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A binuclear copper-substituted phosphomolybdate with reactive oxygen species catalytic ability and antimicrobial activity[†]

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A novel 1-D phosphomolybdate based on a dinuclear coppersubstituted Strandberg structure was successfully designed and synthesized. It not only possesses reactive oxygen species (ROS) catalytic ability in aqueous solution, by synergizing the Cu clusters with the building blocks, but also shows good antimicrobial activity.

Research into new multifunctional materials, particularly antimicrobial materials, has received more and more interest from both academia and industry.^{1,2} Such materials are in high demand in the consumer marketplace, for example in hotel and catering equipment, water filtration systems and medical supplies.³ Silver has been recognized as an antibacterial material for decades.⁴ However, its cost severely limits its range of applications. Therefore, searching for inexpensive transition metals to replace noble metals for synthesizing antibacterial materials has become a research hotspot.⁵

Copper and silver belong to the same subfamily in the periodic table, which may make copper a preferred alternative to silver. Biochemical research has indicated that the coordination of silver ions with thiol groups (-SH) may play a key role in inactivation of bacteria, which inhibit basic cell functions such as oxidative phosphorylation and respiratory chain enzymes.⁶ Furthermore, Ag⁺ is believed to catalyze the production of reactive oxygen species (ROS), which destroy the subcellular structure of the bacteria directly.⁷ Cu²⁺ is not only a Lewis soft acid, which is easy to coordinate with a Lewis soft base such as –SH, but also can catalyze ROS generation by valence interchange of +1 and +2 in the internal environment.⁸ Therefore, seeking a suitable auxiliary to synergize with Cu^+/Cu^{2+} to maximize its effectiveness becomes the essential step.

Polyoxometalates (POMs) are a class of metal oxygen clusters which have multitudinous structures and fascinating properties.⁹⁻¹² Of a variety of building blocks, Strandbergtype ([P₂Mo₅O₂₃]⁶⁻) fragments (Fig. S1[†]) have several inherent, irreplaceable advantages such as nano size, a nucleophilic oxygen-enriched surface and poly-bond-making sites. These features endow the clusters with the ability to serve as bulky polydentate ligands to incorporate into multiple transitionmetal cations with flexible coordination modes.¹³⁻¹⁵ Furthermore, many researchers have demonstrated that POMs with a Strandberg-type fragment possess excellent oxidation catalytic capacity, such as ketalization of cyclohexanone with glycol and oxidation of styrene.^{13,16,17} These properties may be beneficial to its synergistic effect with copper in catalyzing the production of ROS. Hence, combination of Cu ions and $[P_2Mo_5O_{23}]^{6-}$ in one hybrid material may not only retain the desirable properties of all the precursor components, but also express them in a synergistic manner.

Here we report a newly designed POM, (H₂en)[Cu(en)(H₂O) Cu(en)(H₂O)₃[P₂Mo₅O₂₃]·5.5H₂O (Fig. 1, abbreviated as CPM), which was derived from the pure inorganic structure [P₂Mo₅O₂₃]⁶⁻ linked with a dinuclear Cu complex. Notably, CPM is able not only to catalyze generation of reactive oxygen species (ROS), but also to inhibit the proliferation of Escherichia coli (E. coli). Hitherto, most investigations of antibiotic POMs have mainly focused on polyoxotungstates (POTs),¹⁸ especially on organoantimony(m)-containing POTs.^{19,20} By contrast, antimicrobial activity of polyoxomolybdates (POMos) remains largely unexplored, with only Keggin- and Anderson-type structures having been tested.¹⁸ To our knowledge, CPM represents a novel antibacterial POMo based on a Strandberg-type structure, and provides a good opportunity to exploit the antibacterial applications of POMos.

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Fig. 1 (A) Combined polyhedral/ball-and-stick view of the 1-D linear structure of CPM. (B) Combined polyhedral/ball-and-stick representation of one CPM subunit in the crystal. (C) Polyhedral view of the coordination mode of the dinuclear Cu cluster in CPM (lattice water molecules and protonated en molecules are omitted).

CPM was synthesized by reacting $CuCl_2 \cdot 2H_2O$, $Na_2MoO_4 \cdot 2H_2O$, $Na_2HPO_4 \cdot 12H_2O$ and ethylenediamine (en) in the mole ratio of 3:3:2:1 at 85 °C in an acidic solution.

The mazarine crystals of CPM were obtained by volatilizing the solution at room temperature over one week. The structure of CPM was characterized by single-crystal X-ray diffraction analysis. The crystallographic data, selected bond lengths and angles are summarized in Tables S1–S3.† X-ray structural analysis reveals that the molecular structural unit of CPM consists of a $[P_2Mo_5O_{23}]^{6-}$ cluster, a dinuclear Cu complex $[Cu(en)(H_2O)Cu (en)(H_2O)_3]^{4+}$, 5.5 lattice water molecules and one protonated en molecule as counter cation, and the $[P_2Mo_5O_{23}]^{6-}$ clusters and Cu complex construct the backbone of CPM.

The geometry of the $[P_2Mo_5O_{23}]^{6-}$ cluster can be deemed as a puckered ring of five nearly coplanar corner-sharing/ edge-sharing distorted MoO₆ octahedra [Mo-O: 1.702(5)-2.458(4) Å] with two capping PO₄ tetrahedra [P-O: 1.527(4)-1.560(4) Å] on both poles of the $\{Mo_5O_{21}\}$ ring centers (Fig. S1[†]). As shown in Fig. 1A, $[Cu(en)]^{2+}$ acts as a linker connected to two adjacent $[P_2Mo_5O_{23}]^{6-}$ clusters by sharing the terminal oxygen on the PO₄ tetrahedron to form a 1-D linear structure, in which the angles of P1-O-Cu1 and P2-O-Cu1 are 123.4(2)° and 129.0(3)° respectively. As shown in Fig. 1B, another Cu complex, $[Cu(en)(H_2O)_3]^{2+}$, is connected to the 1-D chain linker [Cu(en)]²⁺, forming a dinuclear Cu cluster by sharing an oxygen atom. Notably, the two Cu atoms in the dinuclear cluster exhibit different coordination configurations. As shown in Fig. 1C, Cu1 adopts a fivecoordinated square pyramid configuration. Cu2 is coordinated by two nitrogen atoms from an en (Cu-N: 2.000(6)-2.006(5) Å), one O atom shared with Cu1 (Cu-O: 2.596(5) Å) and three H₂O (Cu2-O1/2 W: 1.965(5)-1.979(5) Å, Cu-O3W: 2.574(9) Å). As a result of Jahn-Teller distortion, Cu2 adopts a six-coordinated, distorted octahedral configuration, and exposes O1W outside the 1-D linear framework.

Interestingly, when the amount of en is doubled, another linear, copper-substituted, Strandberg-type POM, $[H_2(en)]_2$

 $[Cu(en)(H_2O)_2][P_2Mo_5O_{23}]\cdot 3.5H_2O$ (abbreviated as C1), is synthesized. The crystallographic data and selected bond lengths and angles are summarized in Tables S4–S6.† As shown in Fig. 2A, C1 can be considered as a 1-D structure formed by alternately connecting $[Cu(en)(H_2O)_2]^{2+}$ with $[P_2Mo_5O_{23}]^{6-}$. C1 is similar to the reported classic 1-D chain Cu-substituted Strandberg-type POM,²¹ and the only difference is whether the Cu atom is in a five-coordinate configuration for the reported structure (Fig. S2†) or a six-coordinate configuration for C1 (Fig. 2C).

The remarkable characteristic of CPM is that dinuclear Cu clusters alternate with [P2M05023]6- clusters in onedimensional chains. This distinctive structural feature of CPM, compared with either the reported structure or that of C1, is likely to improve its performance. To the best of our knowledge, Cu ions can catalyze the formation of ROS in aqueous solution by valence interchange of +1 and +2.8 Since the copper ions in the cluster can transfer electrons quickly, the catalytic performance may be much higher than for a single copper ion. Moreover, ferromagnetic properties are only generated when more than two Cu²⁺ ions are within a certain distance.²² Hence, CPM may have ferromagnetism, and this may facilitate post-treatment of CPM after water purification by using magnetic separation of antimicrobial materials and purification materials. Furthermore, compared with the POM-containing copper clusters constructed using other building blocks, such as the Keggin-type unit (Fig. S1[†]), CPM constructed by Strandberg-type fragments has natural structural advantages for antibacterial activity. In the literature, the building blocks that can induce the formation of copper clusters often seal the transition-metal ion clusters inside the POM structure,^{16,23} causing the Cu ions to lose coordinated active sites with -SH. CPM largely preserves the potential coordinated sites of Cu ions (see Fig. 1C), which may enhance the antibacterial ability.

The X-ray powder diffraction patterns of samples are consistent with those from the single-crystal structure analyses (Fig. S3[†]), indicating the phase purity. The composition of



Fig. 2 (A) Combined polyhedral/ball-and-stick view of the 1-D linear structure of C1. (B) Combined polyhedral/ball-and-stick representation of one C1 subunit in the crystal. (C) Polyhedral view of the coordination mode of Cu ions in C1 (lattice water molecules and protonated en molecules are omitted).

CPM and C1 on the crystal surface was studied by EDX-SEM. The SEM images (Fig. S4 and S5[†]) show that several points are randomly selected for testing on the surface of the CPM and C1 crystals. EDX data (Fig. S6 and S7[†]) show that the abundance of Cu on the surface of CPM is about 70% higher than that of C1 based on Mo, which indicates that the formation of dinuclear Cu clusters is beneficial to increasing the abundance of Cu on the surface of materials. These results have a positive significance for making antibacterial materials that are loaded on the immobilization phase.

The IR spectra of CPM and C1 were also investigated (Fig. S8[†]). The spectra of CPM and C1 are similar and both exhibit the characteristic peaks of the Strandberg-type POM in low wave-number regions, with the bands at about 900 cm⁻¹ and 565-688 cm⁻¹ being assigned to $v(Mo-O_t)$ and v(Mo-O-Mo)bonds, respectively. The characteristic bands between 1010 and 1105 cm⁻¹ are attributed to the v(P–O) bond.²⁴ In addition, the occurrence of characteristic vibrations at about 3140-3160 cm^{-1} and 1405–1630 cm^{-1} can be attributed to the v(N-H) bond and confirm the presence of en ligands.²⁵ A broad feature of peaks at about 3440 cm⁻¹ can be attributed to absorptions of coordinated and lattice water molecules.25 The IR spectra of CPM and C1 show significant differences in intensity in the range 1405–1630 cm⁻¹, which originates from the differences between the content of en coordinated with copper and protonated en.²⁶ The TG curve of CPM exhibits three steps of weight loss (Fig. S9[†]). The first weight loss step is 7.75% (calc. 7.12%) in the range 25-85 °C, corresponding to release of lattice water molecules. The second weight loss step is 4.38% (calc. 4.46%) in the range 86-200 °C, corresponding to release of an en molecule, which indicates that the framework of CPM is beginning to collapse. The third weight loss step is 16.22% (calc. 16.64%) in the range 200-520 °C, corresponding to release of coordinated water and P₂O₅ molecules. These results indicate that CPM is stable below 85 °C.

Further investigation using X-ray photoelectron spectra (XPS) has been carried out to detect the valences of Cu, Mo and P. As shown in Fig. 3A, there are two broad peaks with a shoulder peak located at 933 and 953 eV, which were assigned to $Cu2p_{3/2}$ and $Cu2p_{1/2}$, respectively.²⁷ The fitted curves in Fig. 3A (dashed lines) suggest that Cu²⁺ (2p_{3/2}, 933.9 eV; 2p_{1/2}, 953.9 eV) and Cu⁺ (2p_{3/2}, 932.5 eV; 2p_{1/2}, 952.5 eV) are involved in the peaks of Cu_{2p}.²⁷ These results indicate that Cu ions in the +2 and +1 valence states coexist in the Cu clusters of CPM. The peak style of C1 is similar to that of CPM, as shown in Fig. 3B, indicating that Cu ions also exist in C1 with mixed valence states of +1 and +2. The valence of Cu in CPM and C1 was further calculated by using the crystallographic data (Tables S2 and S5[†]), XPS (Fig. 3), and bond valence sums (\sum s) (Fig. S10 and Fig. S11⁺), according to reported methods.²⁸ The calculation results show that the average valence of Cu(1) is 1.6216, and that of Cu(2) is 1.7740 in CPM (Tables S7 and S8[†]). These calculations are basically consistent with the data obtained from the XPS experiments (Fig. 3A). Therefore, the existence of a mixed valence state in the dinuclear Cu clusters makes it possible



Fig. 3 X-ray photoelectron spectra (XPS) of Cu in CPM (A) and C1 (B).

for CPM to have highly efficient ROS catalytic properties. The valence states of Mo and P in CPM and C1 were also calculated by bond valence sum (Tables S7 and S8†). The results show that all Mo and P are +6 and +5 in both CPM and C1, which was confirmed by the results of the XPS experiment (Fig. S12†).^{29,30}

ROS are considered to be a major component accounting for the antimicrobial properties of many compounds.31,32 Recently, it has been reported that transition metal-substituted POMs possess the ability of catalytic oxidation.^{33,34} Hence, it is likely that they synergize with Cu ions to further enhance antibacterial activity. The effect of CPM on mediated ROS generation was therefore investigated by a dichlorofluoroscein (DCF) assay. DCF is a fluorescent marker derived from the reaction of non-fluorescent 2',7'-dichlorofluorescein (DCFH) with ROS in the presence of horseradish peroxidase (HRP), which can indicate the total output of ROS from the system.35 As shown in Fig. 4, the fluorescence intensity of CPM and C1 are higher than that of the control, indicating that the production of ROS with CPM and C1 is greater than without them. Furthermore, the fluorescence intensity of CPM is 1.5-2 times higher than that of C1, which confirms that the dinuclear Cu cluster of CPM has a stronger catalytic capacity than the single-core Cu of C1. Interestingly, as shown in the inset of Fig. 4, the experimental group with Cu²⁺ produced significantly less ROS, even lower than that of the control group. This phenomenon may be attributed to the interaction



Fig. 4 Fluorescence intensity of DCF (λ_{ex} = 485 nm, λ_{em} = 650 nm) by CPM, C1, Cu²⁺, Cu²⁺ + GSH and blank (inset, the expanded graph of the fluorescence intensity in the range of 0 to 15) from 0 to 3000 min.



Fig. 5 Inhibition effect on the growth of *E. coli* with CPM or C1 in the growth media.

between Cu^{2+} and the HRP enzyme, which deactivates it. In fact, in certain microenvironments, bacteria can secrete a considerable number of proteins, polypeptides and chelators, which may coordinate with Cu^{2+} and make it lose its catalytic position.³³ We used glutathione (GSH), a short polypeptide commonly found in organisms, to coordinate with Cu^{2+} and found that the production of ROS was totally suppressed. Therefore, the combination of a Strandberg-type fragment and Cu ions not only contributes to the synergistic production of ROS, but also protects the Cu catalytic centers from the interference of external proteins and chelators.

The antibacterial activity of CPM was tested by using a kinetic growth assay.³⁶ CPM, C1 and control groups were incubated with *E. coli* in LB broth. Bacterial growth was studied by visual observation as indicated by turbidity, with lack of turbidity corresponding to low bacterial growth.³⁷ As shown in Fig. 5, in the first 250 min, the growth curves of the group with CPM and C1 are almost the same as the control group. Afterwards, the turbidity of the control group increased rapidly and the intensity was obviously higher than that with CPM or C1, indicating that the production of *E. coli* without CPM or C1 is more than that with them. From 250 to 400 min, although the instantaneous growth rates of both the CPM group and C1 group were increasing, the growth rate of the CPM group was slower than that of C1. Then, from 400 to 800 min, the growth rate of the CPM group reduced, and the growth rate of C1 continued to rise. From 600 to 800 min, the turbidity of C1 remained higher than that of the group with CPM. These results reveal that both CPM and C1 can inhibit the growth of *E. coli*, and that CPM is more efficient.

Conclusions

In this study, two linear Cu substituted phosphomolybdate complexes, $(H_2en)[Cu(en)(H_2O)Cu(en)(H_2O)_3][P_2Mo_5O_{23}]$ $\cdot 5.5H_2O$ (CPM) and $[H_2(en)]_2[Cu(en)(H_2O)_2][P_2Mo_5O_{23}] \cdot 3.5H_2O$ (C1), have been designed and synthesized successfully, with both possessing Cu⁺ and Cu²⁺ ions in their structures. As expected, both CPM and C1 can catalyze the production of ROS efficiently and can inhibit the proliferation of *E. coli* to some extent. In both cases, the catalytic and inhibitory effects of CPM are superior, which may be due to the existence of dinuclear Cu clusters. Moreover, CPM has a ferromagnetic effect due to the presence of a certain amount of dinuclear Cu²⁺ clusters. To our knowledge, CPM represents the first magnetic antibacterial POM and may have broad applications in research into non-Ag antibacterial materials.

Conflicts of interest

There are no conflicts to declare.

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