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Intrinsic Apyrase-Like Activity of Cerium-Based Metal-Organic Frameworks: Dephosphorylation of Adenosine Tri- and Diphosphate

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Abstract: Apyrase represents an important family of extracellular enzymes that catalyze the hydrolysis of high-energy phosphate bonds (HEPBs) in ATP and ADP, thereby modulating many physiological processes and driving life activities. Here, we report an unexpected discovery that cerium-based metal-organic frameworks (Ce-MOFs) of UiO-66(Ce) possess intrinsic apyrase-like activity for the intervention of ATP/ADP-related physiological processes. The abundant Ce(III)/Ce(IV) couple sites of Ce-MOFs endow them with the ability to selectively catalyse the hydrolysis of HEPBs of ATP and ADP under physiological condition. Compared to natural enzymes, they could resist to extreme pH and temperature, and present a broad range of working conditions. Based on this finding, a significant inhibitory effect on ADP-induced platelet aggregation was observed upon exposing the platelet-rich plasma (PRP) to the biomimetic UiO-66(Ce) films, prefiguring their wide application potentials in medicine and biotechnology.

The dephosphorylation of ATP is an important energy transfer process to drive life activities through the catalytic hydrolysis of high-energy phosphate bonds (HEPBs). Meanwhile, many important physiological processes, such as blood clotting, inflammation, immune response as well as neurotransmitters, are regulated with ATP and ADP as signaling molecules through the catalytic hydrolysis of their HEPBs using apyrase (nucleotide triphosphate diphosphohydrolases) as a catalyst (**Figure 1a**).[1] Despite the extensive distribution and evolution of apyrase family in plants, microorganisms and mammals,[2] there is few reports, if any, on the development of biomimetic materials to satisfy with its enzymatic mimics for the intervention of ATP/ADP-related physiological processes.

MOFs represent a rapidly growing class of crystalline materials with broad applications.[3] Their ordered topology provides high-density accessible metal centers with well-defined metallocluster structure and spatial arrangement, making MOFs singularly attractive as biomimetic catalytic materials.[4] In recent years, a few studies have demonstrated that selected MOFs with specific metal nodes could serve as efficient mimics for various metalloenzymes.[5] In view of the important roles of ATP and ADP played in many physiological processes through dephosphorylation, it naturally promotes us to explore the possibility of using periodically aligned metalloclusters in MOFs to mimic apyrase for the selective hydrolysis of HEPBs.

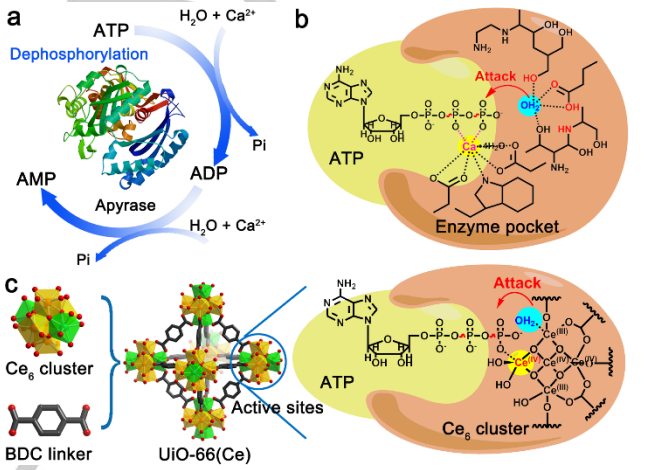

Figure 1. Schematic illustration of (a) the catalytic hydrolysis process and dephosphorylation mechanism of ATP over (b) apyrase and (c) UiO-66(Ce). In the form of a plan view, molecular structure of the surface Ce_6 node of UiO-66(Ce) shows five of the eight bound BDC ligands, since three linkers are overlapped.

The dephosphorylation of ATP over natural apyrase generally consists of two main steps (**Figure 1b**): (i) two phosphate groups of substrate directly coordinate with a divalent metal cation and enter into the catalytic pocket of enzyme; (ii) a nucleophilic water molecule approaches several adjacent amino acid residues of apyrase and further attacks the terminal phosphate group to drive the dephosphorylation process.[1b] To mimic the functions of natural apyrase, the key element is to provide active sites which afford appropriate affinity and enough catalytic activity toward the hydrolysis of HEPBs. Meanwhile, the hydrolyzed product of inorganic phosphates is subject to leave the active sites. After screening numerous MOFs family, we made an unexpected discovery that Ce-MOFs of UiO-66(Ce) indeed featured intrinsic apyrase-like activity (**Figure 1c**). Compared to natural apyrase family, the biomimetic UiO-66(Ce) nanoparticles (NPs) could drive the dephosphorylation process in the absence of divalent cation, and rapidly convert a part of ATP into AMP. More importantly, they present an excellent stability against extreme temperature and pH, as well as broad working range. It is

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experimentally revealed that Ce(IV)-OH groups function as the active sites for the polarization and hydrolysis of HEPBs while Ce(III) species might work as synergistic sites to attract H_2O molecules for the promotion of hydrolysis process (**Figure 1c**, **right**). Given the apyrase-like activity of UiO-66(Ce) NPs, we fabricated flexible UiO-66(Ce) film as a bionic antithrombotic coating to inhibit ADP-induced platelet adhesion, exemplifying their wide application potentials for the intervention of ATP/ADP-related physiological processes in life sciences.

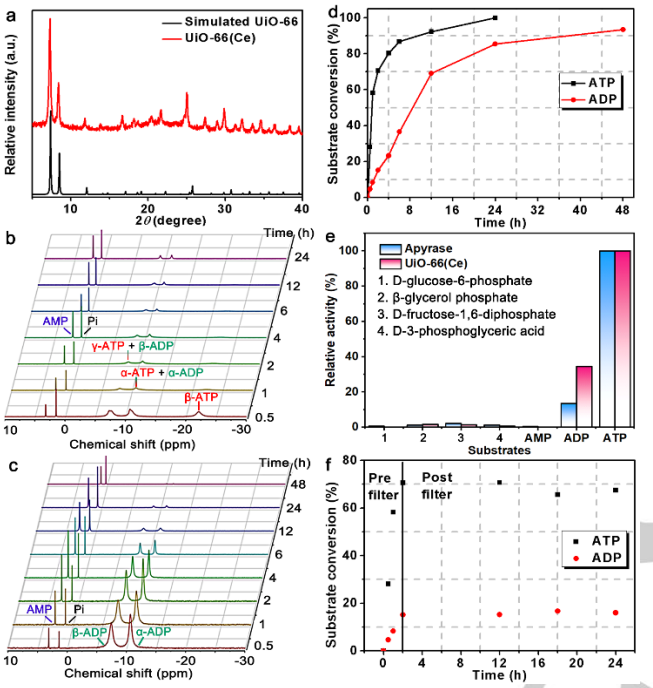

Figure 2. (a) XRD patterns of the UiO-66(Ce). ^{31}P-NMR spectra of the catalytic hydrolysis process for (b) ATP and (c) ADP by UiO-66(Ce) in physiological conditions (pH = 7.4; 37 °C). (d) Conversion percentage of substrates versus time over UiO-66(Ce). (e) The relative activities of UiO-66(Ce) and apyrase toward the catalytic hydrolysis of various phosphate bond-containing substrates. (f) Hydrolysis profiles of ATP and ADP in the presence of UiO-66(Ce) and after the removal of Ce-MOFs by filtration.

The preparation of UiO-66(Ce) was optimized through a modified solvothermal reaction (**Figures S1 and S2**).[6] The XRD patterns reveal that the pure phase of UiO-66(Ce) is obtained (**Figure 2a**). Meanwhile, their BET surface area is determined to be about 1318 m^2 g^{-1}, comparable to the reported value (**Figure S3**).[6] Based on the TGA profile, the number of linker deficiencies of per Ce_6 formula unit is calculated to be about 1.23 (**Figure S4**). ^{31}P-NMR spectra were employed to monitor the ATP hydrolysis process over UiO-66(Ce) in physiological condition with apyrase as comparison. Similar to a typical apyrase catalytic pathway (**Figure S5a**),[7] it could be observed that the characteristic peak of β-ATP gradually disappears within 24 h and converts into those of α-ADP, β-ADP, AMP and phosphate over UiO-66(Ce) (**Figures 2b and S6**). Meanwhile, the characteristic peak of pyrophosphate (around -5.3 ppm) is not detected,[8] demonstrating that ATP converts into AMP through a sequential hydrolysis of their terminal phosphate over UiO-66(Ce). The similar catalytic phenomena were also observed when ADP was directly employed as the substrate over UiO-66(Ce) and apyrase (**Figures 2c and S5b**). Interestingly, different from the apyrase-catalytic pathway, an obvious characteristic peak of AMP is rapidly formed at the initial 30 min during the ATP hydrolysis process with UiO-66(Ce) (**Figure 2b**), similar to the catalytic behavior of CD39 oligomers.[9] The presence of the high-density periodically aligned active catalytic centers of metalloclusters on the UiO-66(Ce) might rationalize the fact that a lot of ATP could rapidly convert into AMP. A part of ADP intermediate released from the cerium sites might be immediately recombined by a large number of adjacent catalytic centers and further hydrolyzed to AMP, so that they could reduce the accumulation of ADP during the hydrolysis process of ATP.

Kinetic curves display that the hydrolysis rate of ATP over Ce-MOFs is much quicker than that of ADP (**Figure 2d**), similar to the catalytic process using apyrase as a catalyst (**Figure S5c**). On the other hand, AMP plays an important role in many physiological metabolisms and participates in ATP regeneration cycle through rephosphorylation,[10] thus the selective hydrolysis of HEPBs is of great significance for apyrase mimics. Fortunately, UiO-66(Ce) could selectively dephosphorylate ATP and ADP without the obvious destruction of phosphomonoester bonds in AMP and other nonnucleoside phosphates (**Figure 2e**). To further verify that the observed activity really results from UiO-66(Ce), the reaction mixtures were filtered to remove the mimic enzyme of Ce-MOFs during the reaction process.[11] As shown in **Figure 2f**, the catalytic reactions were terminated immediately upon removing Ce-MOFs. Furthermore, the hydrolysis of ATP and ADP was negligible when no UiO-66(Ce) was applied to the reaction system as the control measurement verified (**Figure S7**), further confirming that the occurrence of dephosphorylation was indeed due to the presence of Ce-MOFs.

Temperature, pH and divalent cations are important factors that impact the catalytic activity of apyrase.[1b,12] It could be observed that UiO-66(Ce) could directly dephosphorylate ATP/ADP substrate, in which the catalytic efficiency is independent on the addition of Ca^{2+} (**Figures S8 and S9**). It matches well with the fact that the metalloclusters on the surface of UiO-66(Ce) play active sites to catalyze the hydrolysis of the terminal phosphate group of ATP/ADP. The optimal pH for UiO-66(Ce) is determined to be approximately 7.4 through a standard malachite green assay (**Figures 3a and S10**),[13] which is similar to the value for apyrase (**Figure S11a**). Additionally, apyrase presents the optimal catalytic activity between 30 to 40 °C, while its activity is significantly inhibited at higher temperature (**Figures 3b and S11b**). In contrast, the catalytic activity of UiO-66(Ce) constantly increased upon elevating the temperature to 60 °C. Obviously, the excellent stability of Ce-MOFs could enable them to resist higher reaction temperature and to promote the hydrolysis efficiency of substrate. To test this, we measured their catalytic activity after the pre-incubation under various pHs and temperatures. The UiO-66(Ce) were indeed found to preserve their catalytic activity after pre-treatment (**Figures 3c, 3d and S12**). In contrast, the apyrase enzyme only maintains their activity after the mild treatment at pHs between 5 to 9, or temperatures lower than 50 °C. Given that the activity of apyrase is susceptible to temperature, pH and extensive protease, the robustness of UiO-66(Ce) NPs makes them suitable for a wide range of applications in the biotechnology.

Since ATP molecule is too large to access the interior of UiO-66, thus the catalysis mainly occurs on the Ce_6 clusters on the surface of MOFs.[14] To investigate the mechanism of the apyrase-like activity of UiO-66(Ce), XPS spectra were firstly employed to

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reveal the detailed surface compositions of UiO-66(Ce). The Ce3d XPS spectra of UiO-66(Ce) disclose that Ce ions exist in different valence states (**Figure 3e**).[15] The ratio of Ce(III)/Ce(IV) on the surface is estimated to be around 2 : 4 (**Table S1**), which means each $Ce_6O_4(OH)_4$ cluster on the surface contains two Ce(III) and four Ce(IV) ions on average. The O1s XPS spectra reveal that approximate 67% oxygen presents in the form of surface Ce-OH groups (**Figure S13**),[16] further confirming the presence of dense and exposed Ce(III)/Ce(IV) hydroxyl active sites for the catalytic reaction. After the catalytic hydrolysis of ATP, UiO-66(Ce)-ATP sample exhibit negligible change of surficial Ce(III)/Ce(IV) ratio (**Figure S14 and Table S2**), indicating that the reaction would not affect the catalytic sites thanks to the excellent chemical stability of UiO-66(Ce).

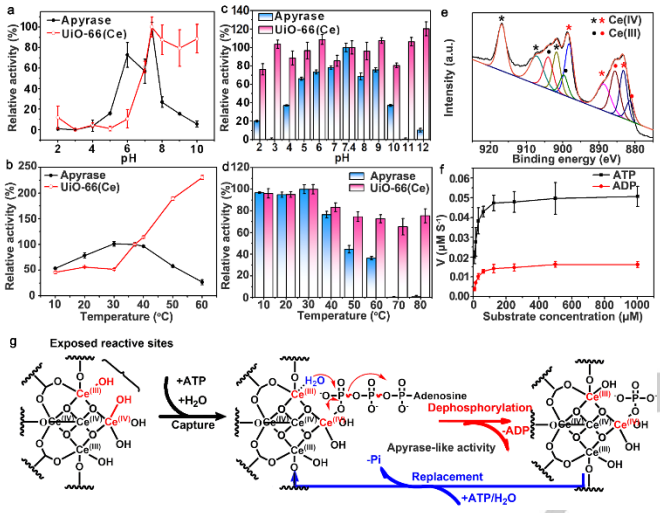

Figure 3. Effects of (a) pH and (b) temperature on ATP hydrolysis over apyrase and UiO-66(Ce). Catalytic activities of apyrase and UiO-66(Ce) after incubation at (c) various pHs and (d) temperatures. (e) The magnified Ce3d XPS spectra of UiO-66(Ce). (f) The Michaelis–Menten plots for UiO-66(Ce) with various concentrations of ATP and ADP substrates. (g) The possible reaction process of ATP hydrolysis over Ce_6 cluster on the surface of UiO-66(Ce).

To further determine the roles of Ce(IV)-OH and Ce(III)-OH sites played in apyrase-like catalysis, the control experiments were performed on Ce hydroxocomplexes systems containing various ratios of Ce(III)/Ce(IV) (**Section S4.4, Figures S15-S17**). The control experiments exhibit that Ce(IV) hydroxocomplexes solution could continuously dephosphorylate ATP substrate and form the product of phosphate. In contrast, Ce(III) solution have negligible effect on the dephosphorylation of ATP (**Figure S15**). It indicates that Ce(IV)-OH is decisive active site to hydrolyze the HEPBs of ATP. Interestingly, the introduction of a small amount of Ce(III) can increase the ATP hydrolysis efficiency of the Ce(IV) hydroxocomplexes system (**Figure S16**), indicating that Ce(III) could promote the hydrolysis ability of Ce(IV)-OH sites. The Ce(III)-related effect was also observed in the cluster-catalyzed phosphate esters hydrolysis.[17] Based on the dephosphorylation mechanism of phosphate esters,[18] the Ce(IV)-OH sites is required here because Ce(IV) is necessary to activate the HEPBs of ATP and to make it more susceptible for the following nucleophilic attack (**Figures 1c and 3g**).[18b] In the following step, the surface OH group or bound water molecule on Ce_6 cluster would attack the P atom and causes the cleavage of HEPBs. The Ce(III)-bound water molecule was reported as a more efficient nucleophilic agent than hydroxyl group bound to Ce(IV).[18b,19] Hence, Ce(III) sites might work as synergistic sites to provide a more effective nucleophilic attack towards the attached P atom of ATP, which could promote the hydrolysis process.

Within the suitable concentrations range of ATP and ADP substrates, typical Michaelis–Menten curves were achieved for both UiO-66(Ce) (**Figures 3f and S18**) and apyrase (**Figure S19**). The apparent K_m values of the UiO-66(Ce) with ATP and ADP as the substrate were lower than those of apyrase (**Tables S3 and S4**), indicating that UiO-66(Ce) NPs present higher affinity toward substrates than apyrase.[20] This is reasonable due to the fact that the cerium hydroxyl groups are densely distributed on the surface of UiO-66(Ce) and are well exposed to the substrates in the reaction. Besides cerium cluster, it has been well documented that other metal clusters in MOFs could also present affinity toward phosphate bond.[5b,18] However, the other stable MOFs exhibit no obvious catalytic activity for the hydrolysis of ATP (**Figures S20 and S21**), indicating that the catalytic characteristic of hydrolyzing HEPBs is unique to Ce-MOFs.

This unique apyrase-like activity of UiO-66(Ce) NPs endows them with great potential to intervene the ATP/ADP-related physiological processes in life sciences. Extracellular ADP (eADP) functions as an important signaling molecule to induce platelets aggregation and subsequent coagulation cascade through the interaction of eADP and P2 receptors on platelets (**Figure 4a, left**).[1a] Correspondingly, apyrase-induced dephosphorylation of eADP could effectively inhibit the platelets aggregation,[1a,21] just as this principle is utilized by hematophagous arthropods to block host coagulation response in nature.[22] Inspired by this nature phenomenon, we designed a flexible UiO-66(Ce)-embedded polyvinylidene difluoride (PVDF) film (**Figures 4b (inset) and S22-S25**) as a bionic antithrombotic surface to catalytically hydrolyze eADP and to inhibit platelet aggregation (**Figure 4a, right**),[23] which has the potential to improve long-term patency of biomedical devices such as vascular stents and catheters. The surface image of UiO-66(Ce) film shows the full exposure of MOFs crystallites without the coverage of PVDF (**Figure 4b**), ensuring the effective contact between eADP and active sites of Ce-MOFs. To examine the anti-adhesion ability of platelets on various surfaces, platelet-rich plasma (PRP) was incubated on glass, PVDF and UiO-66(Ce) film, in the presence or absence of ADP activator. Celltracker Green (CMFDA) was employed to track the adhered platelets on the surface of materials.[21] It was observed that small amounts of platelets adhered on glass and PVDF film with sporadic distribution of green fluorescence in the absence of ADP (**Figures 4c and 4d**). Upon the activation with ADP, severe platelet adhesion would occur on the surface of these materials (**Figures 4f and 4g**). On the contrast, the UiO-66(Ce) film significantly inhibited platelet adhesion even in the presence of ADP activator (**Figures 4e and 4h**) thanks to the apyrase-like activity of embedded Ce-MOFs for the dephosphorylation of eADP and consequently block its interaction with P2 receptors.[1a] SEM images further illustrate that under the action of ADP activator, the surfaces of glass and PVDF sample are attached with compact and aggregated platelets, while almost no aggregated platelets are observed on the surface of UiO-66(Ce) film (**Figures 4i-4k**),[24] in good agreement with the observation of the inverted fluorescence microscope. We believe that these easily prepared coatings can provide potential options for the preparation of

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blood-contacting biomedical devices to reduce the formation of thrombosis. Meanwhile, the experimental results also indicate that the dephosphorylation process could be effectively intervened to regulate many ATP/ADP-related life activities in the future.

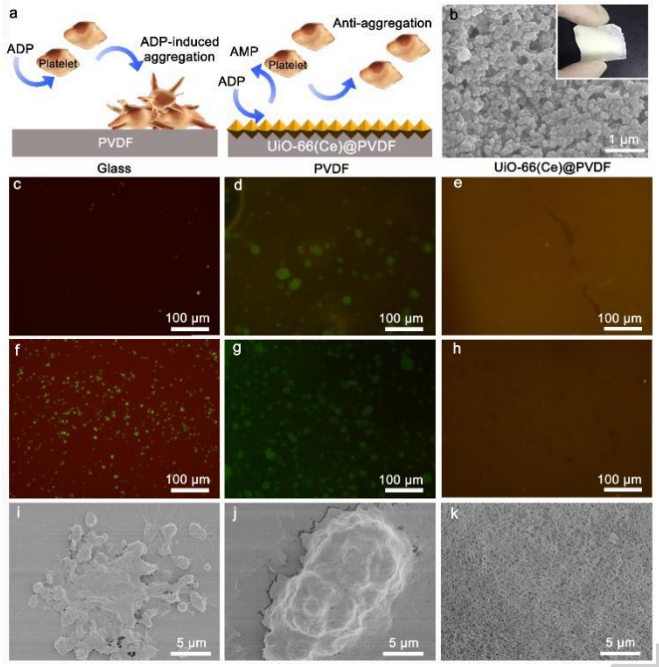

Figure 4. (a) Scheme of UiO-66(Ce) film to suppress platelet adhesion against the ADP inducement of platelet aggregation. (b) SEM image and the inset photograph of flexible UiO-66(Ce) film. The platelets were stained with CMFDA and observed through fluorescent inverted microscope after their incubation on glass (c, f), PVDF (d, g) and UiO-66(Ce) film (e, h) in the absence or presence of ADP (10 μM). The platelets were observed through SEM after their incubation on glass (i), PVDF (j) and UiO-66(Ce) film (k) in the presence of ADP.

In conclusion, we provide the report that Ce-MOFs can mimic apyrase to selectively catalyze the hydrolysis of HEPBs in ATP and ADP. UiO-66(Ce) NPs exhibit divalent cation independence and excellent chemical stability during the dephosphorylation of ATP, which is significantly different with that of apyrase. The Ce(III)/Ce(IV) couple sites play important roles in which Ce(IV)-OH serves as the bonding sites for the polarization and hydrolysis of HEPBs, and Ce(III) might work as a synergistic site to attract H_2O for the nucleophilic attack. Furthermore, the development of flexible UiO-66(Ce) films and its anti-aggregation effect of platelet exemplify their potential applications as an antithrombotic coating for blood-contacting medical devices. We expected that this finding would promote the development of biomimetic materials and open up potential applications to regulate ATP/ADP-related physiological processes such as energy supply, inflammation, immune response and blood clotting.

Acknowledgements

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Keywords: apyrase • adenosine triphosphate • biomimetic chemistry • high-energy phosphate bonds • metal-organic frameworks

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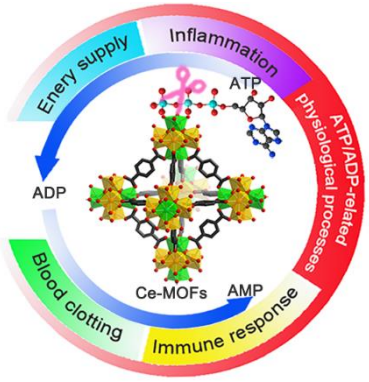

Cerium-based MOFs present intrinsic apyrase-like activity for the selective dephosphorylation of ATP and ADP through the catalytic hydrolysis of their high-energy phosphate bonds, and subsequently their intervention toward ATP/ADP-related physiological process was exemplified to demonstrate their great application potentials in life science.