = 4,4'-bipyridine-*N*,*N'*-dioxide ; [b] MPGN = monolayer protected gold nanoparticles.

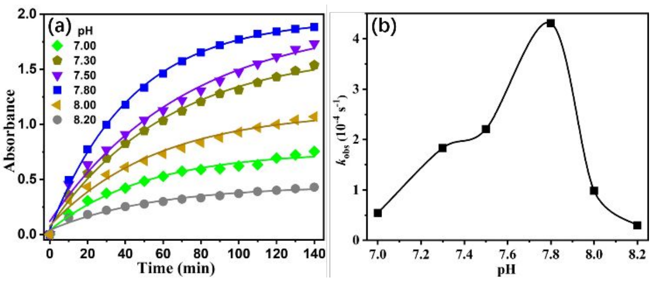


Figure 4. (a) The hydrolysis of BNPP activity at different pHs, monitored by absorption at 400 nm and (b) the observed first-order rate constant for 0.75 mM BNPP hydrolysis catalyzed by 5.0 mg of UiO-67-bpydc-Zn at the various pHs with the corresponding buffer solutions as the references (308 K). Ionic strength (0.1 M) was adjusted with $NaClO_4$.

This improved activity may be attributed to multiple factors. It is well-known that the Zr^{4+} ion in MOFs can behave as a Lewis acid to activate P-O bonds, facilitating efficient nucleophilic attack by water or hydroxide.[37,38] The Lewis basicity of zinc hydroxide in the linker may further promote the catalytic efficiency for hydrolysis. pH effects on catalyst activity were further studied (Figure 4a) over a range of pH 7.0-8.2 with the corresponding buffer solutions as references (308 K). The ionic strength (0.1 M) was adjusted with $NaClO_4$. Compared to UiO-67-bpydc-Zn, the pure buffer solutions exhibited a very slow catalytic rate for BNPP hydrolysis (Figure S7), although its hydrolysis performance enhanced slightly with increasing pH (7.0 - 8.2). The relationship between calculated k_{obs} and pH values presents as a bell curve (Figure 4b), which suggests the optimal catalytic activity can be obtained at pH 7.8. Rapid decay of k_{obs} is observed when the pH is higher than 7.8, or slightly smaller than 7.8. This phenomenon is similar to a reported work on organophosphate hydrolysis catalyzed by UiO-66, in which the rate constant decreases under higher pH conditions due to excess OH^- anions firmly occupying open sites on the Zr^{4+} ions, inhibiting the interaction between the Zr^{4+} ions and the phosphodiesters.[39] To further investigate the pH influence on UiO-67-bpydc-Zn, potentiometric titrations were performed. The pH titration curve of UiO-67-bpydc-Zn (Figure 5a) in aqueous solution exhibited three equivalence points (pH ~4.5, 7.9, and 9.6), in contrast to UiO-67-bpydc (Figure 5b) with only two equivalence points. The equivalence points at pH 4.5 and 9.6 can be attributed to the deprotonation of aryl formic acid (pK_a ~4.2) and the formation of zirconium hydroxide (pK_a 9.2), respectively. [40,41] The equivalence point at pH 7.9 for UiO-67-bpydc-Zn can be assigned to zinc center deprotonation. This pH value is also in excellent agreement with the optimal pH value (7.8) for hydrolysis of BNPP. Therefore, the above results further confirm that improved catalytic activity of UiO-67-bpydc-Zn can be attributed to the combination of zirconium ions in the SBU acting as Lewis acids and the Lewis base zinc hydroxide species in the MOF linker, as illustrated in Figure 5c.

Additionally, the kinetics of catalytic BNPP hydrolysis promoted by UiO-67-bpydc-Zn was carried out at different temperatures. As shown in Figure 6, the catalytic rate of BNPP hydrolysis by UiO-67-bpydc-Zn increased with elevating temperature. The logarithm of the rate constants (ln*k*) and the reciprocal of temperature (1/T) complied with Arrhenius Law, where the value of the activation energy (E_a) was calculated to be 37.66 kJ mol^{-1}. The E_a value of UiO-67-bpydc-Zn surpasses that of most literature-recorded zirconium heterogeneous catalysts for P-O bond cleavage, [42,43] suggesting a favorable transition state with a lower activation barrier in the catalytic process.

The recyclability of UiO-67-bpydc-Zn was also investigated at 308 K and pH 7.8. As shown in Figure S8, the catalytic activity slightly decreased *ca.* 7% after the fifth run with centrifugation of the catalyst. From PXRD analysis (Figure S9), UiO-67-bpydc-Zn maintained the framework structure after five runs. This indicates good reusability of the catalyst in the cleavage of P-O bonds.

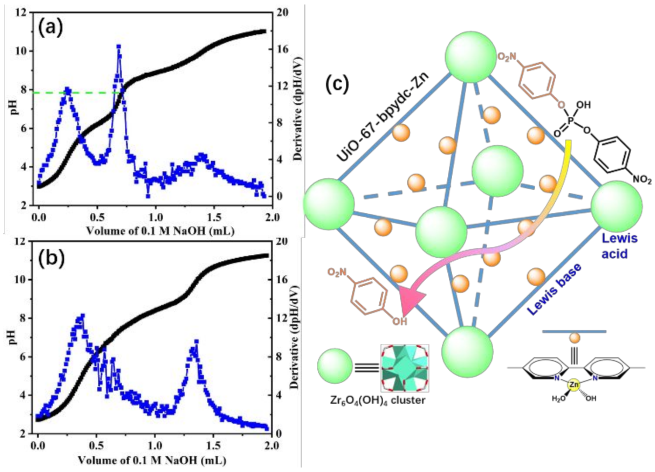


Figure 5. Titration curves of pH values (black solid line, left *y*-axis) and differential values of d(pH)/dV (blue dotted line, right *y*-axis) as a function of additional NaOH volume for (a) UiO-67-bpydc-Zn and (b) UiO-67-bpydc at 308 K. The green horizontal dotted line is located at pH = 7.9. (c) The proposed illustration of BNPP hydrolysis catalyzed by UiO-67-bpydc-Zn with bifunctional Lewis acidic-basic sites.

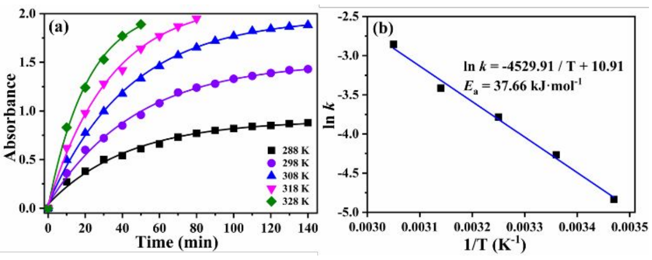


Figure 6. (a) The kinetics of catalytic BNPP hydrolysis catalyzed by UiO-67-bpydc-Zn were surveyed at various temperatures (T = 288 - 328 K) at pH 7.8. (b) The Arrhenius plot was obtained by the dependence of logarithm of rate constants on the reciprocal of temperature.

Conclusions

UiO-67-bpydc-Zn MOF has been designed and easily synthesized to serve as the catalyst for cleavage of BNPP as a DNA model compound. This heterogeneous catalyst contains isolated multi-catalytic active sites located at separated positions in the MOF. The enhanced activity of BNPP hydrolysis over UiO-67-bpydc-Zn may be attributed to the combination catalysis provided by the Lewis acid from the zirconium center at the node and the zinc hydroxide Lewis base in the linkers, distinguishing this heterogeneous catalyst from previously reported molecular catalysts. Analysis reveals that this heterogeneous catalyst exhibits remarkable catalytic performance compared to most reported zinc molecular catalysts, likely due to inherent benefits obtained from the dual-functional catalytic centers in the MOF structure. These findings may serve as a foundation for constructing phosphatase mimics for potential applications in DNA cleavage agents and degradation of toxic organophosphorus.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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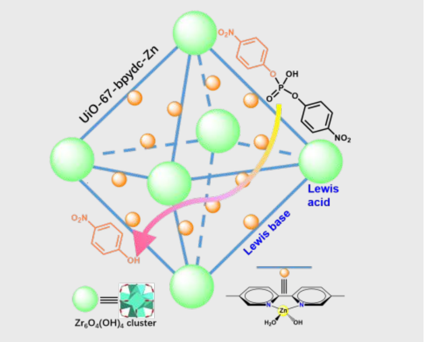
Table of Content

UiO-67-bpydc-Zn with isolated multi-catalytic active sites was fabricated as catalysts for the hydrolysis of bis(*p*-nitrophenyl) phosphate as a DNA model. The enhanced activity may likely be contributed to the cooperation effects between the Lewis acid from the zirconium center at the node and the zinc hydroxide Lewis base in the linkers, which distinguishes this heterogeneous catalyst from previously reported molecular catalysts.



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