Remarkably Large Positive and Negative Allosteric Effects on Ion Recognition by the Formation of a Novel Helical Pseudocryptand

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In supramolecular chemistry,[1] a great deal of attention has focused on regulating guest binding via an external stimulus since molecular devices and intelligent molecules must respond to information at the molecular level. In biological and artificial systems allosteric regulation is effective in controlling molecular functions such as molecular recognition and catalytic activity.[2] Pseudomacrocycles are cyclic structures that are maintained by coordination bonds, and drastic conformational changes at the binding site occur as a result of the metal coordination,[3] which makes pseudomacrocycles suitable candidates for the allosteric regulation of host−guest interactions. The macrocyclic effect, which is derived from metal-assisted cyclization, efficiently controls the guest affinity. To utilize the same effector for both highly guest-selective positive and negative allosteric effects, however, stricter and more precise regulation of the host structure is required because the flexible structure of the host makes the induced-fit recognition difficult to control. Herein we report a novel allosteric host **1** using Fe(II) as an effector. The complexation of **1** with Fe(II) affords the *pseudocryptand,* **1**·Fe(II), which bears a cavity that is surrounded by three polyether chains in a helical fashion (Figure 1).[4,5] The combination of the macrobicyclic effect and the intramolecular interchain interactions finely controls the positive and negative allosteric effects, which depend on the size of the guest.

The UV−vis and ^{1}H NMR titrations indicate that a 1:1 complexation between **1** and Fe(II) is quantitative. ESI-MS spectroscopy and elemental analysis[6] confirm the 1:1 complexation of **1** and Fe(II). **1**·Fe(II) in MeOH shows MLCT absorption (517 nm, ϵ = 7500),[7] which is characteristic of an octahedral bipyridine-Fe(II) complex. Since the ^{1}H NMR signals of both free **1** and the complex are observed when up to 1 equiv of Fe(II) is titrated, ligand exchange is slow on the NMR time scale. It is noteworthy that the signals assigned to the picolyl methylene protons (H$_{(a)}$) and the polyether moieties are inequivalent. This result is ascribed to the helical structure of the pseudocryptand, as suggested by inspecting the CPK model and X-ray analysis (vide infra).

Different guests had varying effects on the ^{1}H NMR signals in the polyether and aromatic regions of **1**·Fe(II). Cs$^+$ and Rb$^+$ caused noticeable changes. Slight chemical shifts were observed with K$^+$, but the signals were unchanged with excess Na$^+$. Only one of the H$_{(a)}$ displayed a tremendous upfield shift ($\Delta\delta$ 1.27 ppm) with excess Cs$^+$ due to the ring current of the benzene moiety, while the other H$_{(a)}$ signal shifted less ($\Delta\delta$ 0.69 ppm) (Figure 2). The difference indicates that only one H$_{(a)}$ moved very close to the ring upon the induced-fit binding to Cs$^+$.

The 1:1 complexation of **1**·Fe(II) with the alkali metal ions is supported by ^{1}H NMR titration and ESI-MS spectroscopy ([**1**·Fe-(PF$_6$)$_2$·M]$^+$, M = alkali metal). K_a values (Table 1) were determined by analyzing the titration isotherms by nonlinear-least-squares

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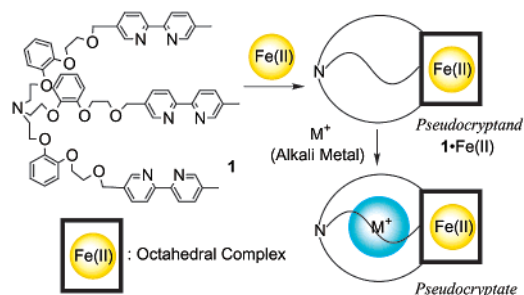
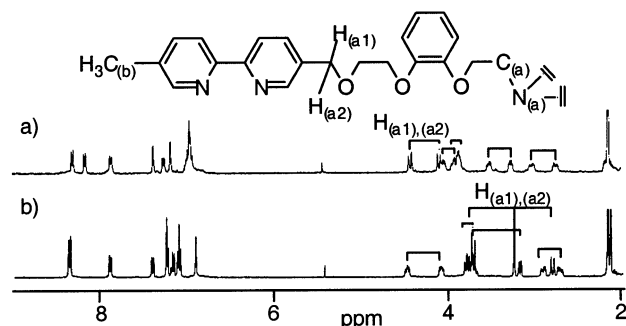**Figure 1.** Pseudocryptand **1**·Fe(II) as an allosteric host.

Figure 2. 400 MHz ^{1}H NMR spectral changes of **1**·Fe(II) in CD$_3$CN. a) [**1**·Fe(II)] = 1.7 × 10^{-3} M. b) [**1**·Fe(II)] = 1.7 × 10^{-3} M, [CsClO$_4$] = 8.5 × 10^{-3} M.

Table 1. Association Constants K_a (M^{-1}) between the Hosts and Alkali Metal Ions[a]

host	guest			
	Na$^+$	K$^+$	Rb$^+$	Cs$^+$
1	650	610	280	120
1·Fe(II)	*c*	110	630	4700
		(0.18)[b]	(2.2)[b]	(39)[b]

[a] Determined by ^{1}H NMR spectroscopy in CD$_3$CN at 25 °C. [b] The ratio of the association constants of **1**·Fe(II) and **1**, $K_{a,1·Fe(II)}/K_{a,1}$, is shown in parentheses. [c] Too small to be determined.

regression. The K_a for Cs$^+$ (4700 M^{-1}) increased dramatically (39-fold) upon complexation of **1** with Fe(II), while moderate enhancement is observed for Rb$^+$ (from 280 to 630 M^{-1}). Formation of the cryptand-like framework should be the most prominent factor for this positive effect. In contrast, Fe(II) caused large negative allostery for Na$^+$ and K$^+$. As a result, the binding selectivity of **1** (Na$^+$ > K$^+$ > Rb$^+$ > Cs$^+$) is the opposite of **1**·Fe(II) (Cs$^+$ > Rb$^+$ > K$^+$ > Na$^+$).

Single-ion transport through a liquid membrane[3a,b] shows ion selectivity similar to the equilibrium constants. Compared to that for **1**, the transport rate for Cs$^+$ and Rb$^+$ each significantly increases and decreases for K$^+$ (Table 2). Consequently, the effector successfully performs a high Cs$^+$ transport selectivity over K$^+$ (Cs$^+$/

Table 2. Single-Ion Transport of Alkali Metal Ions

host	guest		
	K$^+$	Rb$^+$	Cs$^+$
1	7.3 ± 0.7^b	4.1 ± 0.1^b	2.6 ± 0.3^b
1·Fe(II)	1.1 ± 0.2^b	8.3 ± 0.1^b	13.4 ± 2.1^b
none	0^b	0^b	0^b
	$(0.15)^c$	$(2.0)^c$	$(5.2)^c$

^{a} [Metal]$_{initial, source phase}$ = 5.0×10^{-2} M, [host]$_{org. phase (1,2-dichloroethane)}$ = 2.0×10^{-4} M. ^{b} [Metal]$_{receiving phase}$ (10^{-4} M), determined by flame spectroscopy after 216 h. ^{c} The ratio of the amount of the transported ions by **1**·Fe(II) and **1** is shown in parentheses.
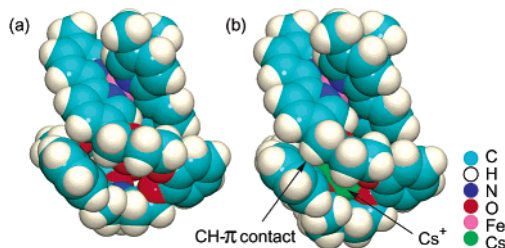

Figure 3. Molecular structures of (a) [**1**·Fe]$^{2+}$ and (b) [**1**·Fe·Cs]$^{3+}$. The *M* isomers in the racemic crystals are shown.

K$^+$ = 12). This result indicates that an external stimulus can control the kinetic ion-recognition process. To the best of our knowledge, this is the first example of an allosteric recognition system, in which the same effector, that is, Fe(II), exhibits both large positive and negative allosteric effects on equilibrium and dynamic recognition events.

X-ray analysis for **1**·Fe(II)·Cs$^+$ reveals that a Cs$^+$ ion fits in the cavity of **1**·Fe(II) with a facial octahedral geometry, which consists of the polyether chains assembled in a helical fashion (Figure 3).[8] It is interesting that one of the methylene protons H$_{(a)}$ (denoted as H$_{(a1)}$) points toward the center of the benzene ring in another chain while the other H$_{(a2)}$ points away from the ring. The distance between H$_{(a1)}$ and the ring is 2.6 Å, indicative of CH−π interaction that stabilizes the ternary complex **1**·Fe(II)·Cs$^+$,[9] but the longer distance (3.0 Å) of H$_{(a1)}$ in **1**·Fe(II) indicates that there is negligible CH−π interactions, which causes flexible polyether chains. The X-ray analysis and ^{1}H NMR examination indicate that the relative positions of H$_{(a1)}$ and H$_{(a2)}$ to the benzenes ring in **1**·Fe(II)·Cs$^+$ are nearly the same whether in solution or the solid state. Due to cooperative contributions of the effective coordination of the chains to Cs$^+$ and the attractive CH−π interactions, complexation of **1**·Fe(II) with Cs$^+$ causes conformational changes to the binding site that are favorable for the induced-fit recognition. The increase in acidity of H$_{(a)}$ due to the electron-withdrawing property of the Fe(II) complex moiety may enhance the CH−π interaction.[9] The negative allostery in Na$^+$ and K$^+$ is rationalized by the steric repulsion between H$_{(a1)}$ and the ring. For Na$^+$ and K$^+$ to bind the helical cavity must shrink considerably because of their small ionic radii, but contact between H$_{(a1)}$ and the aromatic ring prohibits this cavity contraction.

Furthermore, Cs$^+$ complexation extends and twists **1**·Fe(II) because the distance between the pivotal nitrogen and the Fe(II) atoms increases from 8.67 Å (*relaxed state*) to 9.55 Å (*tense state*) and is accompanied by an increase in the helical torsion (average dihedral angle of C$_{(a)}$−N$_{(a)}$−Fe−C$_{(b)}$, from 167° to 197°).[10] Since

the length and torsion of **1**·Fe(II) are controlled by Cs$^+$, **1**·Fe(II) is regarded as a molecular spring or coil responding to an external stimulus.

In general, regulation of the induced-fit-binding seems to be very difficult because a rigid structure is necessary to avoid conformational changes, which can accommodate an undesirable guest. The intramolecular interchain interactions work efficiently to dramatically change the guest-binding affinity and to reverse the selectivity.

In conclusion, the remarkable positive and negative allosteric effects have been achieved by the macrobicyclic effect and interchain interactions. The helical framework opens a new general method for constructing more sophisticated, controllable receptors for helical biomolecules, for example, DNA and proteins, and helical molecular devices responding to a stimulus. Further investigation into the binding affinity of **1**·Fe(II) to charged organic molecules such as amino acid derivatives is in progress.

Supporting Information Available: Synthetic procedures, spectroscopic and X-ray structural data (PDF/CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Crystal data for [**1**·Fe·H$_2$O](PF$_6$)$_2$: Red crystal, trigonal, *R*-3*c*, *a* = 13.7573(5) Å, *c* = 125.440(6) Å, *V* = 20560.4(14) Å^3, *T* = 296 K, *Z* = 12, *R*1 = 0.0751 (*I* > 2σ(*I*)), *wR*2 = 0.1936 (all data). Crystal data for [**1**·Fe·Cs](PF$_6$)$_2$(ClO$_4$)·CH$_3$CN: Red crystal, monoclinic, *P*2$_1$/*n*, *a* = 22.896(8) Å, *b* = 13.887(6) Å, *c* = 24.427(6) Å, β = 106.36(2)°, *V* = 7452(4) Å^3, *T* = 296 K, *Z* = 4, *R* = 0.0610, *R$_w$* = 0.0615 (*F* > 3σ(*F*)).
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