Self-Assembled Multivalent Ag-SR Coordination Polymers with Phosphatase-Like Activity

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Abstract: We show herein the phosphatase-like catalytic activity of coordination polymers obtained after adding Ag$^+$-ions to thiols bearing hydrophobic alkyl chains terminated with a 1,4,7-triazacyclononane (TACN) group. The subsequent addition of Zn^{2+}-ions to the self-assembled polymers resulted in the formation of multivalent metal coordination polymers capable of catalysing the transphosphorylation of an RNA-model compound (2-hydroxypropyl-4-nitrophenyl phosphate, HPNPP) with high reactivity. Analysis of a series of metal ions showed that the highest catalytic activity was obtained when Ag$^+$-ions were used as the first metal ions to construct the backbone of the coordination polymer through interaction with the -SH group followed by Zn^{2+}-ions as the second metal ions complexed by the TACN-macrocycle. Furthermore, it was demonstrated that the catalytic activity could be modulated by changing the length of the hydrophobic alkyl chain.

The ability of enzymes to accelerate chemical reactions is of utmost importance to living systems.[1] Selectivity in substrate recognition allows enzymes to carry out their specific task in the complex intracellular environment. The unrivalled catalytic activity of proteases originates from the spontaneous folding of the peptide chains in an ingenious tertiary structure in which the remote catalytic sites are brought into close proximity in the active pocket.[2] However, the protein folding is a delicate process and the enzyme structure is generally easily disrupted by environmental conditions, such as temperature, pH, salt concentration, and organic solvents. This limits a practical application of enzymes in chemo- or biosensing,[3] because of an incompatibility with the requested reaction conditions. Artificial enzymes, in particular nanozymes, are rapidly gaining interest as robust synthetic analogs of enzymes.[4] These artificial enzymes are expected to overcome the operational limitations of natural enzymes, while maintaining an acceptable catalytic activity. In fact, numerous artificial enzymes for a wide variety of chemical reactions have been developed over the past two decades.[5] One class of nanozymes that has received prominent attention are artificial phosphatases used for the transphosphorylation of phosphodiesters.[6–9] The design of these nanozymes typically relied on the incorporation of multiple copies of 1,4,7-triazacyclononane·Zn^{2+} (TACN·Zn^{2+}) complexes in a wide variety of structures ranging from simple molecules,[6] to multivalent systems, like micelles,[7] vesicles,[8] and dendrimers (Figure 1).[9] A key feature of the catalysis is its cooperative nature, implying that (at least) two TACN·Zn^{2+} complexes are required in the active site. Although multivalent structures showed impressive properties owing to the installment of cooperative effects between neighboring (TACN·Zn^{2+}) complexes, for practical applications the low stability of amphiphile-based assemblies (as pointed out by Scrimin et al.)[10] and the synthetic accessibility of dendrimers pose limitations.[11] These limitations have been overcome using gold nanoparticles as inorganic scaffold for the immobilization of a monolayer of alkyl thiols terminating with TACN·Zn^{2+} complexes. Formation of the monolayer occurs through a self-assembly process and the strength of the Au—S bond confers a high stability to the resulting structure. Compared to the other classes, these monolayer protected gold nanoparticles were shown to have superior catalytic properties in the cleavage of phosphodiesters.[10a,12] Nonetheless, the synthesis of the monolayer protected Au nanoparticles is a multistep procedure and the purification requires size-exclusion chromatography. Here, we demonstrate a new class of multivalent coordination polymeric systems with excellent catalytic activity as transphosphorylation catalysts that can be prepared using facile procedures and does not require any kind of purification.

In recent years, coordination polymers based on Ag-SR interactions have been studied by us and others.[13] These metal coordination polymers could be obtained *in situ* by simply mixing Ag$^+$-ions and thiols. Stimulated by these findings, we decided to study whether the *in situ* formation of metal coordination polymers upon mixing equal amounts of Ag$^+$-ions

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Figure 1. Schematic comparison of previously reported artificial phosphatases (a), and *in situ* formation of metal coordination polymers by using HS-C$_n$-TACN with various lengths of alkyl chain (n = 5-20), and catalytic cleavage reaction of these systems in this work (b).

and alkyl thiols containing a TACN-moiety would be a viable method to obtain multivalent systems with catalytic activity in transphosphorylation reactions (Figure 1). In these systems, Ag$^+$-ions would act as the linking "nodes" to connect the thiols and bring TACN-moieties in close proximity via strong Ag–S bond. Subsequent addition of Zn^{2+}-ions would lead to complexation by TACN and activate the system for catalysis. It was expected that the catalytic activity could be modulated by the thiol alkyl chain length. This expectation was based on the consideration that the formation of an efficient catalytic pocket between neighboring TACN·Zn^{2+}-complexes would benefit from some degree of conformational flexibility and the polarity of the local environment. This very simple "mix-and-catalyse" method would give access to a novel class of multivalent artificial phosphatases.

With this procedure in mind, a series of thiols (HS-C$_n$-TACN) bearing alkyl chains of various lengths (n = 5–20) were synthesized by a procedure which required three reaction steps[14] (see SI, Figure S1). The substrate 2-hydroxypropyl-4-nitrophenyl phosphate (HPNPP) was synthesized via a one-step ring-opening reaction (Figure S2).[15] The synthesized thiols and HPNPP were characterized by ^{1}H NMR, ^{13}C NMR and ESI-MS (SI). To study whether the metal coordination polymers could be *in situ* generated when Ag$^+$- ions were mixed with the synthesized thiols, a UV-vis titration experiment was carried out using HS-C$_{14}$-TACN (20 μM) in aqueous buffer ([HEPES] = 10 mM, pH 8.0). Before Ag$^+$-ions were added, no absorption peaks appeared in the measured wavelength window (200–550 nm). When Ag$^+$-ions were gradually introduced, a new absorption peak at a wavelength of ~280 nm emerged and continued to increase in intensity upon the further addition of Ag$^+$-ions (Figure S3). This

band could be attributed to Ligand-to-Metal Charge Transfer facilitated by argentophilicity.[13] The absorbance at 280 nm linearly increased with increasing Ag$^+$-ion concentration, but reached a maximum value when the concentration reached 20 μM. The correspondence with the thiol concentration (20 μM), together with the observation of a maximum at χ[HS-C$_{14}$-TACN] = 0.5 in the Job's plot (Figure S4), indicated the formation of a structure with a 1:1 stoichiometry between Ag$^+$-ion and the thiol-moiety of HS-C$_{14}$-TACN. The formation of a coordination polymer was supported by DLS measurements, which illustrated the presence of structures with an estimated hydrodynamic diameter of around 41 nm (Figure S5). Further experimental evidence for the formation of Ag-(S-C$_{14}$-TACN) coordination polymers was directly obtained from the observation of small fragments of the polymer in MALDI-TOF MS experiments (Figure 2a). We found convincing evidence for the formation of coordination polymers also in the Ag-(S-C$_5$-TACN) system (Figure S6). A worm-like morphology of Ag-(S-C$_{14}$-TACN) system was revealed by high resolution transmission electron microscope (HRTEM, Figure S7) and scan electron microscope (SEM, Figure S8). However, a clear metal lattice diffraction in the selected diffraction area, which would have given unambiguous proof for the polymers, was regrettably not observed.

To probe the difference in hydrophobic domains between the structures, fluorescence titrations were carried out using the fluorescent dye, Nile Red (Figures S9–10). Increasing amounts of Ag-(S-C$_n$-TACN) (n = 5–16) were titrated to a fixed amount of dye (5 μM) in the presence of Zn^{2+}. It was observed that an increase in the alkyl chain length (C$_n$) led to an enhanced affinity for Nile Red, evidenced by a more efficient uptake of dye at lower polymer concentrations. These results suggested
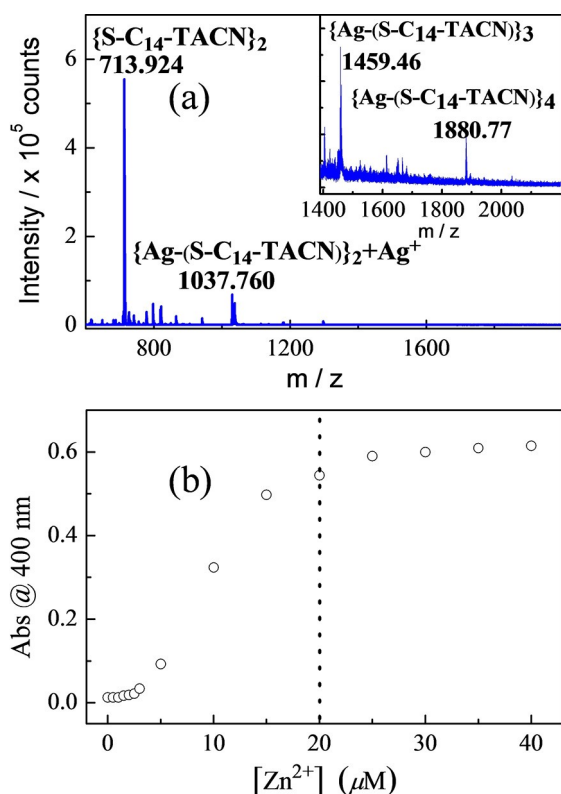
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Figure 2. (a) MALDI-TOF result of Ag-(S-C$_{14}$-TACN) system (the molar ratio of Ag$^+$-ion to HS-C$_{14}$-TACN was 1:1); (b) The relationship between Zn^{2+}-ion concentration and absorbance at 400 nm in the hydrolysis of HPNPP catalyzed by Ag-(S-C$_{14}$-TACN)-Zn^{2+} system. Experiment conditions: [HS-C$_{14}$-TACN] = 20 μM, [Ag$^+$] = 20 μM, [HPNPP] = 80 μM; 10 mM HEPES buffer solution of pH of 8.0; temperature of 37 °C; reaction time of 30 min.

an increased hydrophobicity of the system upon an increase of the length, n, of the alkyl chain. Next, kinetic titration experiments were carried out to evaluate whether the complexation of Zn^{2+}-ions by the TACN-macrocycles would activate the systems for catalysis. The first experiment consisted in the measurement of p-nitrophenol (PNP) release upon the addition of an equimolar amount of Zn^{2+}-ions (20 μM) to a solution of the Ag-(S-C$_{14}$-TACN) coordination polymer ([TACN] = 20 μM) in the presence of the substrate 2-hydroxypropyl-p-nitrophenyl phosphate (HPNPP, 80 μM). We were pleased to observe that the absorbance at 400 nm gradually increased in time (Figure S11) indicating that the self-assembled structure is capable of cleaving HPNPP.[9] A kinetic equivalent of a Job's plot revealed the highest catalytic activity when TACN and Zn^{2+}-ions were present in a 1:1 molar ratio (Figure S12). Furthermore, the observation of a sigmoidal reactivity profile when increasing amounts of Zn^{2+}-ions were added to a constant concentration of Ag-(S-C$_{14}$-TACN) indicated that the catalysis should originate from the cooperative effect between two adjacent TACN·Zn^{2+} complexes (Figure 2b), similar to that observed for related multivalent systems.[16] Importantly, a series of control experiments involving mixtures of Ag$^+$ + HPNPP, Zn^{2+} + HPNPP, HS-C$_{14}$-TACN + Ag$^+$ + HPNPP, HS-C$_{14}$-TACN + Zn^{2+} + HPNPP, HS-C$_{14}$-TACN + HPNPP, and just HPNPP, revealed

hardly any increase in absorption at ~400 nm under similar experimental conditions (Figure S13). These observations illustrate that all three components, i.e. HS-C$_{14}$-TACN, Ag$^+$-ion and Zn^{2+}-ion are required to obtain a functional multivalent catalyst for the cleavage of HPNPP.

Considering the importance of two different kinds of metal ions in defining the structure and activity of the system, we investigated their possible substitution with other metal ions. When Ag$^+$-ions were substituted by other metal ions, fixing Zn^{2+}-ions as the second metal ion, catalytic activity was only observed for Cd^{2+}, Cu^{2+}, and Zn^{2+}-ions, but far lower than that observed for Ag$^+$-ions (Figure 3a). Similarly, when Zn^{2+}-ions were substituted by other metal ions, fixing Ag$^+$-ions as the firstly added metal ions, only the systems with Cu^{2+}, Cd^{2+}, Co^{2+} and Ni^{2+}-ions demonstrated catalytic activity, but also in this case far lower than that of the Zn^{2+}-system (Figure 3b). These results further supported the role of Ag$^+$-ions in creating polymeric structure and the role of Zn^{2+}-ions in creating catalytic pockets. A study of the catalytic activity as a function of pH in Ag-(S-C$_{14}$-TACN)-Zn^{2+} system showed a bell-shaped profile with an apparent pK_a of ca. 8.0 which is similar to that observed for a related Au nanoparticle-based system reported by Scrimin's group[12] (Figure S14).

The saturation profile obtained when plotting the initial rate as a function of substrate concentration could be fitted to the Michaelis−Menten equation to afford a K_M value of 0.13 ± 0.001 mM and a k_{cat} value of 0.014 ± 0.0003 s^{-1} for the cleavage of HPNPP by the Ag-(S-C$_{14}$-TACN)-Zn^{2+} system (Figure 4a). Therefore, the corresponding second-order rate constant ($k_2 = k_{cat}/K_M$) was calculated as 109 ± 3 M^{-1}s^{-1} which is more than 15000 times higher than that of the mononuclear metal complex catalyst with a TACN head ($k_2 = 0.007$ M^{-1}s^{-1}) thus lacking structural elements capable of bringing the two metal ions in close proximity.[10a] It is also far higher than the value reported for a dinuclear Zn^{2+} complex (k_2 of 0.25 M^{-1}s^{-1}),[17] for vesicular assemblies with similar alkyl chain length (k_2 of 5.7 M^{-1}s^{-1}),[8b] and even for the inclusion complex formed by γ-
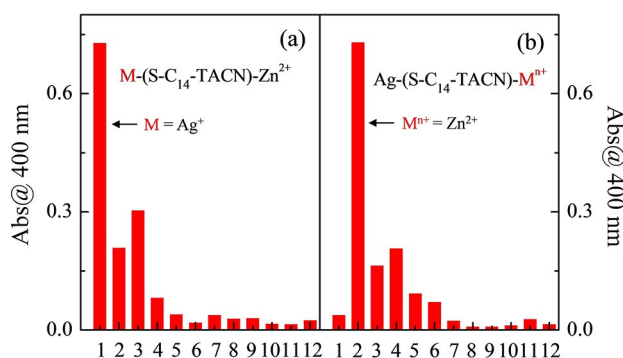

Figure 3. The comparison of absorbance at 400 nm in the presence of HS-C$_{14}$-TACN and HPNPP, (a) the identity of the first metal ion was varied while the second metal ion was fixed as Zn^{2+}-ion; and (b) the first metal ion was fixed as Ag$^+$-ion while the identity of the second metal ion was varied. M or M^{n+} = 1. Ag$^+$; 2. Zn^{2+}; 3. Cd^{2+}; 4. Cu^{2+}; 5. Co^{2+}; 6. Ni^{2+}; 7. Na$^+$; 8. K$^+$; 9. Fe^{3+}; 10. Al^{3+}; 11. Cr^{3+}; 12. Hg^{2+}. Experimental conditions: [thiol] = 20 μM; [metal ion] = 20 μM; [HPNPP] = 80 μM; temperature of 37 °C; mixing time of catalyst with HPNPP of 30 min.

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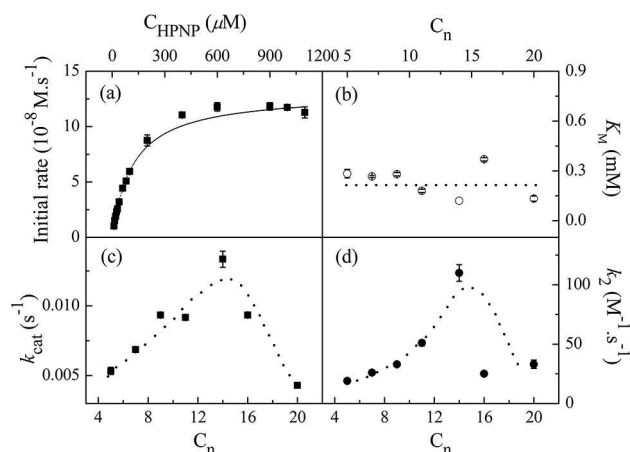European Chemical
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Figure 4. Reaction rate of HPNPP cleavage catalyzed by Ag-(S-C$_{14}$-TACN)-Zn^{2+} system as a function of HPNPP concentration (a), the relationship between K_M (b), k_{cat} (c), k_2 (d) and alkyl chain length (C$_n$ is from 5 to 20). Experimental condition: [Ag-(S-C$_n$-TACN)-Zn^{2+}] = 20 μM (the molar ratio of Ag$^+$-ion to thiol to Zn^{2+}-ion was fixed as 1:1:1); [HPNPP] = 80 μM; temperature of 37°C; 10 mM HEPES buffer solution of pH 8.0. The solid line in (a) is the fitted Michaelis−Menten equation curve. The dot lines in (b), (c), and (d) are the change tendency guided by eyes.

cyclodextrin (γ-CD) and a bimetallic Zn^{2+} complex (k_2 of 3.6 M^{-1}s^{-1}).[16a] Interestingly, the k_2-value of this system is comparable to, or even higher than, those reported for monolayer-passivated Au nanoparticles containing TACN-Zn^{2+} complexes (k_2 of 81.6 M^{-1}s^{-1} and 4.4 M^{-1}s^{-1}).[10a,18] The comparative values reported in Table 1, clearly reveal that the *in situ* formed Ag-(S-C$_{14}$-TACN)-Zn^{2+} polymer system is an excellent catalyst for HPNPP cleavage. The high reactivity is ascribed to the *in situ* formation of a Ag−S coordination polymer, which serves as multivalent scaffold that for compacting the TACN-Zn^{2+} complexes attached to flexible chains in close proximity, thus creating "catalytic pockets" that can express cooperativity.

To further study the catalytic properties, several additional experiments were performed. The periodic batch-wise addition of HPNPP revealed that after each addition of 40 μM HPNPP into a 40 μM Ag-(S-C$_{14}$-TACN)-Zn^{2+} solution, the absorbance at 400 nm gradually increased to a saturating value. The ability to repeat 6 cycles shows that the system displays substrate turnover, which provides evidence for the catalytic nature of Ag-(S-C$_{14}$-TACN)-Zn^{2+} (Figure S15). It is noted that the reaction rate progressively slowed down, which likely originated from the inhibition effect of the anionic cyclic phosphate. Reaction time-dependent ^{31}P NMR experiments demonstrated that the

chemical shift at −5.09 ppm, originated from HPNPP gradually decreased, while a new signal at 17.75 ppm, attributed to that of cyclic phosphate, appeared and increased in time (Figure S16). On the other hand, the signal of −5.09 ppm of HPNPP remained almost unchanged in the absence of Ag-(S-C$_{14}$-TACN)-Zn^{2+} (Figure S17). Dialysis experiments showed that the absorbance at 400 nm of HPNPP solution in Ag-(S-C$_{14}$-TACN)-Zn^{2+} system gradually decreased with increasing dialysis time (Figure S18), which further supports the fact that this absorption peak originates from PNP anion rather than from other species, such as Ag-nanoparticles. Observation of the anion by ESI-MS measurements afforded further evidence for catalytic substrate hydrolysis reaction(Figure S19). Finally, we also investigated the change in initial rate of HPNPP-transphosphorylation upon treating the coordination polymer with increasing amounts of the reducing agent NaBH$_4$ before adding Zn^{2+}-ions. It was found that the initial rate substantially decreased with increasing NaBH$_4$ concentrations, eventually reaching a final level when the NaBH$_4$ concentration exceeded 400 μM (Figure S20). HRTEM experiments revealed that small and uniform Ag nanoparticles with average size of ~2 nm had formed under the reducing conditions imposed by NaBH$_4$ (Figure S21). Control experiments indicated that the decrease in initial rate was not caused by BO$_2^-$ anions, as no significant inhibition effect on the catalytic reaction was observed when BO$_2^-$ anions were added to the reaction mixture. These observations demonstrate that the catalytic reactivity of the Ag-(S-C$_{14}$-TACN)-Zn^{2+} coordination polymers is higher than that of the corresponding Ag@(S-C$_{14}$-TACN)-Zn^{2+} nanoparticle system.

Previous studies on related Au NP systems have revealed that the alkyl chain length plays an important role in determining the catalytic activity of the system.[12] To investigate to which extent the catalytic activity of the Ag-SR coordination polymers would be affected by structural changes, thiols containing hydrophobic alkyl chains with lengths varying from C$_5$ to C$_{20}$ and terminating with a TACN group were employed. As shown in Figure S5, the hydrodynamic diameters of Ag-(S-C$_n$-TACN) determined by DLS showed a significant enhancement with increasing the thiol chain length.[19] This indicates that the size of *in situ* formed Ag-SR coordination polymers could possibly increase for increasing thiol chain lengths. The complexation between other thiols and Ag$^+$-ions via strong Ag−S bond was supported by UV-vis absorption spectral titration, featured by a molar ratio of 1:1 (Figure S22). Michaelis-Menten saturation kinetics were measured to determine the effect of the increased alkyl chain length on the catalytic parameters. Intriguingly, the K_M values, which are the reciprocal of the affinity constants of the substrate HPNPP for the catalyst, do virtually not vary as a function of the length of the hydrophobic chain. This indicates that hydrophobic interactions contribute little to substrate binding, which appears therefore more driven by electrostatic interactions. On the other hand, the k_{cat} values significantly increase with increasing the alkyl chain length. The maximum value is observed for C$_{14}$, which is *ca.* 5-fold higher than the lowest value (Figure 4c, Table S1). The significant difference in k_{cat} likely results from the polarity difference in the pseudophase formed by the hydro-

Table 1. Comparison of K_M, k_{cat}, and k_2 for HPNPP cleavage in the presence of Ag-(S-C$_{14}$-TACN)-Zn^{2+} system and other reported catalyst systems

Catalyst	K_M / mM	k_{cat} / s^{-1}	k_2 / M^{-1}.s^{-1}
Dinuclear complex [17]	16	0.0041	0.25
C$_{18}$-TACN.Zn^{2+} [8b]	0.53	0.003	5.7
Au NP-(S-C$_{10}$-TACN).Zn^{2+} [18]	0.38	0.031	81.6
Au NP-(S-C$_8$-TACN).Zn^{2+} [10a]	0.93	0.0042	4.4
Bimetallic complex-γ-CD [16a]	3.3	0.012	3.6
Ag-(S-C$_{14}$-TACN).Zn^{2+} (this work)	0.13	0.0137	109

phobic side chains. Overall, the results suggest that the presence of the hydrophobic domains is important for the catalytic efficiency of the catalytic site, but not for substrate binding.[12,18] It is noted that in C_{16} and C_{20} cases the reactivity is significantly lower, which appeared to be caused by the formation of larger aggregates as indicated by DLS (Figure S5) The decreased stability in solution is likely caused by the long chain length, which facilitates disorderly entanglement. Intriguingly, from C_5 to C_{14} case, the hydrodynamic diameters before and after the catalytic reaction remain nearly unchanged while changes could be observed for C_{16} and C_{20}, indicating the lower stability of the latter (Figure S23).

In conclusion, *in situ* formed Ag-(S-C_n-TACN)-Zn^{2+} multivalent metal coordination polymers, obtained via a facile "mix-and-catalyse" mode, emerge as an exciting new class of multivalent catalysts with phosphatase-activity. Compared to other reported artificial phosphatase systems, such as micelles, vesicles, dendrimers, and monolayer protected Au nanoparticles, the catalysts in this work show higher or comparable catalytic reactivity, but allow for a straightforward preparation that gives access to stable structures. The similar strategy, exploiting thiols bearing other catalytic units like His/Ser-containing dipeptides are currently being employed in our lab to develop novel artificial carboxylic acid esterases.

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Conflict of Interest

The authors declare no conflict of interest.

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[19] It is noted that that DLS theoretically requires spherical systems to provide an accurate size. In this work DLS was used only to provide rough estimates for the diameter to detect the trend in size change of Ag-(S-C_n-TACN) as a function of the alkyl chain length.