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Allosteric anion recognition by metal complexation of tris(bipyridine–imidazolium) ligand

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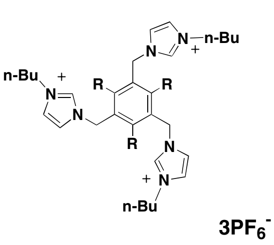
Abstract—A new tripodal imidazolium ligand **2** comprising three 2,2′-bipyridine–imidazolium subunits connected through a mesityl spacer has been synthesized and 1:1 complexes of **2** with Fe(II) and Ru(II) ions have been prepared. ^{1}H NMR spectroscopy including NOE analysis and molecular modeling study established that the complexes exist as a pseudocryptand type twisted structure in solution. The Fe(II) and Ru(II) complexes show strong 1:1 binding of Cl^-, Br^-, and I^- anions in MeCN-d_3 with a large enhancement of the guest selectivity ($Cl^- > Br^- > I^-$) upon metal complexation.

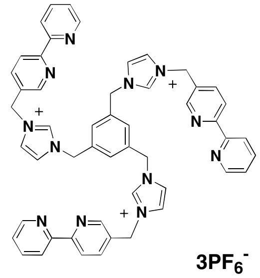
Metal-directed self-assembly has received considerable attention in the area of molecular recognition and supramolecular chemistry because of the efficiency provided for generation of well-defined structures.[1] In particular, there is an increasing interest in metal-templated hosts, since the ability of a transition metal to organize binding subunits around its coordination sphere has emerged as a versatile strategy to create a specific recognition site.[2] Such metal-induced cooperative systems controlling their molecular recognition properties by *allosteric regulation* have recently been reported by several groups.[3]

On the other hand, molecular recognition of anions by synthetic receptors is now an expanding field of research.[4] Receptors with flexible multi-podal structures have good affinity for guest species because the geometry and orientation of the host molecule favors formation of a stable host–guest complex. Our previously reported tripodal receptor **1a**, in which three imidazolium (imd) groups compose an efficient binding subunit for anions through electrostatic force and [C–H···X$^-$] type hydrogen bonding, also showed strong binding ability for halide ions.[5]

We present herein the formation of a metal-templated pseudocryptand[3e,g,h,j] type host by complexation between transition metal ions (Fe(II), Co(II), Ni(II), and Ru(II)) and new tripodal ligand **2**, which were equipped with 2,2′-bipyridine (bpy) units instead of the *n*-butyl groups in **1b**. And we also report preliminary results of anion recognition properties of the pseudocryptand Fe(II)[14] and Ru(II) complexes (**2**·Fe(II) and **2**·Ru(II)).



1a: R = Me
1b: R = H



2

Compound **2** was prepared by the reaction of three equivalents of 5-(bromomethyl)-2,2′-bipyridine[6] with 1,3,5-tris(1-imidazolylmethyl)benzene[7] in acetonitrile followed by counterion exchange with NH_4PF_6 (Scheme 1).

The Fe(II) complex of **2** was obtained by similar synthesis with Fe(II)–tripode complexes.[8] To a solution of the

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Keywords: Anion recognition; [C–H···X$^-$] hydrogen bonding; Allosteric effect; Pseudocryptand; Imidazolium.

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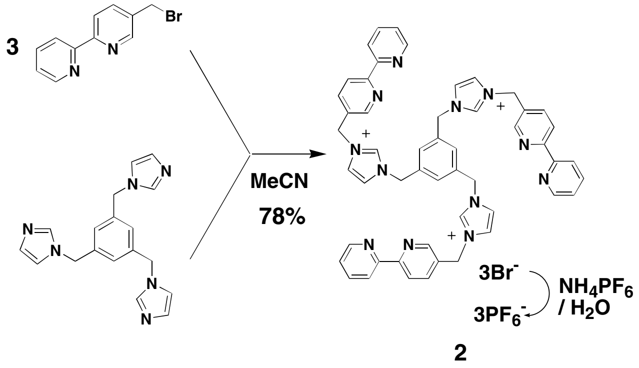


Scheme 1. Synthesis of tripodal ligand **2**.

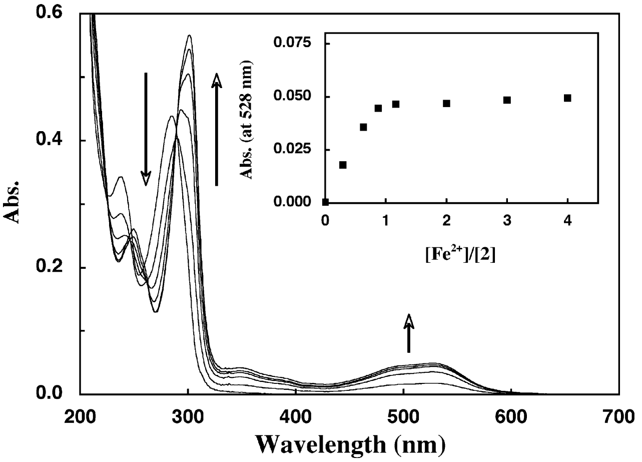
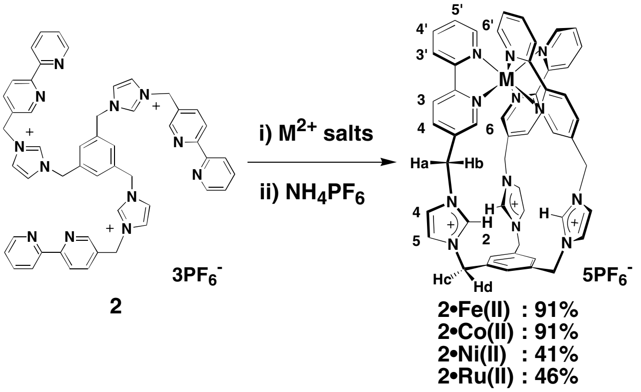


Figure 1. Absorption spectra of **2** (0.01 mM) in CH_3CN–H_2O (50:50 v/v) for varying $FeSO_4$ concentrations.

ligand **2** was added a solution of $FeSO_4 \cdot 7H_2O$ in 50% aqueous acetonitrile at room temperature to give characteristic deep-violet complex with MLCT absorption band at $\lambda_{max} = 528$ nm. The UV–vis titration indicated 1:1 metal–ligand complex formation (Fig. 1). After exchange of the counterion using an aqueous solution of NH_4PF_6, the complex [**2**·Fe(II)]$(PF_6)_5$[†] was obtained in a good yield (91%) and characterized by ^{1}H NMR, ESI-MS, and UV–vis spectroscopy and elemental analysis. The Co(II) and Ni(II) complexes were also obtained similarly.[9]



Scheme 2. Synthesis of metal complexes **2**·M(II).

In the case of the Ru(II) complex, self-assembly into the pseudocryptand structure is much more difficult due to slow ligand substitution between Ru(II) ion and bpy. The complex was prepared by the reaction of equimolar amounts of **2** and $Ru(DMSO)Cl_2$ in ethylene glycol/DMF (5:2) at 90 °C for 6 h. After counterion exchange into PF_6^- salt, the crude product can be purified by gel-column chromatography on Sephadex® LH-20 eluting with acetonitrile–methanol (1:1). The red-orange colored [**2**·Ru(II)]$(PF_6)_5$[‡] was isolated in 46% yield (see Scheme 2).

Complexation of the metal ion rigidifies the ligand and induces pronounced changes in the ^{1}H NMR spectrum (Fig. 2). In the case of [**2**·Fe(II)]$(PF_6)_5$, the signals of the 6,6′-protons of bpy subunits are moved upfield by $\Delta\delta = 1.26$ and 1.43 ppm, respectively. This strong shielding is due to octahedral complexation of the bpy subunits in which the 6,6′-protons *ortho* to the chelating nitrogen atoms lie above the plane of neighboring bpy units. The CH_2 signals, seen as two singlets in the free ligand **2** at $\delta = 5.44$ (bpy–CH_2–imd) and 5.31 ppm (imd–CH_2–benzene), are split into AB coupling patterns upon complexation (Fig. 2, middle). This is due to the fact that the CH_2-protons locate unequivalently around the C_3 symmetry axis of the complex in the NMR time scale. The spectrum of [**2**·Ru(II)]$(PF_6)_5$ is nearly identical to that of the [**2**·Fe(II)]$(PF_6)_5$ except for the chemical shifts of 6,6′-protons. The signals for 6,6′-protons of **2**·Ru(II) are lower upfield shift by 0.2–0.4 ppm compared with that of **2**·Fe(II). Such a difference between

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[†] {1,3,5-Tris[3-(2,2′-bipyridin-5-yl)methylimidozolio-1-methyl]benzene}iron(II) penta-hexafluorophosphate. ^{1}H NMR (270 MHz, CD_3CN): δ 8.55 (d, $J = 8.4$ Hz, 3H, bpy-3), 8.55 (d, $J = 8.4$ Hz, 3H, bpy-3′), 8.22 (d, $J = 8.4$ Hz, 3H, bpy-4), 8.11 (dd, $J = 8.4$ and 7.5 Hz, 3H, bpy-4′), 7.71 (s, 3H, imd-4), 7.65 (s, 3H, benzene–H), 7.63 (s, 3H, imd-5), 7.43 (s, 3H, bpy-6), 7.43 (s, 3H, imd-2), 7.35 (dd, $J = 7.5$ and 5.4 Hz, 3H, bpy-5′), 7.24 (d, $J = 5.4$ Hz, 3H, bpy-6′), 5.32 (d, $J = 14.6$ Hz, 3H, imd–CH_{2c}–benzene), 5.27 (d, $J = 14.6$ Hz, 3H, imd–CH_{2d}–benzene), 5.10 (d, $J = 15.1$ Hz, 3H, bpy–CH_{2a}–imd), 4.87 ppm (d, $J = 15.1$ Hz, 3H, bpy–CH_{2b}–imd). UV–vis (CH_3CN): $\lambda_{max} = 528$ nm ($\varepsilon = 5.3 \times 10^3$ M^{-1} cm^{-1}), 302 nm ($\varepsilon = 5.9 \times 10^4$ M^{-1} cm^{-1}). MS (ESI) *m/z* 1462 $[M-PF_6]^+$, 658 $[(M-2PF_6)/2]^+$. Anal. Calcd for $C_{51}H_{45}N_{12}P_5F_{30}Fe$: C, 38.12; H, 2.82; N, 10.46. Found: C, 38.15; H, 2.97; N, 10.43.

[‡] {1,3,5-Tris[3-(2,2′-bipyridin-5-yl)methylimidozolio-1-methyl]benzene}ruthenium(II) penta-hexafluorophosphate. ^{1}H NMR (270 MHz, CD_3CN): δ 8.52 (d, $J = 8.6$ Hz, 3H, bpy-3), 8.50 (d, $J = 8.1$ Hz, 3H, bpy-3′), 8.16 (d, $J = 8.6$ Hz, 3H, bpy-4), 8.04 (dd, $J = 8.1$ and 7.2 Hz, 3H, bpy-4′), 7.70 (s, 3H, imd-4), 7.67 (s, 3H, imd-2), 7.64 (s, 3H, imd-5), 7.60 (s, 3H, bpy-6), 7.60 (s, 3H, benzene–H), 7.33 (dd, $J = 7.2$ and 5.3 Hz, 3H, bpy-5′), 7.59 (d, $J = 5.3$ Hz, 3H, bpy-6′), 5.28 (d, $J = 14.3$ Hz, 3H, imd–CH_{2a}–benzene), 5.20 (d, $J = 14.3$ Hz, 3H, imd–CH_{2c}–benzene), 5.11 (d, $J = 15.1$ Hz, 3H, bpy–CH_{2d}–imd), 4.88 ppm (d, $J = 15.1$ Hz, 3H, bpy–CH_{2b}–imd). UV–vis (CH_3CN): $\lambda_{max} = 457$ nm ($\varepsilon = 1.2 \times 10^4$ M^{-1} cm^{-1}), 291 nm ($\varepsilon = 8.2 \times 10^4$ M^{-1} cm^{-1}). Fluorescence (CH_3CN): $\lambda_{max} = 640$ nm. MS (ESI) *m/z* 405 $[(M-3PF_6)/3]^+$. Anal. Calcd for $C_{51}H_{45}N_{12}P_5F_{30}Ru$: C, 37.08; H, 2.75; N, 10.18. Found: C, 37.13; H, 3.02; N, 9.95.

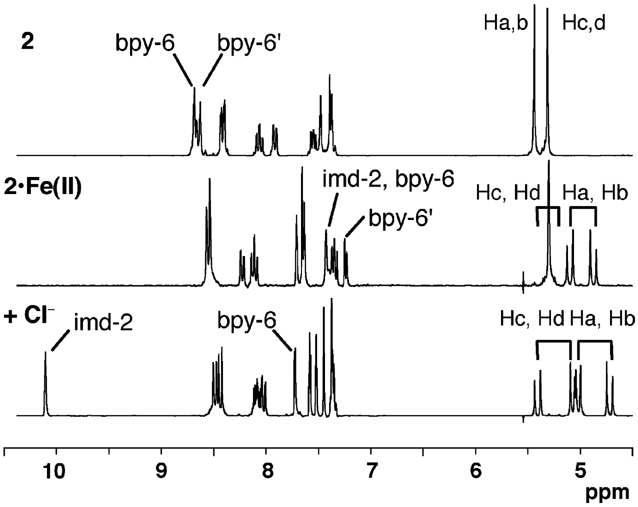


Figure 2. ^{1}H NMR spectra (270 MHz, 0.5 mM in CD_3CN) of **2** (upper), **2**·Fe(II) (middle), and **2**·Fe(II) with 1 equiv of $Bu_4N^+Cl^-$ (bottom).

$Fe(II)(bpy)_3$ and $Ru(II)(bpy)_3$ complexes has been observed and attributed to the size of the central metal ions, that is, the smaller size Fe(II) ion causes lager shielding effect of bpy ligand than Ru(II) ion.[8b,c]

Molecular modeling study (CAChe® ver4.4, MM3) of the Fe(II) complex predicted two stable structures as shown in Figure 3. The structure **A**, in which twisting conformation turns at the CH_2 linker of bpy–CH_2–imd, is slightly stable (ca. 2 kcal/mol) than the structure **B**, which has an overall helical conformation around the central benzene/Fe axis. However, NOE measurement in CD_3CN confirmed that the Fe(II) complex predominantly exists in the structure **A** in the solution. When the upper field bpy–C*H*$_2$–imd proton (Hb) was irradiated, strong NOE interactions are observed with bpy-6 and imd-2 protons, while the other lower-side proton (Ha) shows same strong NOE interactions with bpy-4 and imd-4 protons (Scheme 3). These observations are consistent with the structure **A**.

The recognition of anions was investigated using ^{1}H NMR titration. The addition of 1 equiv of tetrabutylammonium chloride to a CD_3CN solution of **2**·Fe(II) resulted in significant downfield shifts of the C(2)–H of imidazolium (imd-2) and 6-proton of bipyridine (bpy-6) units up to $\Delta\delta = 2.67$ and 0.30 ppm, respectively, and gave rise to large separation of CH_2 signals (Hc and Hd) of the imd–CH_2–benzene (Fig. 2, bottom). Further addition of Cl^- resulted in a saturation of the chemical shift changes. The similar behaviors were observed with bromide and iodide (Fig. 4). These ^{1}H NMR titration experiments suggest that **2**·Fe(II) formed stable 1:1 stoichiometric inclusion complex with halide ions. The similar observation was obtained for **2**·Ru(II). Association constants were determined from the titration curves by using a nonlinear least-squares curve-fitting method. However, the association constants of **2**·Fe(II) and **2**·Ru(II) for Cl^- and Br^- were too large ($K_a > 10^5\ M^{-1}$) to be measured accurately by simple ^{1}H NMR titration, those values were determined by competitive titration method[10] (Table 1).

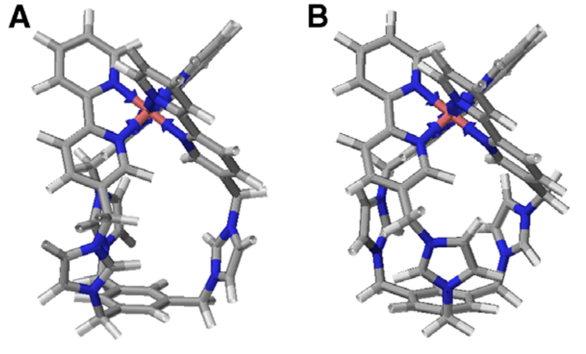
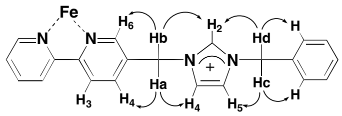


Figure 3. Two energy optimized structures (CAChe®, MM3) of **2**·Fe(II). Structure **A** is slightly stable than structure **B**.



Scheme 3. The strong intra-ligand NOE signals in **2**·Fe(II).

On the other hand, titration of the metal free ligand **2** with halide ions gave association constants, $K_a = 2.5 \times 10^4$ (Cl^-), 8.2×10^3 (Br^-), and

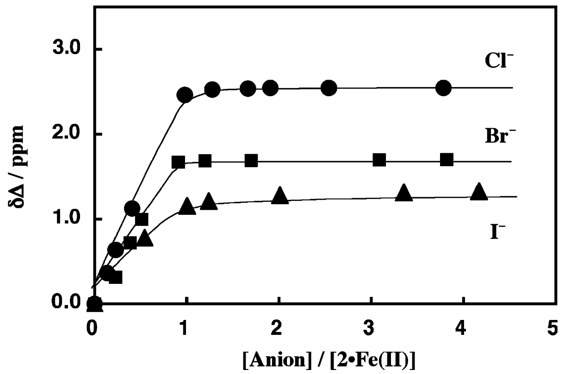


Figure 4. ^{1}H NMR titration curves of the receptor $[2\cdot Fe(II)](PF_6)_5$ (0.5 mM in CD_3CN) with halide anions. $\Delta\delta$ is the shift difference in ppm of the imidazolium C(2)–H proton.

Table 1. Association constants K_a for 1:1 complex of the receptors **1a**, **1b**, **2**, **2**·Fe(II), and **2**·Ru(II) with halide anions (as tetrabutylammonium salts) determined by ^{1}H NMR titration in CD_3CN at 298 K

Receptor	K_a[a]/M^{-1}		
	Cl^-	Br^-	I^-
1a[b]	7.5×10^4	4.6×10^4	7.2×10^3
1b	1.5×10^3	7.0×10^2	4.4×10^2
2	2.5×10^4	8.2×10^3	3.8×10^3
2·Fe(II)	1.4×10^6[c]	3.2×10^5[c]	3.5×10^4
2·Ru(II)	5.1×10^7[c]	3.2×10^5[c]	8.1×10^3

[a] Errors are estimated to be <10%.

[b] Data taken from Ref. 5.

[c] Obtained by competitive titrations.

$3.8 \times 10^3\ \mathrm{M}^{-1}$ (I^-), respectively. The pseudocryptands, **2**·Fe(II) and **2**·Ru(II), bind Cl^- ion ca. 60 and 2000 times stronger than **2**, respectively, whereas, only 2–40 times larger with Br^- and I^-, thus the amplification affinity and selectivity for chloride anion is attained by the complexation of metal ion. This selectivity can be explained by the size complementarity and rigidity of the binding site. Interestingly, rigid connection of Ru(II) ion to the bpy ligands renders **2**·Ru(II) much more size-selective binding compared to **2**·Fe(II).

In summary, the novel tripodal bipyridine–imidazolium ligand **2** forms a stable 1:1 metal complex with Fe(II) and Ru(II) ions and shows positive allosteric anion-binding behavior. Initial binding of the metal ion preorganizes the bicyclic anion-binding site and results in an increase of the affinity and selectivity for chloride anion. The pseudocryptands, **2**·Fe(II) and **2**·Ru(II), are also expected to be electrochemical and optical anion sensing receptors.[11,12] We are currently investigating various receptors incorporated with imidazolium rings as anion-binding subunits.[13]

Acknowledgement

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