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A preliminary step toward molecular spring driven by cooperative guest binding

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ABSTRACT

A macrocyclic host molecule that comprised two different rotating modules, cerium(IV) bis(porphyrinate)s and ferrocenyl rotating units, exhibiting contraction/expansion motion was synthesized, which can be regarded as a prototype of artificial molecular spring driven by cooperative guest binding in 1:6 stoichiometry.

The design of molecular machines in which the functions are controlled by photo-, redox- and host-guest-type interactions has attracted growing attention.[1] Interest has been particularly focused on synthetic molecular muscle that exhibits contraction/expansion motion because myosin, a typical biological molecular machine, can directly convert chemical energy derived from ATP hydrolysis into mechanical motion with extremely high efficiency. In synthetic system, in addition to macromolecular[2] and supramolecular[3] approach, it was recently demonstrated that rotaxanes enable to contract and expand their structures via sliding motion by external stimuli.[4] Challenges still remain in the design and synthesis of synthetic machines that deliberately undergo structural changes in length toward organic mechano-responsive materials.

We have been interested in the construction of synthetic positive homotropic allosteric systems[5] utilizing cerium (IV) bis(porphyrinate)s as dynamic rotating modules. The pivotal feature of positive homotropic allostery is a non-linear sigmoidal response via its conformational change to outside information, for example, the effector and/or substrate concentration, which then generates bistable OFF/ON state from multi-equilibrium[6]; we thus expect that the combination of non-linear response toward substrates (guest molecules) with contraction/expansion motion would allow the generation of actuating molecules. We report herein the synthesis and dynamic cooperative guest response of a macrocyclic compound (**DDPy12**) comprising two different rotating modules, in which two rotatable cerium(IV) bis(porphyrinate)s are connected to ferrocenyl rotating units by rigid *p*-phenylene spacers (Scheme 1). Each double-decker porphyrin complex moiety has six pyridine substituents at *meso*-positions (six pairs of pyridines in total) for the recognition of 1R,2R-cyclohexane dicarboxylic acid (RR-**CHDA**) working as modulators for the motion of contraction/expansion. The binding events of RR-**CHDA** to a double-decker complex can transmit one another through rotational motion of ferrocenes; recently ferrocenyl rotating units have been widely used as mechano-transducers of molecular scissors and pincers.[7] As a result of the bindings of six RR-**CHDA** guests, the intramolecular contraction/expansion motions of **DDPy12** take place together with the decrement in length between Fe–Fe centers and the increase in length between Ce–Ce centers (Scheme 2). **DDy12** has been synthesized by condensation reaction between 1,1′-ferrocene dicarbonyl dichloride and amino-functionalized cerium(IV) bis(porphyrinate)s (see Supplementary data), and was identified by ^{1}H NMR, ^{1}H–^{1}H COSY, and MALDI-TOF MS spectroscopic evidence.

To appraise the recognition-driven conformational change, we first evaluated the formation of the **DDPy12-**RR-**CHDA** complex in a tetrachloroethane (TCE)–tetrahydrofuran (THF) 30:1 (v/v) mixed solvent at 298 K using the circular dichroism (CD) and UV–vis spectral change that is induced upon the successive addition of RR-**CHDA**. No change in absorption spectrum upon addition of RR-**CHDA** was observed; meanwhile, the value of CD

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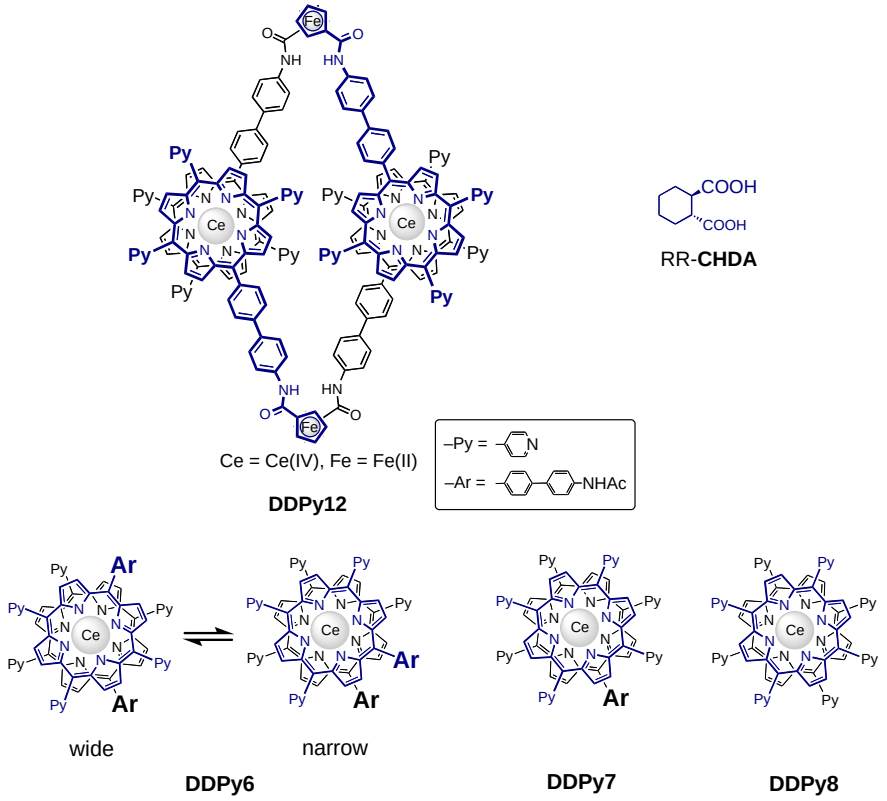
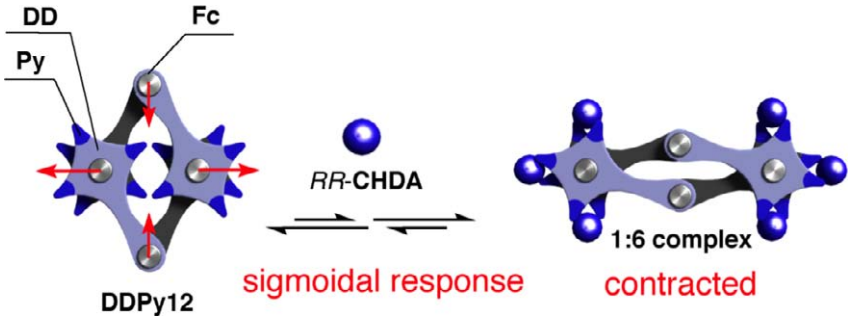


Scheme 1. Chemical structures of **DDPy12**, **DDPy6**, **DDPy7**, **DDPy8**, and RR-**CHDA**.



Scheme 2. Schematic illustration of the conformational change of **DDPy12** upon guest bindings.

intensity at 310 nm (π–π^* transition band of the 4-pyridyl moiety) increased for RR-**CHDA** with tight isosbestic points. These changes and the shape of the CD signals are consistent with those observed for cooperative recognition systems of **DDPy6**-**CHDA** and **DDPy8**-**CHDA**[8] (see Supplementary data). As we have reported,[8b] the $[\theta]_{obs}$ at 310 nm, derived from the chirally twisted pyridine pairs, is linearly correlated with the complex concentration and the saturated values are proportional to the number of pyridine pairs. Therefore, it is clear that one pair of pyridine moieties binds one **CHDA** guest to produce **DDPy12**-RR-**CHDA** complexes. In Figure 1, the $[\theta]_{obs}$ at 310 nm is plotted against the guest concentration. It can be seen clearly from Figure 1 that the plots feature sigmoidal curvature, indicating that the guest-binding to **DDPy12** would proceed in such a manner that **DDPy8** and **DDPy6** cooperatively recognize RR-**CHDA**. This nonlinear guest-binding process was analyzed firstly according to the Hill equation[9]; we obtained Hill coefficient n_H of 2.1 for the formation of **DDPy12**-RR-**CHDA** complex (see Supplementary data). The n_H value of 2.1 implies that **CHDA** binding takes place cooperatively, since a higher value of n_H (>1.0) is related to a higher degree of cooperativity. We then reanalyzed the binding isotherms for **DDPy12**, **DDPy8**, and **DDPy6** by a non-linear least-squares method assuming the stepwise association scheme; we determined the association constants and the saturated [θ] values ($[\theta]_{sat}$) for **DDPy12**·(RR-**CHDA**)$_6$, **DDPy8**·(RR-**CHDA**)$_4$, and **DDPy6**·(RR-**CHDA**)$_3$ complex to be $\log K_{total}$ = 14.0 (13.8 deg cm^2 dmol^{-1}), 9.7 (9.4 deg cm^2 dmol^{-1}), and 6.8 (6.8 deg cm^2 dmol^{-1}), respectively (correlation coefficient R > 0.999). The linear relationship between the saturated [θ] values and the number of binding sites of **DDPy12**, **DDPy8**, and **DDPy6** demonstrated that **DDPy12** recognizes RR-**CHDA** molecules in 1:6 stoichi-

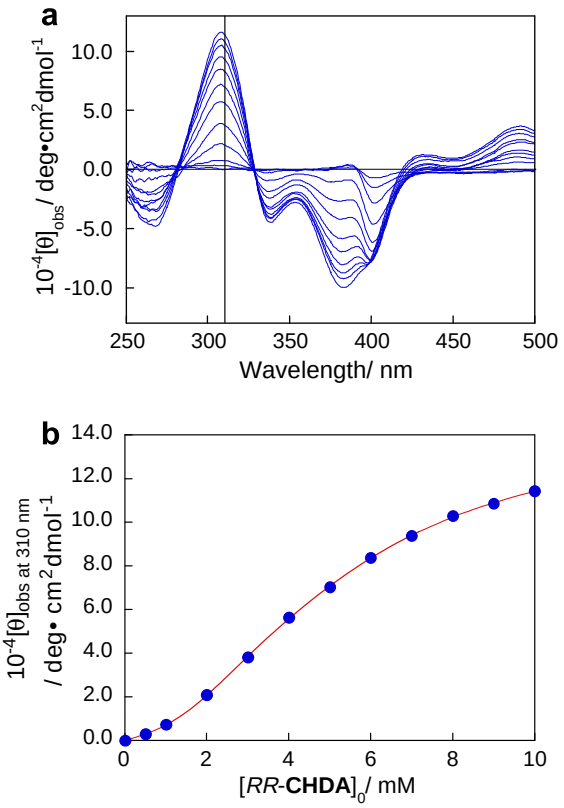


Figure 1. (a) CD spectral change of **DDPy12** (0.10 mM) upon addition of RR-**CHDA** in a TCE–THF 30:1 (v/v) mixed solvent at 298 K (cell length = 0.5 mm). (b) Plots of the CD intensity change at 310 nm of **DDPy12** versus [RR-**CHDA**]$_0$, and the fitted theoretical curve (shown in solid line) for 1:6 complex formation.

ometry (see Supplementary data). Furthermore, the shape of saturated CD signal of **DDPy12**·RR-**CHDA** complex is similar to that of **DDPy6**·(RR-**CHDA**)$_3$ complex, supporting the view that the structure of **DDPy6**·(RR-**CHDA**)$_3$ should be a partial structure factor of **DDPy12**·(RR-**CHDA**)$_6$ complex.[10]

We next used computational methods (Insight II and Discover) to evaluate how **DDPy12** could form a complex with six guest molecules. As illustrated in Figure 2, in the absence of guest molecules **DDPy12** adopts the expanded form by the aid of intramolecular hydrogen bonding between amide moieties in a ferrocene[10,11] (the distance between Ce centers is calculated to be 1.3 nm in the expanded form), whereas the contracted form is allowed as the most stable conformation when complexed with six RR-**CHDA** molecules (the distance between Ce centers is calculated to be 3.5 nm). In 1:6 complex, **DDPy6**·(RR-**CHDA**)$_3$ is indeed a partial structural factor of **DDPy12**·(RR-**CHDA**)$_6$ complex as we discussed in CD spectroscopic studies. Further proof for the conformation of **DDPy12** without guest molecules was revealed by ^{1}H NMR spectroscopic studies in comparison with **DDPy6** and **DDPy7**. In ^{1}H NMR spectrum, **DDPy6** shows the two sets of proton peaks corresponding to two rotational isomers, the wide and the narrow conformations (see Scheme 1) because the rotational rate of cerium (IV) bis(tetraarylporphyrinate)s is much slower than NMR time scale.[12] In contrast, when we compared the proton peaks of **DDPy12** with those of **DDPy6** and **DDPy7**, lower magnetic field shift of endo-*o*-protons of *meso*-phenyls and upper magnetic field shift of endo-*o*- and endo-*m*-protons of *meso*-pyridyls in **DDPy12** were observed, indicating that two cerium(IV) bis(porphyrinate)s are proximate to mesh each other: that is, the expanded form would be dominant in the case of **DDPy12** under conditions we used (see Supplementary data). The spit proton peaks in ferrocene protons support this assertion.[13] In the expanded form of **DDPy12**, four RR-**CHDA** molecules could be recognized without large conformational change (i.e., ring rotation of porphyrinate ligands) that would ascribe to lower Hill coefficient value of 2.1 and the different CD spectral pattern observed in the initial stage of titration (Fig. 1a).

In conclusion, we have successfully synthesized a macrocyclic compound (**DDPy12**) comprising two different rotating modules, which can be regarded as a prototype of artificial molecular spring. The weak but allosteric guest bindings to **DDPy12** modulate the distance between Fe centers in ferrocenes and lead to the contracted conformation from the expanded conformation. Further efforts on installing higher cooperativity into recognition events to achieve high sensitivity toward guest concentration and on polymerizing this macrocyclic compound would lead the generation of a new class of mechano-responsive materials driven by molecular recognition. Work in this line is in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.086.

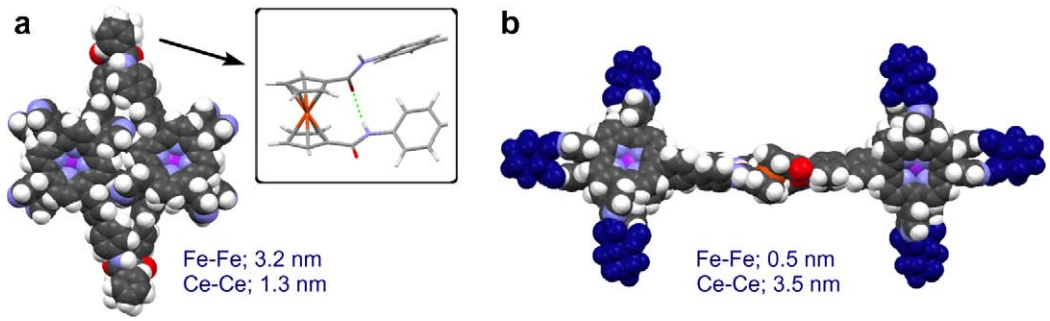

Figure 2. The energy minimized structures of (a) **DDPy12** and (b) **DDPy12**•(RR-**CHDA**)$_6$ as generated by MM2 calculations with Insight II/discover 3.0. C, H, N, O, Ce, and Fe atoms in **DDPy12** are shown in gray, white, light blue, red, purple, and orange, respectively. RR-**CHDA** molecules are shown in dark blue. Distance between Ce or Fe atoms of models is shown in the figure.

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10. Compound **DDPy12** is a chiral compound and we used it as a racemic mixture of *MM*- and *PP*-**DDPy12**. Judging from CPK molecular model and the calculated structure, the exchange between *MM*- and *PP*-**DDPy12** is possible via rotation and twisting motion in rotor units (DD, Fc, and biphenyl linker moieties: please see Supplementary data). The chiral conversion of ferrocene linkers occurs more readily via rotation of ferrocenes unit along the spacer axis. We measured CD spectra of each sample after confirmation of reach at equilibrium (at least 2 h after preparation of samples). Since intermolecular interactions between **DDPy12** and RR-**CHDA** tend to occur through reversible processes in a search for the thermodynamically most stable state, eventually **DDPy12**·RR-**CHDA** complex would become *MM*-**DDPy12**-RR-**CHDA** complex. We believe, therefore, that **DDPy12** should be converted into *MM*-**DDPy12**-RR-**CHDA** complex but not to diastereomeric mixtures; the CD intensity at 310 nm of **DDPy12**-RR-**CHDA** complexes observed here is large enough to support this assertion. We would like to emphasize that we used the CD spectral changes at 310 nm to evaluate this binding system, because that is derived from the chirally twisted pyridine pairs, not from chiral porphyrin planes.
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13. These results, however, cannot rule out the view that **DDPy12** is in both extended and contracted forms in the absence of guest molecules. Valuable temperature (VT) NMR analysis might be a powerful tool to clarify our assertion; however, at lower temperature, serious broadening in the spectra and unexpected precipitation of the complexes occurred in this system.