

## **Supramolecular Complexes and Supramolecular Catalysts Formed by Molecular Assembly of Multinuclear Metal Complexes in Aqueous Solutions**

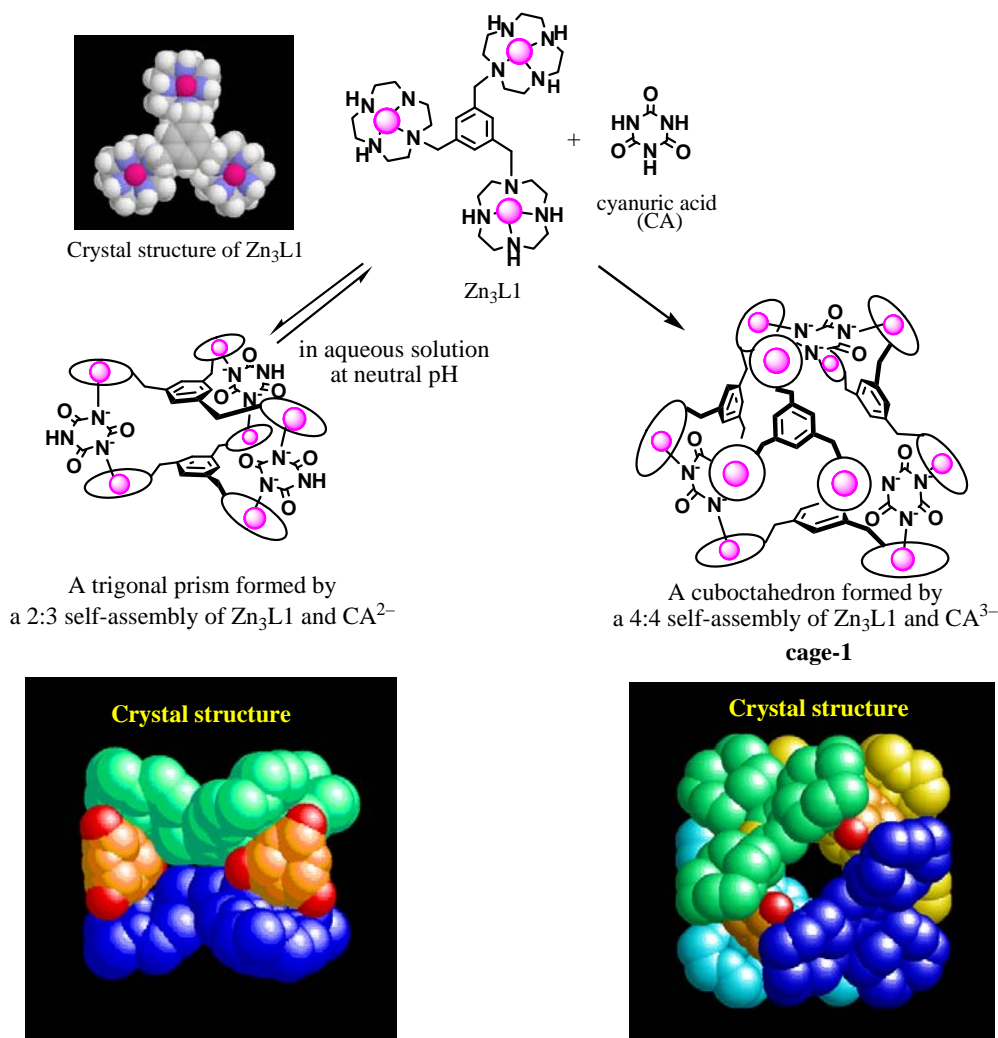
In Nature, organized nanoscale structures such as proteins and enzymes are formed in aqueous media via intermolecular interactions between multicomponents. Supramolecular and self-assembling strategies provide versatile methods for the construction of artificial chemical architectures for controlling reaction rates and the specificities of chemical reactions, but most are designed in hydrophobic environments.

Our methodology for construction of three-dimensional supermolecules in aqueous solution is to assemble multinuclear zinc(II)-cyclen complexes (cyclen = 1,4,7,10-tetraazacyclododecane) with polyanionic compounds by multiple  $\text{Zn}^{2+}$ -anion coordination bonds, hydrogen bondings, and hydrophobic interactions. Structures and chemical (and physical) properties of supramolecular complexes are examined in detail by NMR, potentiometric pH, UV, and fluorescent titration, X-ray crystal structure analysis, and so forth.

## [Supramolecular cages]

We have reported a supramolecular complex having a trigonal prism exterior by a 2:3 self-assembly of a tris( $\text{Zn}^{2+}$ -cyclen) having a mesitylene linker ( $\text{Zn}_3\text{L1}$ ) and a dianion of cyanuric acid ( $\text{CA}^{2-}$ ) (*J. Am. Chem. Soc.*, **2000**, *122*, 576). At the same time, a cuboctahedral 4:4 supramolecular cage ( **cage-1**) formed by self-assembly of a trimeric zinc(II) complex having a mesitylene linker ( $\text{Zn}_3\text{L1}$ ) and a trianion of cyanuric acid ( $\text{CA}^{3-}$ ) was serendipitously isolated from alkaline aqueous solution (Scheme 1).

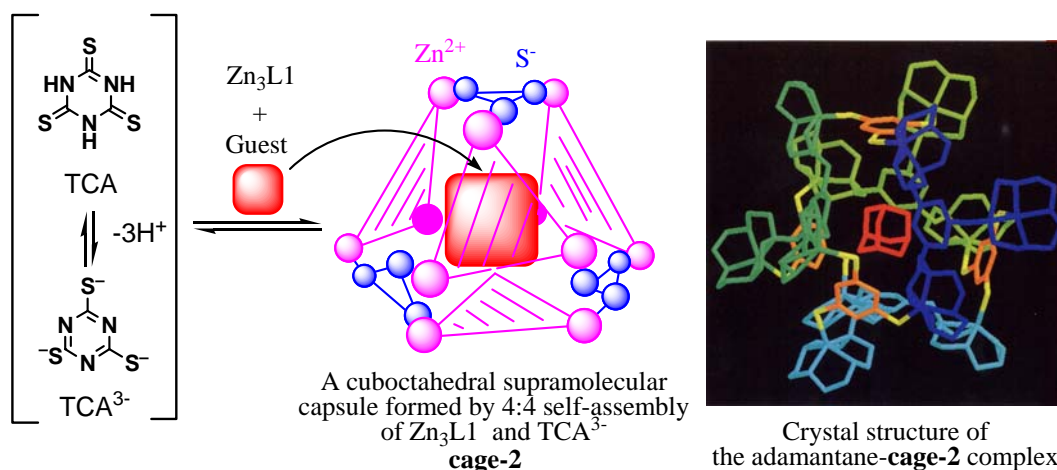
### Scheme 1



Ref) Shin Aoki, Motoo Shiro, Tohru Koike, and Eiichi Kimura, "Three-Dimensional Supermolecules Assembled from a Tris( $\text{Zn}^{2+}$ -cyclen) Complex and Di- and Trianionic Cyanuric Acid in Aqueous Solution (Cyclen = 1,4,7,10-Tetraazacyclododecane)." *Journal of the American Chemical Society*, **2000**, *122* (3): 576–584.

Based on these findings, we synthesized a twisted cuboctahedral cage (**cage-2**) by 4:4 assembly of  $Zn_3L1$  with a trianion of trithiocyanuric acid ( $TCA^{3-}$ ), whose  $pK_a$  values are lower than those of CA (Scheme 2). Formation of **cage-2** is reversible in aqueous solution and stabilized by encapsulating organic guests such as adamantane, nitrophenols, coumarin derivatives,  $Pr_4N^+$ , and ibuprofen, in its hydrophobic inner cavity (*Chem. Eur. J.*, **2002**, 8, 929). Interestingly, **cage-2** is chiral due to the asymmetric arrangement of  $Zn^{2+}$ -cyclen units around  $TCA^{3-}$ . The chirality of **cage-2** is controlled by an encapsulated guest in its inner cavity.

**Scheme 2**



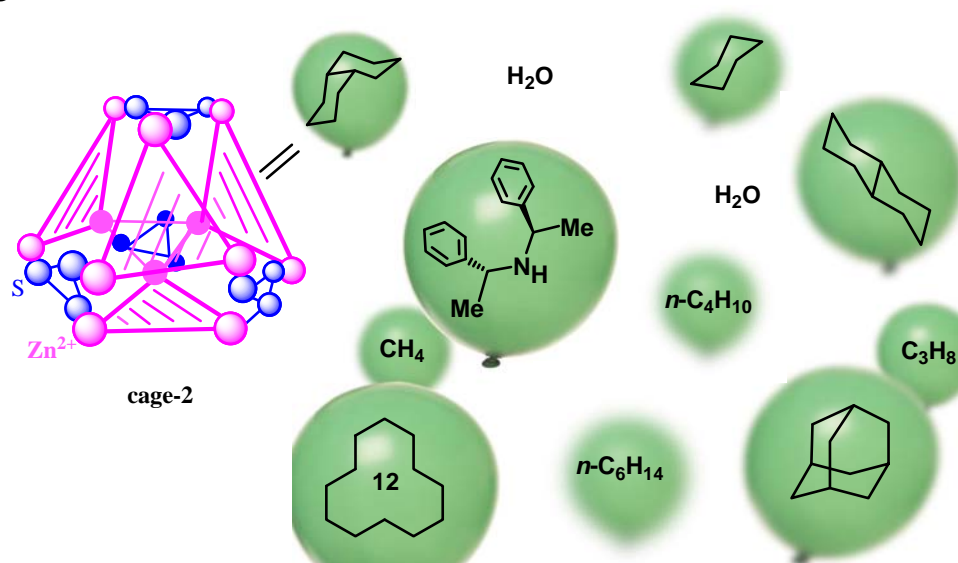
Ref) Shin Aoki, Motoo Shiro, and Eiichi Kimura, "A Cuboctahedral Supramolecular Capsule by 4:4 Self-Assembly of Tris( $Zn^{II}$ -cyclen) and Trianionic Trithiocyanurate in Neutral pH in Aqueous Solution (Cyclen = 1,4,7,10-Tetraazacyclododecane)." *Chemistry– A European Journal*, **2002**, 8 (4), 929–939.

Furthermore, we examined molecular recognition of  $C_1\sim C_{12}$  hydrocarbons ( $C_nH_{(2n+2)}$  ( $n = 1\sim 12$ )), cyclopentane, cyclododecane, *cis*-decalin, and *trans*-decalin by the **cage-2** under normal atmospheric pressure (Scheme 3). On the basis of  $^1H$  NMR data, GC measurements, and X-ray crystal structure analysis, it was confirmed that one molecule of a hydrocarbon such as  $C_nH_{(2n+2)}$  ( $n = 1\sim 10$ ), adamantane, *cis*- and *trans*-decaline, cyclododecane and (*R,R*)-BMBA can be incorporated as guests of **cage-2** (Scheme 3). Computational simulations of **cage-2**-guest complexes using Amber\* of the MacroModel suggested that the **cage-2** has a flexible structure originating from rotation about the  $C-S^-$  bonds of the  $(Zn^{2+})_3-(TCA^{3-})$  unit. The  $\Delta SASA$  values ( $= (SASA_G + SASA_H) - (SASA_{HG})$ ) were calculated as parameters to evaluate the surface

complementarity between guest molecules and the inner cavity of **cage-2**, in order to explain the order of stability determined by the guest replacement experiments.

The storage and release of volatile molecules by **cage-2** in aqueous solution and solid state was also studied. Time-dependent changes in the concentration of propane and *n*-butane under ambient atmosphere were monitored by GC, after sparging these gases in D<sub>2</sub>O solution of **cage-2** at 20 °C. While propane and *n*-butane nearly completely vanish within 5 min in the absence of **cage-2**, propane remained in the solution of **cage-2** for over 6 hr, and butane remained in the solution at a level of 50%, even after 10 hr, indicating that propane, *n*-butane, and pentane can be stored in aqueous solutions of **cage-2** under ambient atmosphere at room temperature for at least several hours and the stability of the **cage-2**–gas complexes is dependent on the boiling points of the guest molecules (*Chem. Asian J.* **2012**, *7*, 944-956).

### Scheme 3



Ref) Shin Aoki, Satoshi Suzuki, Masanori Kitamura, Takeharu Haino, Motoo Shiro, Mohd Zulkefeli, and Eiichi Kimura, “Molecular Recognition of Hydrocarbon Guests by A Supramolecular Capsule Formed by the 4:4 Self-Assembly of Tris(Zn<sup>2+</sup>–cyclen) and Trithiocyanurate in Aqueous Solution (Cyclen = 1,4,7,10-Tetraazacyclododecane).”

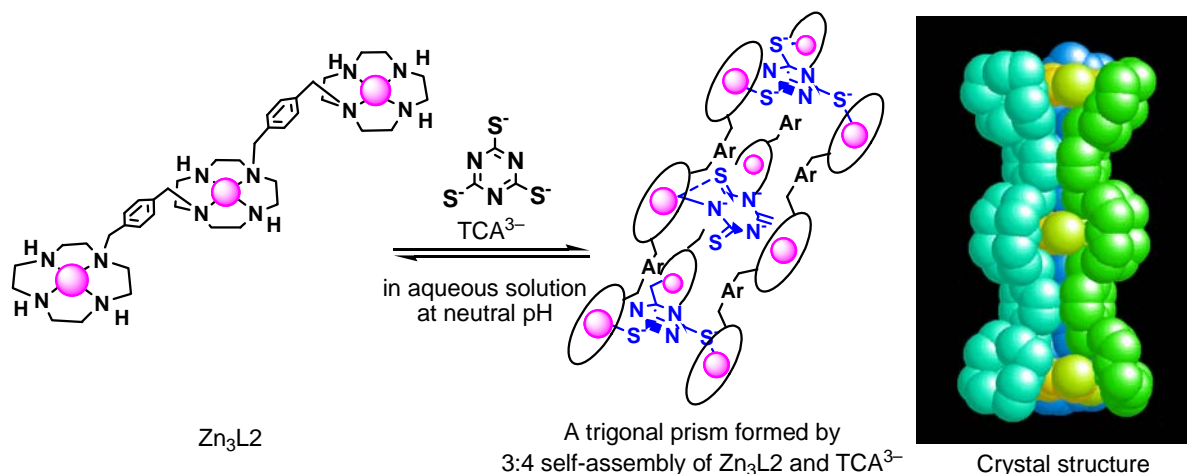
*Chemistry– An Asian Journal*, **2012**, *2012*, *7*, 944-956.

### [Supramolecular prisms]

It was found that a linear trimeric zinc(II) complex (Zn<sub>3</sub>L<sub>2</sub>) and TCA<sup>3-</sup> assemble in a 3:4 ratio without a guest molecule to yield a trigonal prism in aqueous solution at neutral pH (*Proc.*

*Natl Acad. Sci., U.S.A.* **2002**, *99*, 4894) (Scheme 4).

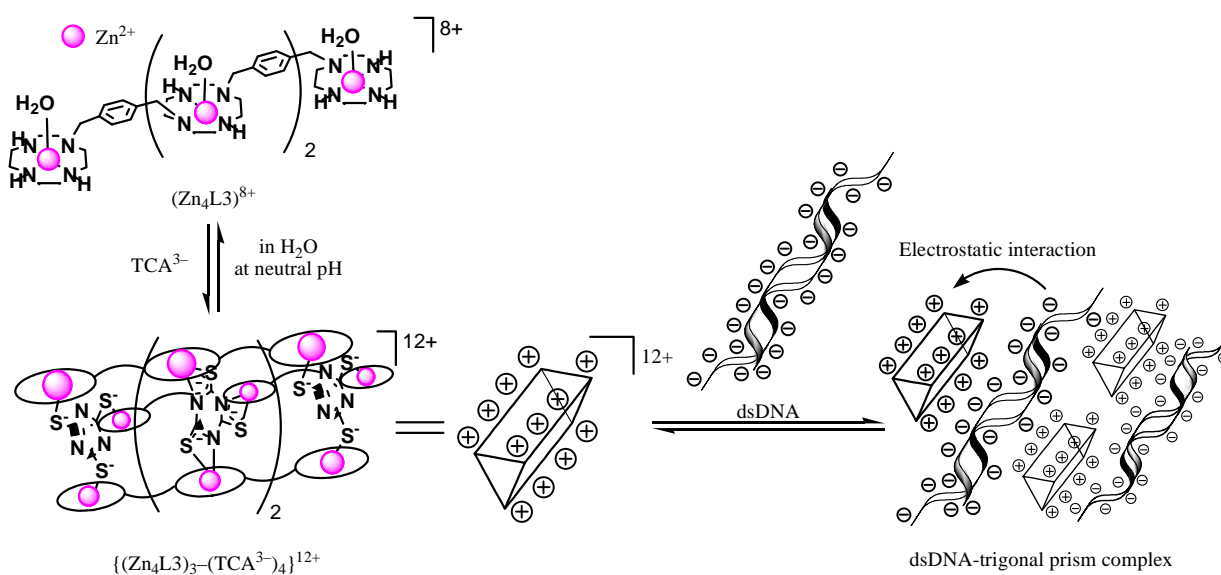
#### Scheme 4



Ref) Mohd Zulkefeli, Tetsuya Sogon, Kei Takeda, Eiichi Kimura, and Shin Aoki, “New Supramolecular Trigonal Prisms from Zinc(II)–Cyclen Complexes and Trithiocyanurate in Aqueous Solution (Cyclen = 1,4,7,10-Tetraazacyclododecane),” *Proceedings of the National Academy of Sciences, U.S.A.* **2002**, *99* (8): 4894–4899.

In addition, a supramolecular trigonal prism,  $(Zn_4L3)_3-(TCA^{3-})_4\}^{12+}$ , was formed by the self-assembly of linear tetrakis(Zn<sup>2+</sup>–cyclen) complex (Zn<sub>4</sub>L3)<sup>8+</sup> with TCA<sup>3-</sup> (Scheme 5). The complex is quite stable at submicromolar concentrations in aqueous solution, as evidenced by <sup>1</sup>H NMR, potentiometric pH titration, UV/Vis spectrophotometric titrations, and MS spectra. The findings also show that  $(Zn_4L3)_3-(TCA^{3-})_4\}^{12+}$  interacts with double-stranded DNA (dsDNA), as confirmed by ethidium bromide (EB) displacement assays and GMSA. Although **7** induced only negligible change in the *T<sub>m</sub>* values of dsDNA, it inhibited the interaction of DNA and DNA-binders such as EB, DAPI, pentamidine, and spermine. The dynamic light scattering (DLS) results indicate that this trigonal prism functions as a polycationic template to induce aggregation of dsDNA, possibly due to the electrostatic interactions. (*Inorg. Chem.* **2002**, *99*, 4894) (Scheme 5).

## Scheme 5



Ref) Mohd Zulkefeli, Tetsuya Sogon, Kei Takeda, Eiichi Kimura, and Shin Aoki, “Design and Synthesis of A Stable Supramolecular Trigonal Prism Formed by the Self-Assembly of A Linear Tetrakis( $Zn^{2+}$ -cyclen) Complex and Trianionic Trithiocyanuric Acid in Aqueous Solution and Its Complexation with DNA (Cyclen = 1,4,7,10-Tetraazacyclododecane)”

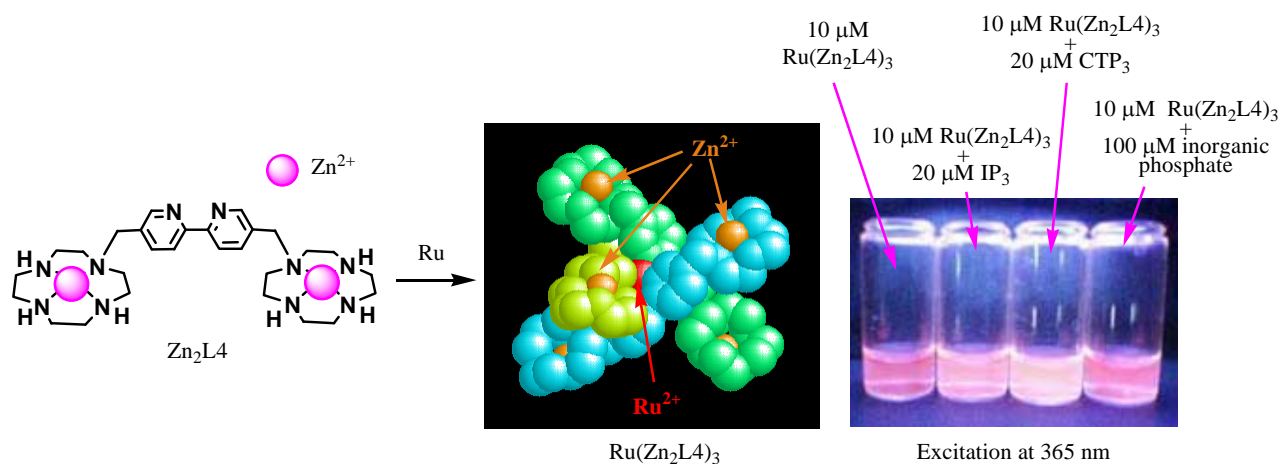
*Inorganic Chemistry*, **2009**, 48 (19), 9567-9578 (DOI: 10.1021/ic901407d)

### [Supramolecular luminescence sensors]

Inositol 1,4,5-triphosphate ( $IP_3$ ) is one of the important second messengers in intracellular signal transduction. The hydrolysis of phosphatidylinositol 4,5-bisphosphate ( $PIP_2$ ) located in the plasma membrane by a specific phospholipase C (PLC) releases  $IP_3$ , which induces an increase of  $Ca^{2+}$  concentrations in living cells. To date, only a few biological and chemical sensing systems for  $IP_3$  and related phosphates have been developed because  $IP_3$  does not have a chromophore, and specific chemical motifs for  $IP_3$  recognition have not been explored.

In this context, a supramolecular complex  $Ru(Zn_2L_4)_3$  possessing a luminescent tris(2,2'-bipyridyl)ruthenium ( $Ru(bpy)_3$ ,  $bpy = 2,2'$ -bipyridine) center was synthesized by Ru-templated assembly of three molecules of a bis( $Zn^{2+}$ -cyclen) having a 2,2'-bipyridyl linker,  $Zn_2L_4$  and its structure was confirmed by X-ray crystal structure analysis (Scheme 6). It was hypothesized that three of six  $Zn^{2+}$ -cyclen moieties of  $Ru(Zn_2L_4)_3$  on opposite sides of the molecule would cooperatively bind to three phosphate groups of  $IP_3$  to yield a 1:2 complex, resulting in a luminescence response to  $IP_3$ .

## Scheme 6



Ref) Shin Aoki, Mohd Zulkefeli, Masanori Kohsako, Motoo Shiro, Kei Takeda, and Eiichi Kimura, "A Luminescence Sensor of Inositol 1,4,5-Triphosphate and Its Model Compound by Ruthenium-Templated Assembly of a Bis( $\text{Zn}^{2+}$ -cyclen) Complex Having a 2,2'-Bipyridyl Linker (Cyclen = 1,4,7,10-Tetraazacyclododecane)."

*Journal of the American Chemical Society*, **2005**, 127(25), 9129–9139.

### [Supramolecular catalysts]

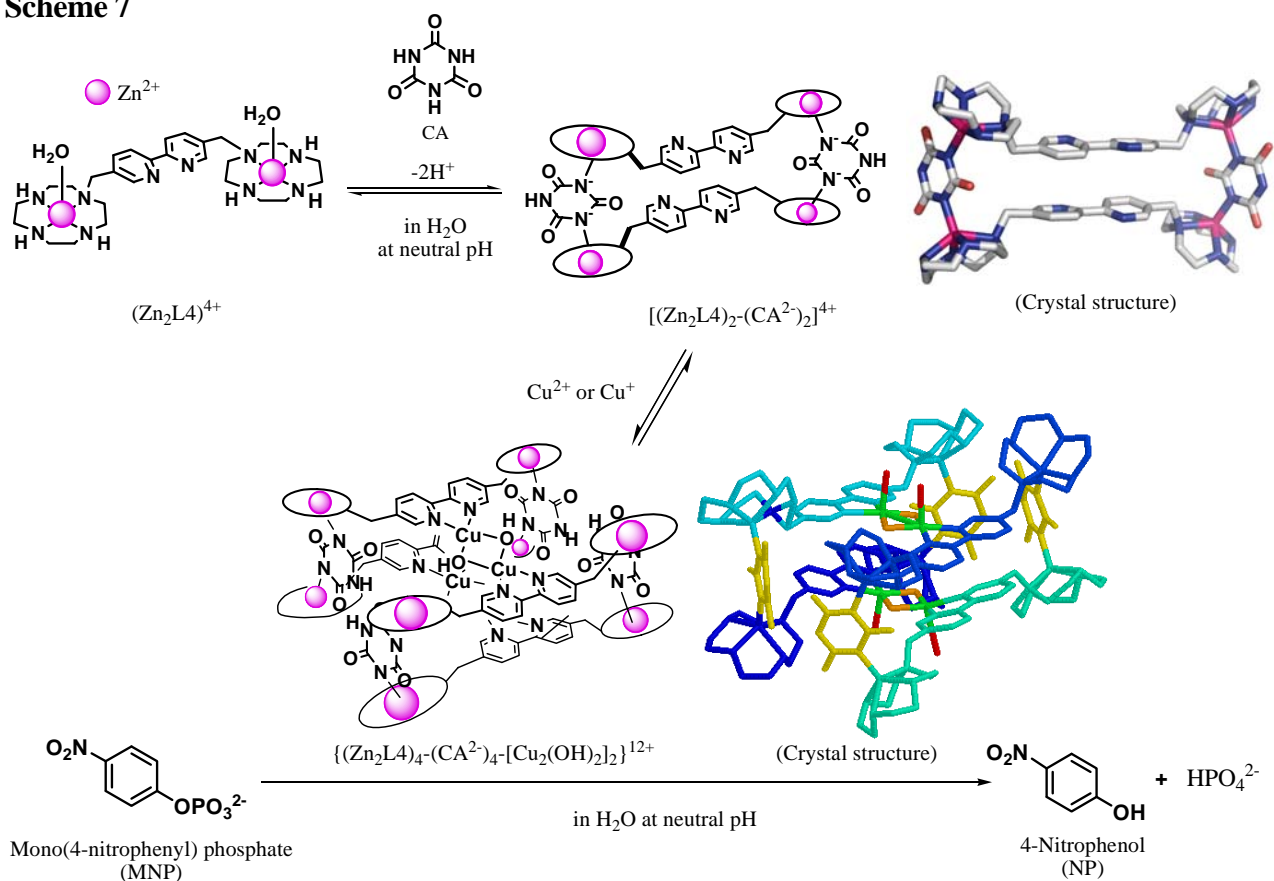
The phosphorylation and dephosphorylation of proteins and enzymes are important processes in intracellular regulation. The dephosphorylation of phosphoserine and phosphothreonine residues in proteins is catalyzed by protein phosphatases, which catalyze the reverse reaction of protein kinases. The structures of several metallophosphatases have been reported, including alkaline phosphatase (AP) from *Escherichia coli* containing  $\text{Zn}^{2+}$ - $\text{Zn}^{2+}$  centers, and kidney bean purple acid phosphatase (KBPAP) and Ser/Thr protein phosphatase I, which contain  $\text{Zn}^{2+}$ - $\text{Fe}^{3+}$  centers. Although the metal cations in these phosphatases are different and the amino acid sequences of the enzymes are not related, the structures of their active sites are similar, in that they include dimetallic diamond cores containing two metal cations, which are coordinated by amino acids and hydroxide ions.

The preparation of artificial catalysts that have potential in aqueous media mimicking natural enzymes such as hydrolases remains a great challenge in the fields of supramolecular chemistry. In this work, the supramolecular catalyst was constructed by self-assembly of the dimeric  $\text{Zn}^{2+}$  complex  $\text{Zn}_2\text{L}_4$ , which is the same building block for the supramolecular  $\text{IP}_3$  sensor

shown in Scheme 6, cyanuric acid (CA) and copper (Scheme 7). By X-ray crystal structure analysis,  $Zn_2L4$  and CA dianion ( $CA^{2-}$ ) form a 2:2 complex ( $[(Zn_2L4)_2-(CA^{2-})_2]^{4+}$ ), which is stabilized by metal-ligand coordination bonds,  $\pi$ - $\pi$  stacking interactions and hydrogen bondings. The addition of copper ion to  $[(Zn_2L4)_2-(CA^{2-})_2]^{4+}$  induced the dimerization this 2:2 complex to form a 4:4:4 complex  $\{(Zn_2L4)_4-(CA^{2-})_4-[Cu_2(OH)_2]^{2+}\}^{12+}$  that contains  $\mu$ - $Cu_2(OH)_2$  cores, mimicking the active centers of dimetallic phosphatases such as alkaline phosphatase.

Interestingly, it was discovered that this 4:4:4 complex selectively accelerates the hydrolysis of a phosphate monoester, mono(4-nitrophenyl)phosphate, at neutral pH. To our knowledge, this 4:4:4 complex represents the first supramolecular phosphatase that is formed by self-assembly and selectively hydrolyzes a phosphate monoester catalytically under physiological conditions. Although CTN is about 2~4, the considerable acceleration of MNP hydrolysis by **3** in aqueous solution at neutral pH is noteworthy (Scheme 7).

**Scheme 7**



Ref) Mohd Zulkefeli, Asami Suzuki, Motoo Shiro, Yosuke Hisamatsu, Eiichi Kimura, and Shin



Aoki, “Selective Hydrolysis of Phosphate Monoester by a Supramolecular Phosphatase Formed by Self-assembly of a Bis( $Zn^{2+}$ -cyclen) Complex, Cyanuric Acid and Copper in Aqueous Solution (Cyclen = 1,4,7,10-Tetraazacyclododecane)”

*Inorganic Chemistry*, **2011**, 50(20), 10113–10123 (DOI: [dx.doi.org/10.1021/ic201072q](https://doi.org/10.1021/ic201072q)) (Selected as an article as soon as publishable (ASAP) article)

Our current research interests include other heteromultinuclear supramolecular complexes by various combinations of multinuclear  $Zn^{2+}$  complexes with other organic anions and metal ions in aqueous solution (Manuscript in preparation).