Communication

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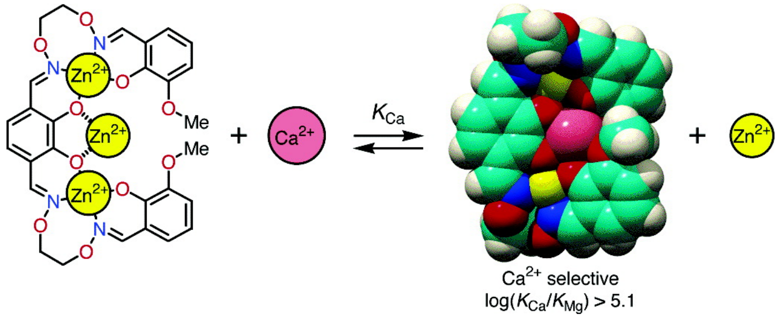

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COMMUNICATIONS

Ca^{2+}- and Ba^{2+}-Selective Receptors Based on Site-Selective Transmetalation of Multinuclear Polyoxime−Zinc(II) Complexes

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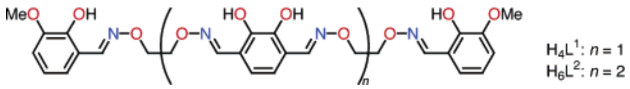
Recently, metallohosts that contain one or more transition metal atoms have been utilized to regulate guest-binding by metal coordination[1] or redox reactions[2] and to construct supramolecular structures.[3] Unique properties of the metallohosts are also applied in sophisticated functions such as transduction of molecular information.[4] We recently reported that, in a cooperative fashion, H_4L^1 and zinc(II) acetate quantitatively form a homotrinuclear zinc(II) complex, $[L^1Zn_3]^{2+}$, which reacts with europium(III) to afford a heterotrinuclear complex, $[L^1Zn_2Eu]^{3+}$, via site-selective transmetalation.[5] This fine exchange of zinc(II) with a lanthanide(III) ion can be utilized to recognize alkaline earth metals, especially Ca^{2+}, since the ionic radius of Ca^{2+} is similar to that of lanthanide(III) and Ca^{2+} usually accepts 6−10 ligands in the inner sphere.[6] Furthermore, the coupled exchange of Zn^{2+} and Ca^{2+} is very interesting since the amount of Zn^{2+} released depends on the Ca^{2+} concentration, which is crucial for the neuronal function in the hippocampus.[7] These facts encouraged us to pursue the Ca^{2+} affinity of $[L^1Zn_3]^{2+}$ and its analogue $[L^2Zn_4]^{2+}$ utilizing a novel transmetalation strategy. In addition, a highly selective detection of Ca^{2+} over Mg^{2+} is very important in vivo since Ca^{2+} concentrations are usually much smaller than those of Mg^{2+} in living cells. Here, we report an extremely selective Ca^{2+} recognition by a trinuclear metallohost, $[L^1Zn_3]^{2+}$, and Ba^{2+} recognition by a larger metallohost, $[L^2Zn_4]^{2+}$ (Chart 1).

Chart 1



When $Ca(ClO_4)_2$ was added to the metallohost $[L^1Zn_3]^{2+}$ in $CDCl_3/CD_3OD$ (1:1), a new set of signals, which is attributed to complexation with Ca^{2+}, appeared in the ^1H NMR spectrum (Figure 1). ^1H NMR titration implies that complexation occurs in a 1:1 stoichiometry. However, ESI mass spectrometry does not indicate a 1:1 complexation between $[L^1Zn_3]^{2+}$ and Ca^{2+}; the formation of a trinuclear complex, $[L^1Zn_2Ca]^{2+}$, was indicated since a strong peak at $m/z = 805.0$ of $[L^1Zn_2Ca(OAc)]^+$ was observed and not $[L^1Zn_3]^{2+}$ peaks. Upon complexation, one Zn^{2+} ion in $[L^1Zn_3]^{2+}$ was liberated and a Ca^{2+} ion was simultaneously bound to the $[L^1Zn_2]$ unit, which is the guest exchange reaction shown in Scheme 1. The equilibrium constant ($K_{Ca} = 32 \pm 3$) was calculated by nonlinear least-squares regression. Thus, 86% of $[L^1Zn_3]^{2+}$ was converted to the calcium complex (defined as C, see Table 1) when 1 equiv of Ca^{2+} was added.

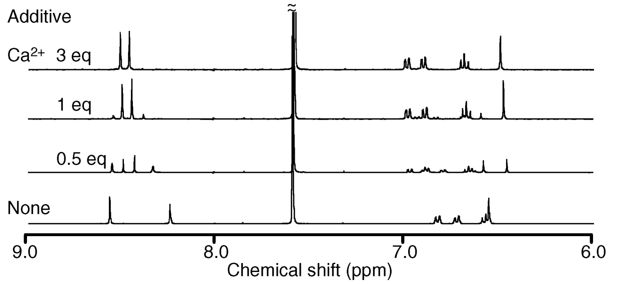


Figure 1. ^1H NMR spectra (400 MHz) of $[L^1Zn_3]^{2+}$ in the absence and in the presence of $Ca(ClO_4)_2$ in $CDCl_3/CD_3OD$ (1:1).

Scheme 1. Equilibrium between the Complexes $[L^1Zn_3]^{2+}$ and $[L^1Zn_2Ca]^{2+}$

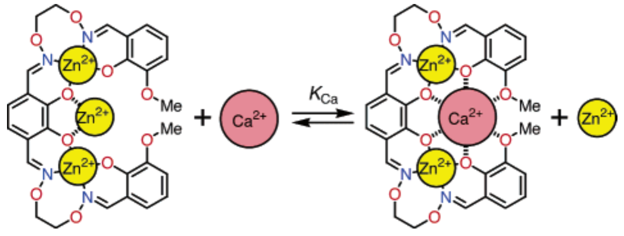


Table 1. Equilibrium Constants and Selectivity Coefficients of Trinuclear Complex $[L^1Zn_3]^{2+}$

guest	C/%[a]	K_M[b]	selectivity[c]
Mg^{2+}	0	–	>5.1[d]
Ca^{2+}	86	32 ± 3	–
Ba^{2+}	40	0.16 ± 0.04	2.3

[a] Conversion of $[L^1Zn_3]^{2+}$ to $[L^1Zn_2M]^{2+}$ (defined as C) when 1 equiv of $M(ClO_4)_2$ is added. [b] Equilibrium constant $K_M = ([[L^1Zn_2M]^{2+}][Zn^{2+}])/([[L^1Zn_3]^{2+}][M^{2+}])$, determined by ^1H NMR spectroscopy. [c] Defined as $\log(K_{Ca}/K_M)$. [d] Estimated by a competition experiment.

The trinuclear metallohost $[L^1Zn_3]^{2+}$ recognizes Ca^{2+} much easier than Ba^{2+}. Adding Ba^{2+} to $[L^1Zn_3]^{2+}$ resulted in similar ^1H NMR signal changes, but the equilibrium constant was much smaller ($K_{Ba} = 0.16 \pm 0.04$) than that for Ca^{2+}. Consequently, the metallohost binds Ca^{2+} 200 times stronger than Ba^{2+}. It is noteworthy that Mg^{2+} does not cause the transmetalation. The heterotrinuclear complex $[L^1Zn_2Mg]^{2+}$ was not observed in the ^1H NMR and ESI mass spectra of a 1:1 mixture of $[L^1Zn_3]^{2+}$ and Mg^{2+}. A competition experiment confirmed the high Ca^{2+} selectivity. Even when 1000 equiv of Mg^{2+} was added to an equimolar mixture of $[L^1Zn_3]^{2+}$ and Ca^{2+} (1 mM), the conversion C estimated by ^1H NMR spectroscopy decreased slightly (C changed from 86% to 80%) and no new signals due to the Mg^{2+} complex were detected. These data indicate that the selectivity coefficient $\log(K_{Ca}/K_{Mg})$ is at least 5.1, which is similar to those of the excellent Ca^{2+} receptors or sensors such as BAPTA[8] (selectivity coefficients[9] = 5.20), Quin2[8] (4.4), and K23E1[10] (5.0).

In contrast, UV−vis and ^1H NMR spectroscopies indicate that $[L^1Zn_3]^{2+}$ does not have an affinity for alkali metal ions (Na^+, K^+, Rb^+, Cs^+). Thus, among the biologically important metal cations (Na^+, K^+, Mg^{2+}, Ca^{2+}), the metallohost $[L^1Zn_3]^{2+}$ exclusively recognizes Ca^{2+}. This metallohost, however, strongly binds all of the rare earth(III) ions (K_M > 1000 for M = Sc^{3+}, Y^{3+}, La^{3+}, Eu^{3+}, Lu^{3+}), too. These facts suggest that the charge of guest cations is a significant factor which affects the cation-binding ability of

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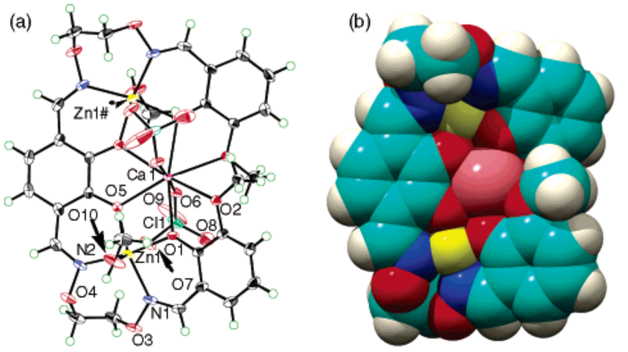


Figure 2. X-ray structure of metallohost−guest complex $[L^1Zn_2Ca]^{2+}$. (a) ORTEP drawing (50% probability). (b) Space-filling representation (counteranions and solvent molecules are omitted for clarity).

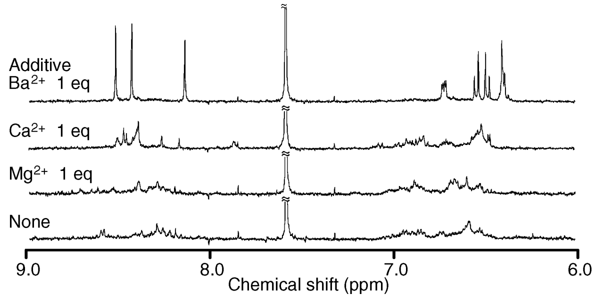


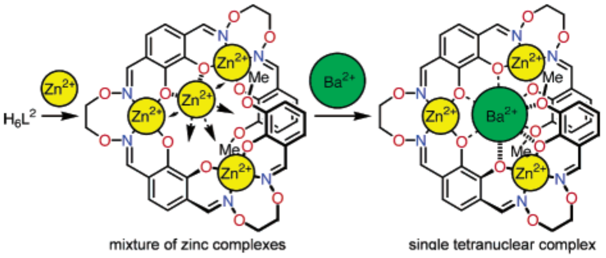
Figure 3. Part of ^1H NMR spectra (400 MHz) of $[L^2Zn_4]^{2+}$ in the absence and in the presence of $M(ClO_4)_2$ (1 equiv, M = Mg, Ca, Ba) in $CDCl_3$/CD_3OD (1:1).

$[L^1Zn_3]^{2+}$ due to the strong electrostatic interaction between the two [Zn(salamo)] moieties and the guest cation M.[11] Moreover, the size-fit principle is important for this ion recognition, because among Mg^{2+}, Ca^{2+}, and Ba^{2+}, only Ca^{2+} ion has the appropriate ionic diameter for the recognition site.

The structure of $[L^1Zn_2Ca]^{2+}$ in the crystalline state was determined by X-ray crystallography (Figure 2).[12] The molecule possesses a crystallographic two-fold axis, and the $[L^1Zn_2]$ moiety forms a one-turn helix surrounding the guest Ca^{2+}. All six oxygen atoms of the inner recognition site of the $[L^1Zn_2]$ moiety coordinate nicely to the Ca^{2+}. The distances between the calcium atom and the oxygen atoms range from 2.396 to 2.606 Å, which again supports the complementary relationship between Ca^{2+} and the cavity.

A longer derivative, tris(salamo) ligand H_6L^2, is expected to form a stable one-turn single helix when the three Zn^{2+} ions are introduced into the chelate moieties. ^1H NMR spectroscopy monitored the conversion of ligand H_6L^2 to the metallohost. Since many peaks were observed in the ^1H NMR spectrum of H_6L^2 in the presence of 4 equiv of zinc(II) acetate, a mixture of complexes was formed by the complexation (Figure 3). However, in the mass spectrum a strong peak at $m/z = 1113.0$ was observed, assigned to $[L^2Zn_4(OAc)]^+$, and peaks were not observed in higher m/z regions. The data suggest that the mixture contains not oligomeric complexes but isomers of complex $[L^2Zn_4]^{2+}$. This result sharply contrasts the shorter analogue H_4L^1, which exclusively gave a single complex, $[L^1Zn_3]^{2+}$, via the complexation with a Zn^{2+} ion. This is probably because the central Zn^{2+} was not tightly fixed in the cavity since $[L^2Zn_3]$ has a larger cavity than the size of Zn^{2+}(Scheme 2).

Scheme 2. Formation of Helical Tetranuclear Complex $[L^2Zn_3Ba]^{2+}$ by Exchanging the Central Zn^{2+} with Ba^{2+}



Interestingly, Ba^{2+} (1 equiv) changed the mixture of the isomers of $[L^2Zn_4]^{2+}$ into a single component ($K_{Ba} > 1000$). A sharp, simple ^1H NMR spectrum (Figure 3) strongly suggests the existence of only one species, which was determined to be $[L^2Zn_3Ba]^{2+}$ on the basis of the strong peak at $m/z = 1185.9$, which was assigned to the heterotetranuclear complex $[L^2Zn_3Ba(OAc)]^+$ in the ESI mass spectrum. These results indicate the binding of Ba^{2+} in the helical cavity and simultaneous release of a Zn^{2+} ion. Among the three CH═N protons of the Ba^{2+} complex, only the terminal one is observed at higher field (8.14 ppm) in the ^1H NMR spectrum, which also suggests the helical structure.[13]

On the other hand, the $[L^2Zn_4(OAc)_2]$ isomers did not change into a single component when ion M (M = K^+, Cs^+, Mg^{2+}, Ca^{2+}) was added due to the lower stability of the heteronuclear complex $[L^2Zn_3M]^{n+}$. ESI mass spectrometry strongly supports that the transmetalation does not effectively occur, since adding Ca^{2+} or Mg^{2+} resulted in complicated spectra. Thus, the tetranuclear complex $[L^2Zn_4(OAc)_2]$ generated by reacting ligand H_6L^2 and Zn^{2+} was found to act as a Ba^{2+}-selective metalloreceptor.

In conclusion, we synthesized a novel ion recognition system based on multinuclear zinc(II) complexes that utilize the selective exchange of metal ions. To utilize it as a novel ion sensor, we are currently investigating the addition of fluorophores at the end of the linear ligands.

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Supporting Information Available: Synthetic procedure (PDF); crystallographic data for $[L^1Zn_2Ca(ClO_4)_2(MeOH)_2]$ (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) $[L^2Zn_4]^{2+}$ also strongly binds La^{3+} to form $[L^2Zn_3La]^{3+}$. Very recently we have determined the structure of $[L^2Zn_3La(OAc)_3]$ to be helical by X-ray analysis.
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