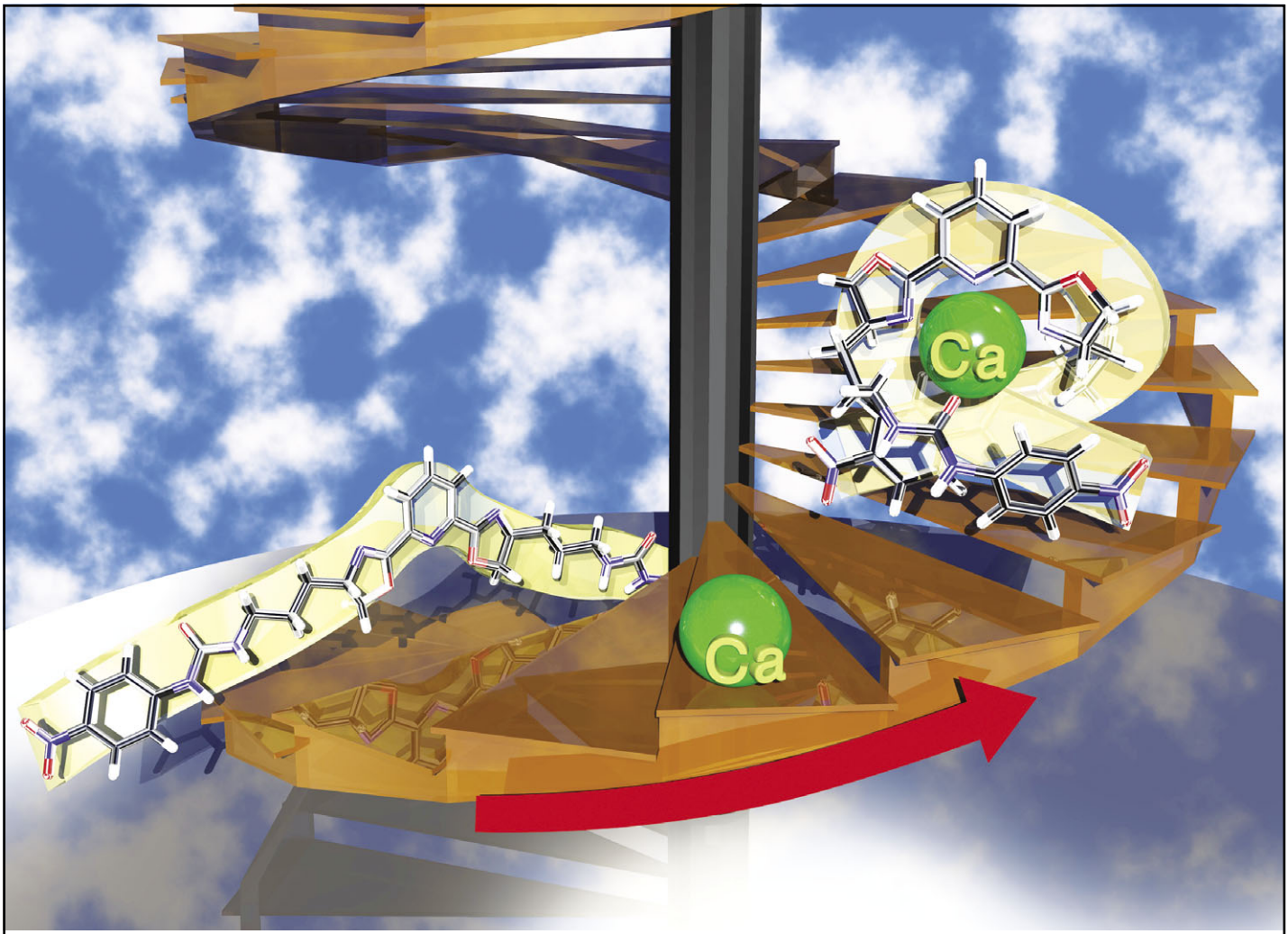

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Ca^{2+}-induced folding of a chiral ditopic receptor based on a Pybox ligand and enhancement of anion recognition

A chiral Pybox ligand bearing two urea units was developed for a Ca^{2+}-responsive artificial folding system inspired by Ca^{2+}-controlled biological processes. The Ca^{2+}·Pybox foldamer showed stronger halide-ion affinity than the corresponding Ca^{2+}-free ligand; thus the Ca^{2+}-induced folding enhanced the halide-ion recognition.

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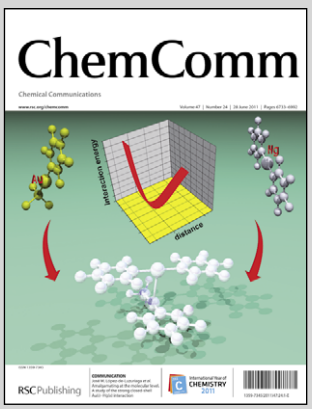

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COMMUNICATION

Ca^{2+}-induced folding of a chiral ditopic receptor based on a Pybox ligand and enhancement of anion recognition†‡

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Received 27th December 2010, Accepted 4th February 2011
DOI: 10.1039/c0cc05799a

A chiral Pybox ligand bearing two urea units was developed for a Ca^{2+}-induced folding ligand. 1 : 1 Ca^{2+} complexation of the Pybox ligand afforded chiral foldamer formation with coordination of the urea carbonyls to Ca^{2+}. The halide-ion affinity of the foldamer was enhanced compared to Ca^{2+}-free Pybox ligands.

In biological systems, a calcium ion plays an important role in controlling biomolecular functions such as reactivity modulation, energy conversion to movement, binding affinity control, and so on.[1] For example, ATP hydrolysis of Ca^{2+}-ATPases starts after binding Ca^{2+} ions, and the Ca^{2+} binding of troponin regulates muscle fiber contraction. These modulations of protein function are accompanied by a Ca^{2+} ion-induced conformational change. In order to develop ion-responsive artificial systems in terms of biomolecular implication, artificial dynamic folding systems, which are analogues for biomolecules such as DNA and α-helix, have been constructed by utilizing metal ion complexation.[2] Chiral foldamers have attracted much attention because of their application to chiral molecule sensors, asymmetric catalysts, and chiral optical materials. However, there have been only a few reports of foldamer formation triggered by Ca^{2+} ions,[3] though analogous foldamers with transition metals have been well studied.[4] Transition metal-induced transoid–cisoid conformational changes in bipyridine and terpyridine derivatives are suitable for forming artificial foldamers and related supramolecules.[5] 2,6-Bis(oxazolinyl)pyridine (Pybox) ligand, an *NNN*-tridentate ligand, is expected to be more useful than a terpyridine for a functional folding module because the Pybox framework can be easily derivatized to a chiral Pybox with a functional unit.[6] The chiral Pybox ligands have been widely utilized for catalytic asymmetric reactions.[6] The recent reports on Ca^{2+}-catalyzed asymmetric reactions using chiral Pybox demonstrated an advantage of the Pybox·Ca^{2+} complex as a chiral catalytic species.[7] Pybox ligands have also been employed for supramolecular chiral self-assembling[8] and chirality induction.[9] We envisaged that a Ca^{2+} complex of Pybox has a potential for Ca^{2+}-triggered folding modules because metal complexation of Pybox would drive the equilibrium to the transoid structure useful for helical folding.

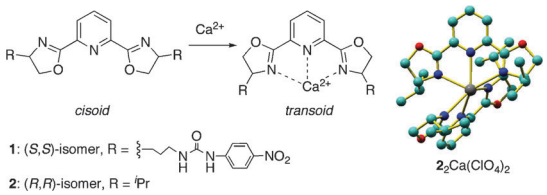

Fig. 1 Schematic complexation process of Pybox with Ca^{2+} and the crystal structure of $\mathbf{2}_2Ca(ClO_4)_2$. Hydrogen atoms and the counter anions, ClO_4^-, were omitted for clarity.

First, we clarified the structure of a Pybox·Ca^{2+} complex because none of the Pybox·Ca^{2+} complexes have been well characterized. The crystal structure of $\mathbf{2}_2Ca(ClO_4)_2$ (Fig. 1) clearly showed the transoid conformer with an *NNN* ligation.[10] Conversely, the cisoid conformer of the free Pybox ligand is a global energy-minimized structure at a DFT calculation level, and hence the complexation process should afford the conformational change in Pybox from cisoid to transoid.[11] The Ca^{2+}-induced conformational change encouraged us to design and synthesize Pybox-based ditopic receptor **1** bearing 4-nitrophenylurea groups, which act as a ligand to a metal[12] as well as an anion-detecting unit by utilizing optical and chiroptical changes.[13]

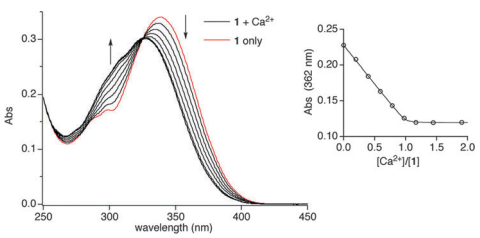

Fig. 2 UV-vis spectral change in **1** on the addition of Ca^{2+} in 1 : 4 MeCN/$CHCl_3$, [**1**] = 10 μM. Inset shows the titration curve plotted at 362 nm.

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† This article is part of a ChemComm 'Supramolecular Chemistry' web-based themed issue marking the International Year of Chemistry 2011.

‡ Electronic supplementary information (ESI) available: Synthesis and characterization of **1** and X-ray analysis of $\mathbf{2}_2Ca(ClO_4)_2$ and all spectroscopic titration experiments. CCDC 805519. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc05799a

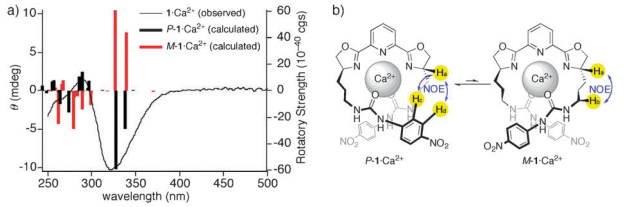

Fig. 3 (a) CD spectrum and calculated rotatory strengths of **1**·Ca^{2+}. Calculations were carried out at a two-layered ONIOM TD-DFT theory level. (b) *P*- and *M*-isomers of **1**·Ca^{2+}.

In the UV-vis spectroscopic titration of **1** with $Ca(ClO_4)_2$, a blue shift of λ_{max} assigned to the transition of nitrophenylurea moieties (340 nm to 328 nm) was observed with an isosbestic point. The binding isotherm clearly showed a strong 1 : 1 complexation (log $K_c > 7$) in 1 : 4 MeCN/$CHCl_3$ (Fig. 2). The ESI-MS also confirmed the 1 : 1 stoichiometry because a signal assigned to **1**·Ca^{2+} (m/z = 349.6) was observed without any other species such as $\mathbf{1}_n$·Ca^{2+} ($n \geq 2$). These results are noteworthy because Pybox ligands without side chains can afford a 1 : 2 complex with various metal ions.[14] The ancillary coordination of the urea carbonyls to Ca^{2+} may contribute to the discrete formation of the 1 : 1 complex. A 2D NOESY spectrum of **1**·Ca^{2+} showed significant NOE correlation peaks between protons of the oxazoline rings (H_a shown in Fig. 3b) and the side chains (H_b, H_c, H_d). These NOE correlation peaks indicate the close proximity between the oxazoline rings and side chains, which may result from the coordination of the urea carbonyls to the Ca^{2+} ion (Fig. 3b). In contrast, the corresponding NOE peaks were not observed in the case of **1** at all. The IR spectroscopy indicated the effective coordination of the urea carbonyls to the Ca^{2+} ion.[15] The C=O stretching band of the urea group of **1** in 1 : 4 MeCN/$CHCl_3$ was significantly shifted from 1704 to 1620 cm^{-1} by the addition of Ca^{2+} ions, showing the C=O bond elongation induced by ligation of the carbonyl oxygen to the Ca^{2+} ion. The UV-vis, ESI-MS, NMR, and IR spectra confirmed the foldamer formation by the 1 : 1 complexation of **1** with a Ca^{2+} ion.

Due to the chirality in the oxazoline ring, the foldamer **1**·Ca^{2+} has two diastereomers, *P* and *M*-helical isomers. In the DFT-optimized structure of the *P*-isomer, the distance between H_a and H_c is shorter than 3 Å to be detectable in NOE. In the case of the *M*-isomer, the NOE correlation between H_a and H_b should be observed. Because the observed NOE peaks were assigned to both the diastereomers, the two isomers were found to exist in equilibrium. Only one set of sharp signals were observed in the ^{1}H NMR spectra, indicating that the signals of the two diastereomers were averaged on the NMR time scale. The CD spectra of **1**·Ca^{2+} showed a drastic increase in the Cotton effect upon complexation (Fig. 3). The Cotton effects were observed as an S-shape in the absorption region for the 4-nitrophenylurea groups, which means that the circular dichroism was derived from exciton coupling of the two chromogenic fragments.[16] The transition rotatory strengths were calculated on the basis of a TD-DFT method, which proved that the negative Cotton effect is assigned to the *P*-isomer and that the predicted CD signal of the *M*-isomer is positive.[11,17] The TD-DFT results indicate that the major conformation of **1**·Ca^{2+} is identified as the *P*-isomer. The calculated energy difference in the two isomers also supports that the *P*-isomer is more stable by 20.3 kJ mol^{-1} than the *M*-isomer.

The anion-recognition ability of **1** and **1**·Ca^{2+} was evaluated by spectroscopic titration. Upon addition of chloride anions to a 1 : 4 MeCN/$CHCl_3$ solution of **1**·Ca^{2+}, a bathochromic shift of **1**·Ca^{2+} (328 nm to 342 nm) was observed in the presence of 5 eq. of Cl^- with isosbestic points (Fig. 4b). Conversely, the bathochromic shift of **1** (340 nm to 342 nm) is very small (Fig. 4a), but both the λ_{max} values of **1** and **1**·Ca^{2+} are almost the same in the saturated region of titration. These spectral changes account for the competitive coordination of the urea carbonyl oxygens and a chloride anion to Ca^{2+}. The coordination of the chloride to Ca^{2+} in **1**·Ca^{2+} would result in a similar λ_{max} (342 nm) to **1** due to disturbance in the carbonyl coordination. The ^{1}H NMR spectra revealed that no Ca^{2+} dissociation from the complex **1**·Ca^{2+} took place in CD_3CN upon the addition of Cl^- because the **1**·Ca^{2+} exclusively existed after the addition of Cl^- ions in CD_3CN. The hydrogen bonding of N–H in **1**·Ca^{2+} to Cl^- should contribute to this Cl^- binding.[12,13] The hydrogen bonding of the urea moieties was evidenced by the lower-field shift of N–H in the ^{1}H NMR spectra

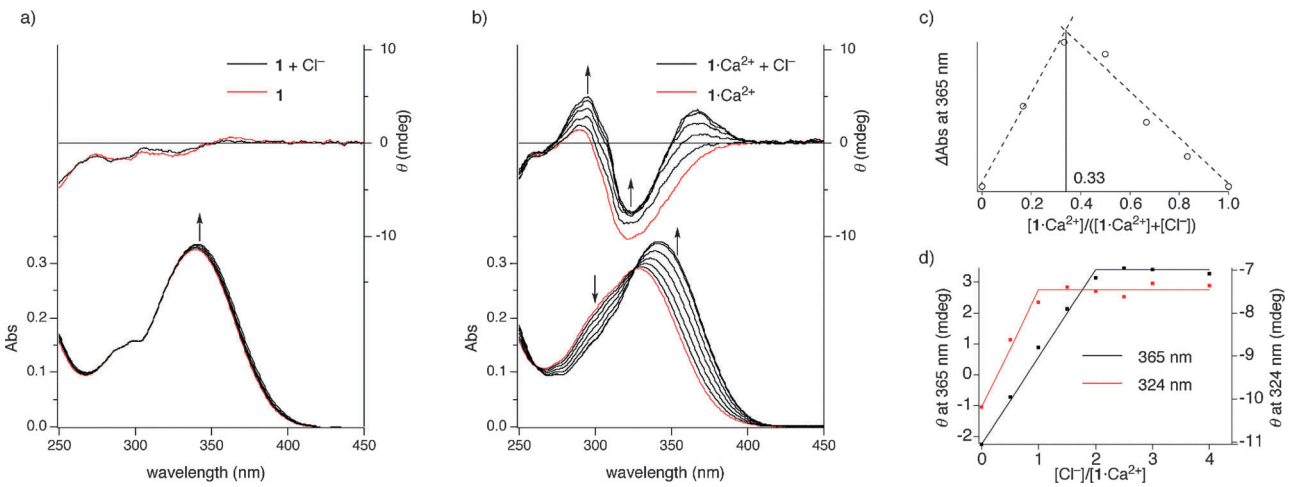

Fig. 4 UV-vis and CD spectral changes on the addition of Cl^- in 1 : 4 MeCN/$CHCl_3$ (a) **1** and (b) **1**·Ca^{2+}. $0 \leq [Cl^-]/[\mathbf{1}] \leq 4$, $[\mathbf{1}] = [\mathbf{1}\cdot Ca^{2+}] = 10\ \mu M$. (c) Job's plot for **1**·Ca^{2+} *vs.* Cl^- and (d) CD titration curves plotted at 365 and 324 nm.

Table 1 Association constants ($\log K_{11}$ and $\log K_{12}$) for a halide anion in MeCN containing 1% H_2O

	Cl^-	Br^-	I^-
1	3.26(4)[a]	—[c]	—[c]
1·Ca^{2+}	6.0(2),[a] 4.06(8)[b]	5.5(1),[a] 3.73(6)[b]	5.50(8),[a] 3.1(2)[b]

[a] $\log K_{11}$ (M^{-1}). [b] $\log K_{12}$ (M^{-1}). [c] Not determined due to too small spectral change.

of the mixture of **1**·Ca^{2+} and Cl^-.[18] The CD spectra of **1**·Ca^{2+} were also changed by the addition of Cl^- accompanied by a bathochromic shift of λ_{max} (Fig. 4b). The change in the Cotton effect indicates that the conformational change in the foldamer was induced by the anion. In contrast, the CD spectra of **1** showed little change upon titration with Cl^- ions (Fig. 4a). These facts suggest that the folded structure of **1**·Ca^{2+} is important for the CD changes. Thus, the formation of the chiral foldamer enabled Cl^- ion detection by UV-vis and CD spectral changes.

The CD spectral titration of **1**·Ca^{2+} with a Cl^- ion and a Job's plot (Fig. 4c and d) clearly showed the 1 : 2 association. Although the binding strength was not accurately estimated due to the multi-stepwise equilibrium and the very strong affinity for Cl^-, the first and the second association constants, $\log K_{11}$ and $\log K_{12}$ (M^{-1}) for **1**·Ca^{2+}, are >7. These values are over 500 times larger than that of **1** ($\log K_{11}$ = 4.27(2)). The most reasonable explanation for the affinity enhancement is that the association with Cl^- was reinforced by electrostatic interaction with the Ca^{2+} ion.[12] The contact of the anion with the cation generally enhanced the association constants as seen in ion pair recognition.[19] To quantitatively estimate the anion affinity, the titration was performed in MeCN containing 1% H_2O because H_2O, a solvent competitive with hydrogen bonding, should decrease the binding affinity. The $\log K_{11}$ values were determined through nonlinear least-squares curve fitting of the titration isotherms. The $\log K_{11}$ value of **1** is 3.26(4) for the Cl^- ion (Table 1). Spectral changes for Br^- and I^- ions were too small to determine the $\log K_{11}$. Conversely, **1**·Ca^{2+} exhibited the two-step binding to anions with association constants, K_{11} and K_{12}. The K_{11} value for Cl^- is 500 times larger than the K_{11} value of **1**. In Br^- and I^-, the association constants are smaller than in Cl^-. The enhancement of the anion affinity and the large spectral change triggered by Ca^{2+} ions facilitated the halide ion detection.

In summary, we described the Ca^{2+}-induced folding behavior of the Pybox-based ditopic receptor **1**, in which the coordination of the urea oxygens to Ca^{2+} was involved. The **1**·Ca^{2+} foldamer showed the UV-vis and CD spectral changes responsive to the halide anions. A chiral information transfer by guest-response of the chiral foldamer is now under investigation.

This study was supported by Grants-in-Aid for Scientific Research from MEXT of Japan.

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