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# Highly cooperative ion-pair recognition of potassium cyanide using a heteroditopic ferrocene-based crown ether–trifluoroacetylcarboxanilide receptor†

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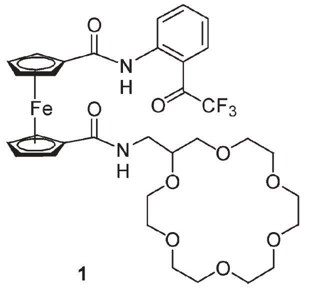
**A heteroditopic receptor having crown ether and trifluoroacetylcarboxanilide groups selectively recognizes both potassium and cyanide ions in acetonitrile with an association constant of as high as $K_a = 1.9 \times 10^7$ $M^{-1}$ through a highly cooperative ion-pair interaction, resulting in two orders of magnitude enhancement in the binding affinity.**

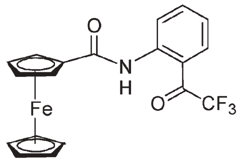
Selective recognition and sensing of specific analytes have attracted much attention among scientists studying supramolecular systems.[1] A number of artificial receptors have been developed for the recognition and sensing of cations or anions; however, the recognition/sensing of ion-pairs by synthetic receptors remain a less explored area. For the recognition/sensing of ion-pairs, heteroditopic receptors having both cation and anion binding sites have been studied.[2,3] When an electrostatic interaction between a "bound" cation and an anion is possible, a positive cooperative binding may result, leading to an increase in the binding affinity. To maximize the cooperative binding, a fine tuning of the receptor structure is required in such a way to accommodate a specific ion-pair species. With a few exceptions, however, weaker or sometimes even negative cooperative effects result where such a geometrical optimization is not fulfilled.[2] Recently we have developed a novel anion recognition motif that recognizes anions through the formation of reversible covalent adducts.[4,5] *o*-Trifluoroacetylcarboxanilide (TFACA) and its analogues thus developed efficiently recognize[4a] and sense[4b] anions such as cyanide and carboxylates. To develop this promising recognition motif into guest-specific receptors and sensors, we have been studying homoditopic[4c] and heteroditopic (hybrid) receptors based on the TFACA binding motif. We reasoned that a highly cooperative binding might be realized with a heteroditopic receptor composed of TFACA as the anion recognition motif because the resulting alkoxide adduct may interact with a bound cation through the electrostatic interaction. Herein, we wish to report such a heteroditopic receptor molecule that shows a very strong and highly positive cooperative binding toward potassium cyanide. In addition, thermodynamic parameters obtained enabled us to delineate distinct ion-pair binding processes involved.

Ferrocene was chosen as a spacer as well as an electroactive label. In addition, the cyclopentadienyl (Cp) units in the ferrocene can rotate like a ball-bearing and thus can readily adjust the two binding sites to a specific substrate in such a way to form an ion-pair complex.[3c] 18-Crown-6-ethers are well known ionophores for metal cations, particularly $K^+$.[6]

Heteroditopic receptor **1** was synthesized from 1,1′-bis(chlorocarbonyl)ferrocene by stepwise amidation reactions.[7] Thus, 1,1′-bis(chlorocarbonyl)ferrocene was treated with an equimolar amount of *o*-trifluoroacetylaniline to give the corresponding monochlorocarbonyl compound, which was separated by $SiO_2$ column chromatography and subsequently treated with an equimolar amount of 2-(aminomethyl)-18-crown-6 to afford the heteroditopic receptor **1** in a 73% isolated yield (see ESI†). Monotopic receptor **2**[4c] was used as a reference compound.



**1**



**2**

We investigated the binding properties of receptor **1** toward cyanide anion ($Bu_4N^+$ salt) and potassium cation ($PF_6^-$ salt) by using $^1H$ and $^{19}F$ NMR spectroscopy in acetonitrile-$d_3$ at 298 K. Upon addition of a sub-equimolar amount of the cyanide anion, two sets of peaks appeared including that of receptor **1** itself. When an equimolar amount of cyanide was added, the receptor peaks disappeared and only the other set of peaks assignable to those of cyanide adduct was observed (Fig. 1). For example, the protons of trifluoroacetophenone moiety of **1**, appearing at 8.57, 7.94, 7.76 and 7.28 ppm, were completely changed to 8.56, 7.50, 7.28 and 6.99 ppm, upon addition of an equivalent of cyanide (Fig. 1(b)). Interestingly, the amide NH proton at the crown ether-side, initially appeared at 6.7 ppm, shifted to 9.2 ppm, indicating that it is involved in H-bonding, plausibly with the anionic adduct. A molecular model suggested that such an H-bonding is geometrically feasible. Also, the other amide NH proton adjacent to the trifluoroacetophenone moiety disappeared, probably owing to its acidic nature. A $^{19}F$ NMR spectrum taken for receptor **1** only showed single peak at 4.8 ppm, which shifted to −5.7 ppm upon addition of an equivalent of cyanide. Both peaks were

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† Electronic supplementary information (ESI) available: Procedures for the synthesis of receptors **1** and **2**, binding analysis (ITC, NMR), and cyclic voltammetry data. See DOI: 10.1039/b715633b

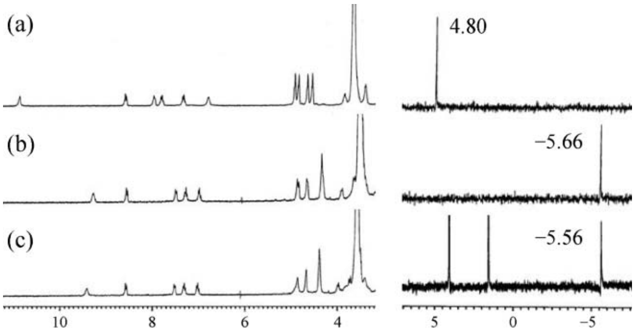

**Fig. 1** Changes in the $^1$H NMR (300 MHz, left) and $^{19}$F NMR spectra (right) of heteroditopic receptor **1** (1.0 mM) upon the addition of $Bu_4N^+CN^-$ and $K^+PF_6^-$: (a) no added substrate, (b) 1.0 equiv. of $Bu_4N^+CN^-$, (c) 1.0 equiv. of $Bu_4N^+CN^-$ and 1.0 equiv. of $K^+PF_6^-$ in acetonitrile-$d_3$ at 298 K (the signals at 4.10 and 1.60 ppm in the $^{19}$F NMR spectrum are due to $PF_6^-$).

**Table 1** Thermodynamic data for the ion/ion-pair complexation by **1** and **2**, determined by ITC analysis[a]

| Entry | Receptor | Substrate[b] | $\Delta H^\circ$ [c] | $-T\Delta S^\circ$ [c] | $K_{ass}$ [d] | $n$[e] |
|---|---|---|---|---|---|---|
| 1 | **1** | $CN^-$ | −12.5 | 5.2 | $1.9 \times 10^5$ | 0.94 |
| 2 | **1** | $K^+$ | −6.4 | −1.1 | $2.5 \times 10^5$ | 0.57 |
| 3 | **1** + $K^+$ | $CN^-$ | −9.1 | −0.3 | $6.5 \times 10^6$ | [f] |
|  | (1 : 1 mixture) |  | 92.4 | −97.3 | $4.4 \times 10^4$ |  |
|  |  |  | −92.3 | 82.1 | $1.9 \times 10^7$ |  |
| 4 | **1** + $CN^-$ | $K^+$ | −5.0 | 2.8 | $4.2 \times 10^5$ | 0.87 |
|  | (1 : 1 mixture) |  |  |  |  |  |
| 5 | **2** | $CN^-$ | −13.8 | 6.3 | $2.2 \times 10^5$ | 1.04 |
| 6 | **2** | $K^+$ | — | — | — | [g] |
| 7 | **2** + $K^+$ | $CN^-$ | −9.9 | 2.3 | $3.0 \times 10^5$ | [f] |
|  | (1 : 1 mixture) |  | −10.3 | 3.8 | $4.7 \times 10^4$ |  |
|  |  |  | −7.5 | −12.5 | $3.8 \times 10^3$ |  |
| 8 | **2** + $CN^-$ | $K^+$ | — | — | Weak binding | — |
|  | (1 : 1 mixture) |  |  |  |  |  |
| 9 | **1** | $AcO^-$ | −16.1 | 9.6 | $5.4 \times 10^4$ | 1.03 |
| 10 | **1** + $K^+$ | $AcO^-$ | −10.8 | 3.7 | $1.3 \times 10^5$ | 0.84 |
|  | (1 : 1 mixture) |  | −140.0 | 133.3 | $4.1 \times 10^4$ | 0.09 |

[a] Determined in $CH_3CN$ at 303 K. [b] As $Bu_4N^+$ or $PF_6^-$ salt. [c] kcal $mol^{-1}$. [d] $M^{-1}$. [e] Binding stoichiometry. [f] Sequential binding. [g] Not detected.

observed when sub-equimolar amounts of the cyanide were added. These results indicate that the cyanide adduct exists as the sole species after the equivalent point.

Next, one equivalent of the potassium ion was added to the equimolar mixture of receptor **1** and the cyanide ion (Fig. 1(c)). Binding of the potassium ion onto the crown-ether ring was best indicated by a change in the chemical shift of the methine proton of the crown-ether ring, from 3.89 to 3.95 ppm. A similar change was observed in the crown-ether part when only potassium ion, no cyanide, was added to a solution of receptor **1**. The signal of the amide NH proton at the crown-ether side slightly shifted from 9.15 to 9.32 ppm. Also, one of the Cp protons, appearing at 4.84 ppm became broad. These NMR changes may be explained by the conformational restriction due to cooperative ion-pair interactions. A $^{19}$F NMR spectrum taken for the mixture showed a slight downfield shift from −5.66 to −5.56 ppm (Fig. 1(c)). The $^1$H and $^{19}$F NMR spectroscopic observations are consistent with the fact that receptor **1** forms a complex with both cyanide and potassium ions.

The binding properties of receptor **1** toward $CN^-$ and $K^+$ were further studied by isothermal titration calorimetry (ITC).[8] In order to investigate the ion-paring effect, an equimolar mixture of **1** and $K^+$ was also titrated with $CN^-$. Table 1 summarizes association constants,‡ enthalpy and entropy changes, and binding stoichiometry obtained from the ITC analysis. The data shows that **1** strongly binds $CN^-$ ($K_{ass} = 1.9 \times 10^5\ M^{-1}$) in acetonitrile. A 1 : 1 binding mode between **1** and $CN^-$ is again supported by the *n* value, the binding stoichiometry, which is close to unity (entry 1).[5a] The monotopic receptor **2** shows a similar binding affinity toward $CN^-$ (entry 5), which indicates that the presence of crown-ether moiety in **1** has little effect on the adduct formation between the TFACA moiety and $CN^-$. Receptor **1** also strongly binds the $K^+$ ($K_{ass} = 2.5 \times 10^5\ M^{-1}$) similar to the case of $CN^-$; however, in this case the *n* value is close to 0.5, suggesting that a 2 : 1 complex preferably forms between **1** and $K^+$§ (entry 2). $^1$H NMR titration of receptor **1** with the $K^+$ also showed a saturation behavior after addition of 0.5 equivalents of the cation (see ESI†). When a preformed equimolar mixture of **1** and $K^+$ was titrated with $CN^-$, interestingly the data analysis suggested a sequential binding mode that involves three binding steps with distinct thermodynamic parameters (entry 3). Among the three binding processes, the second step was accompanied by a large unfavorable enthalpy change ($\Delta H$ = 92.4 kcal $mol^{-1}$) and a large favorable entropy change ($T\Delta S$ = −97.3 kcal $mol^{-1}$, $T$ = 303 K), while the third process showed an opposite trend, showing a large favorable enthalpy change ($\Delta H$ = −92.3 kcal $mol^{-1}$) and a large unfavorable entropy change ($T\Delta S$ = 82.1 kcal $mol^{-1}$, $T$ = 303 K). The association constants obtained for the three binding processes are $K_1 = 6.5 \times 10^6$, $K_2 = 4.4 \times 10^4$, and $K_3 = 1.9 \times 10^7\ M^{-1}$. The largest value, $K_3$, is presumably responsible for the ion-pairing process. From the sequential binding process, we can infer the contribution of the ion-pairing to the overall binding affinity. A tentative mechanism for the sequential binding mode is suggested (Fig. 2) (see also ESI†).

Thus, if we compare the association constant for the cyanide addition to **1** (entry 1, **1** → **I**) with that of the presumed third

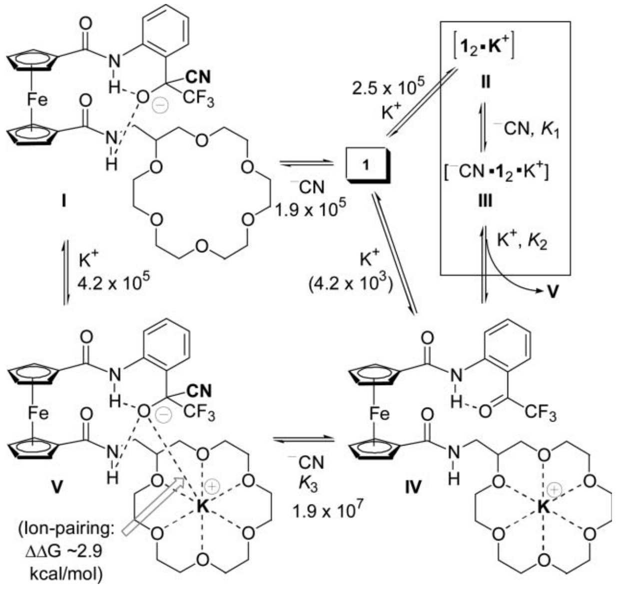

**Fig. 2** Suggested binding modes based on the ITC data. The numerical values are the association constants with unit $M^{-1}$ (those in parentheses are estimated values). For a detailed explanation, see the ESI.†

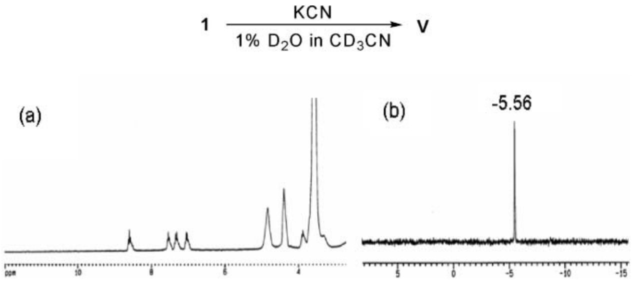

**Fig. 3** (a) $^1$H and (b) $^{19}$F NMR spectra, taken for a mixture of receptor **1** (1.0 mM) and KCN (excess) in 1% $D_2O$–$CD_3CN$ (note that the amide NH protons are missing because of deuterium exchange).

process in entry 3 (**IV** → **V**; $K_3$), we can obtain a 100-times difference in the association constants ($\Delta\Delta G \sim 2.9$ kcal mol$^{-1}$), which amounts to the ion-pair contribution. Such a large positive cooperative effect is comparable to that achieved only with the cyclic receptor of Smith and co-workers.[2e] Also, the formation constant for mono-potassium intermediate **IV** from **1** can be estimated to be $4.2 \times 10^3$ M$^{-1}$ if we subtract the ion-pair contribution from the potassium-binding process **I** → **V** (Fig. 2).

Titration of the potassium complex of monotopic receptor **2** with CN$^-$ also gave a three-step binding mode (entry 7), showing little ion-pair interaction as expected. The binding modes may involve (1) ionic interaction between K$^+$ and CN$^-$, (2) the formation of alkoxide adduct by cyanide addition (3) ionic interaction between the alkoxide adduct with K$^+$. Finally, it is worthy of mention that titration of the potassium complex of **1** with acetate ion (entry 10) gave a smaller increase in the association constant compared to the case between **1** and acetate (entry 9), which should be due to a reduced ion-pair interaction: In this case, also, not a simple binding, but a two-site binding mode was best fit the binding isotherms. Such a complex binding mode is probably due to the sandwich-type potassium complex, $\mathbf{1}_2\cdot$K$^+$.

When Na$^+$ (PF$_6^-$ salt) was used instead of K$^+$, we observed little enhancement in the binding affinity between **1** and CN$^-$. This is due to the smaller size of Na$^+$ compared to that of K$^+$, not fitting well in the cavity of crown-ether, and thus a reduced or negligible cooperative interaction results.

Another evidence of the ion-pairing was obtained from electrochemical behavior of receptor **1**. Cyclic voltammograms were obtained by sequential addition of K$^+$ (as PF$_6^-$ salt) and CN$^-$ (as $Bu_4N^+$ salt) to **1** (1.0 mM, in $CH_3CN$) (see ESI†). The formal oxidation potential of **1** [$E^{\circ\prime}$ = +0.95 V (*vs.* Ag/AgCl)] showed a positive shift (+14 mV) upon addition of one equivalent of K$^+$, which was reversed upon addition of one equivalent of CN$^-$, from +14 mV to +3 mV. The CV data again demonstrates the ion-paring effect.

Because our receptor **1** can recognize both potassium and cyanide ions very strongly, we have examined whether it can recognize KCN salt by NMR spectroscopy. An aqueous solution of KCN (5 μL in $D_2O$) was added to a solution of receptor **1** (495 μL) in $CD_3CN$, which results in a solution of 1% $D_2O$ in $CD_3CN$. The $^1$H and $^{19}$F NMR spectra (Fig. 3) taken for the mixture showed very similar spectra to that shown in Fig. 1(c). Thus, the direct recognition of potassium cyanide in aqueous media is also possible with receptor **1**.

Also, receptor **1** can be used as a "probe" for the detection of anions simply by $^{19}$F NMR spectroscopy. For example, receptor **1** of which $CF_3$ originally appears at +4.80 ppm provides different chemical shifts toward anions such as CN$^-$ (−5.56 ppm) and AcO$^-$ (−9.28 ppm) in $CD_3CN$ containing $H_2O$, from 1% up to 50% (see ESI†).

In conclusion, we have achieved highly cooperative ion-pair recognition with a heteroditopic receptor **1** that is conformationally flexible. The NMR and ITC studies elucidated distinctive binding modes and large positive cooperative ion-pairing interactions between receptor **1** and potassium cyanide. The cooperative binding led to reversible redox potential shifts. Receptor **1** can also be used to detect potassium cyanide in aqueous media simply by $^{19}$F NMR spectroscopy.

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## Notes and references

‡ The association constants were obtained by using a curve-fitting program supplied with an ITC instrument from MicroCal, Inc.

§ The branched nature of the crown-ether moiety seems to be relevant for the formation of unusual sandwich-type complex.

1 *Comprehensive Supramolecular Chemistry*, ed. J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle and K. S. SuslickPergamon, Oxford, 1996.

2 For a review on ditopic receptors, see: (*a*) G. J. Kirkovits, J. A. Shriver, P. A. Gale and J. L. Sessler, *J. Inclusion Phenom. Macrocycl. Chem.*, 2001, **41**, 69. For articles of ion-pair recognitions, see: (*b*) J. Scheerder, J. P. M. van Duynhoven, J. F. J. Engbersen and D. N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1090; (*c*) T. Tozawa, Y. Misawa, S. Tokita and Y. Kubo, *Tetrahedron Lett.*, 2000, **41**, 5219; (*d*) R. Shukla, T. Kida and B. D. Smith, *Org. Lett.*, 2000, **2**, 3099; (*e*) J. M. Mahoney, A. M. Beatty and B. D. Smith, *J. Am. Chem. Soc.*, 2001, **123**, 5847; (*f*) L. H. Uppadine, J. E. Redman, S. W. Dent, M. G. B. Drew and P. D. Beer, *Inorg. Chem.*, 2001, **40**, 2860; (*g*) J. M. Mahoney, J. P. Davis, A. M. Beatty and B. D. Smith, *J. Org. Chem.*, 2003, **68**, 9819; (*h*) P. R. A. Webber and P. D. Beer, *Dalton Trans.*, 2003, 2249; (*i*) J. M. Mahoney, K. A. Stucker, H. Jiang, I. Carmichael, N. R. Brinkmann, A. M. Beatty, B. C. Noll and B. D. Smith, *J. Am. Chem. Soc.*, 2005, **127**, 2922.

3 For articles of ion-pair sensing, see: (*a*) P. D. Beer and S. W. Dent, *Chem. Commun.*, 1998, 825; (*b*) Y.-H. Kim and J.-I. Hong, *Chem. Commun.*, 2002, 512; (*c*) H. Miyaji, S. R. Collinson, I. Prokes and J. H. R. Tucker, *Chem. Commun.*, 2003, 64; (*d*) A. P. de Silva, G. D. McClean and S. Pagliari, *Chem. Commun.*, 2003, 2010; (*e*) S. J. M. Koskela, T. M. Fyles and T. D. James, *Chem. Commun.*, 2005, 945; (*f*) F. Oton, A. Tarraga, M. D. Velasco and P. Molina, *Chem. Commun.*, 2005, 1159.

4 (*a*) Y. K. Kim, Y.-H. Lee, H.-Y. Lee, M.-K. Kim, G. S. Cha and K. H. Ahn, *Org. Lett.*, 2003, **5**, 4003; (*b*) Y. M. Chung, B. Raman, D.-S. Kim and K. H. Ahn, *Chem. Commun.*, 2006, 186; (*c*) D.-S. Kim, H. Miyaji, B.-Y. Chang, S.-M. Park and K. H. Ahn, *Chem. Commun.*, 2006, 3314.

5 For previous trifluoroacetophenone-based ionophores, see: (*a*) M. E. Meyerhoff, E. Pretsch, D. H. Welti and W. Simon, *Anal. Chem.*, 1987, **59**, 144; (*b*) G. J. Mohr, F. Lehmann, U. W. Grummt and W. E. Spichiger-Keller, *Anal. Chim. Acta*, 1997, **344**, 215; (*c*) H. J. Lee, I. J. Yoon, C. L. Yoo, H.-J. Pyun, G. S. Cha and H. Nam, *Anal. Chem.*, 2000, **72**, 4694; (*d*) Y. K. Kim, J. Ha, G. S. Cha and K. H. Ahn, *Bull. Korean Chem. Soc.*, 2002, **23**, 1420.

6 *Crown Compounds: Toward Future Applications*, ed. S. R. Cooper, VCH, Weinheim, 1992.

7 H. Miyaji, G. Gasser, S. J. Green, Y. Molard, S. M. Strawbridge and J. H. R. Tucker, *Chem. Commun.*, 2005, 5355.

8 F. P. Schmidtchen, *Org. Lett.*, 2002, **4**, 431.