Selective recognition and electrochemical sensing of dicarboxylates with a ferrocene-based bis(*o*-trifluoroacetylcarboxanilide) receptor†‡

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A ferrocene-based bis(*o*-trifluoroacetylcarboxanilide) receptor selectively recognizes *m*-phenylene diacetate through cooperative binding; the receptor also displays a significant negative shift in the oxidation potential of ferrocene upon the guest binding.

Anions play important roles in biological and chemical processes,[1] and have implications in medicine, catalysis and the environment.[2] Thus, the selective recognition of anions has been a challenging topic in recent supramolecular chemistry. Receptors that bind guests in a cooperative manner are especially sought for the selective recognition of a specific guest.[3]

Trifluoroacetophenone derivatives have been utilized as unique ionophores for anions that reversibly form anion–ionophore adducts by attacking the trifluoroacetyl carbonyl carbon.[4] Recently, we have demonstrated that introduction of an H-bonding donor such as a carboxamido group to the trifluoroacetophenone moiety stabilizes the anionic adducts and thus significantly enhances the receptor's binding affinity toward anions such as carboxylates to a practically useful level.[5a] This approach of H-bond stabilization also enabled us to introduce a novel fluorescence sensor toward cyanide.[5b] To develop this promising recognition motif into a guest-specific receptor, we have been studying bis-, tris-, and hybrid derivatives of the *o*-trifluoroacetylcarboxanilide (TFACA) system. Here, we wish to report a ferrocene-based bis(TFACA) system **1**, which recognizes and electrochemically senses a specific dicarboxylate in a cooperative manner.

Ferrocene was chosen as a spacer as well as an electro-active label. In addition, the two binding motifs are expected to adjust to form a stable ditopic complex toward a specific guest because the cyclopentadienyl (Cp) units in the ferrocene can rotate like a ball bearing along the vertical axis.[6] Compound **1** was synthesized from 1,1′-ferrocenedicarboxylic acid by amidation with *o*-trifluoroacetylaniline. Compound **2** was also synthesized as a control receptor from ferrocenecarboxylic acid (see ESI‡). All final products were isolated, purified, and fully characterized.

We first investigated the molecular interactions between ditopic receptor **1** and several dicarboxylates **4–6** by NMR spectroscopy. When a subequimolar amount of dicarboxylate **6** was added to ditopic receptor **1** in CD_3CN, both the unshifted Cp peaks corresponding to the receptor and fully shifted adduct Cp peaks appeared, which indicates that the equilibration of host–guest adduct formation is too slow on the NMR timescale. Upon addition of an equimolar amount of dicarboxylate **6**, unshifted receptor peaks completely disappeared and only fully shifted new adduct peaks appeared. The changes in chemical shifts (the NH proton: δ_H = 11.03 → 11.08 ppm; the Cp ring protons: 5.00 → 4.80, 4.64 → 4.36 ppm; the CF_3 fluorine: δ_F = 5.52 → −8.47 ppm) indicated the formation of a (1 : 1) host : guest adduct. Also trifluoroacetyl carbonyl carbon signals of receptor **1** which appeared at δ_C = 183.8 ppm (quartet, J_{C-F} = 0.4 Hz) disappeared after addition of an equimolar amount of dicarboxylate **6** in $CDCl_3$. The Job plot[7] for the interaction between receptor **1** and each of the dicarboxylates (**4**, **5** and **6**)§ was obtained by plotting the molar concentration of the (1 : 1) complex *vs.* mole fraction of the host, which was determined by integrating their Cp ring protons (Fig. 1). The Job plot in the case of dicarboxylate **6** displays a maximum at a mole fraction of 0.5 with a sharp and symmetrical peak, suggesting a strong (1 : 1) host : guest binding mode. In the case of dicarboxylate **4**, however, the Job plot displays a maximum peak at the mole fraction of 0.33, suggesting a major (1 : 2) host : guest binding stoichiometry. Interestingly, the Job plot also shows a maximum at the mole fraction of 0.5 with an unsymmetrical peak shape in the case of dicarboxylate **5**, which suggests a mixed binding mode of plausibly a dominant (1 : 1) host : guest complex mixed with other higher order complexes.¶ These results can be interpreted as: dicarboxylate **6** matches best the ditopic receptor **1** among other guests in view of the distance between the two carboxylate moieties in the guest and the two TFACA units in the host, and thus an efficient cooperative binding is achieved. In the case of dicarboxylate **4**, this geometrical

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† The HTML version of this article has been enhanced with colour images.

‡ Electronic supplementary information (ESI) available: Procedures for the synthesis of receptors **1** and **2**, binding data (Job plot, ITC, MS, NMR) and cyclic voltammetry data. See DOI: 10.1039/b606081a

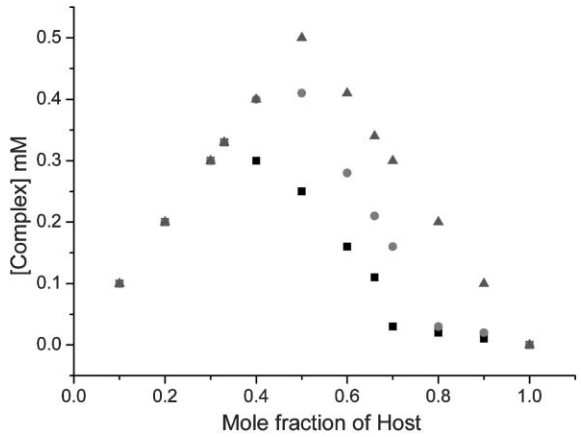

Fig. 1 Job plots for ditopic receptor **1** with the tetrabutylammonium salts of *m*-phenylene diacetate **6** (▲), isophthalate **5** (●), and phthalate **4** (■) in CD_3CN at 298 K ([H] + [G] = 1.0 mM).

match seems to be lost and thus such a cooperative binding is no longer operative. As a control, acetate **3** was also allowed to interact with receptor **1**, which gave a Job plot consistent with a (1 : 2) host : guest binding mode, as was observed in the case of dicarboxylate **4**.

To obtain thermodynamic data for the binding process between the receptors and guests, we carried out isothermal titration calorimetry (ITC). The integrated binding isotherms for several guests are summarized in Fig. 2, and the thermodynamic data obtained by a non-linear least-squares curve fit for the binding isotherms are summarized in Table 1. The ΔH° and $-T\Delta S^\circ$ data in Table 1 indicate that the complex formation is driven by a favorable enthalpy change and unfavorable entropy change in all cases, which also supports the host–guest adduct formation. The isothermal titration curve for ditopic receptor **1** with acetate **3** can be best fit to a sequential binding model with a (1 : 2) host : guest binding mode.[8] The sequential association constants thus obtained (K_1, K_2) are similar to that observed between receptor **2** and acetate **3**. In the case of dicarboxylate **4**, we could not determine an apparent binding mode by ITC (see ESI‡). The inflection point in the binding isotherm between ditopic receptor **1** and dicarboxylate **6** occurred near the molar ratio of 1.0 (n = 1.06), which

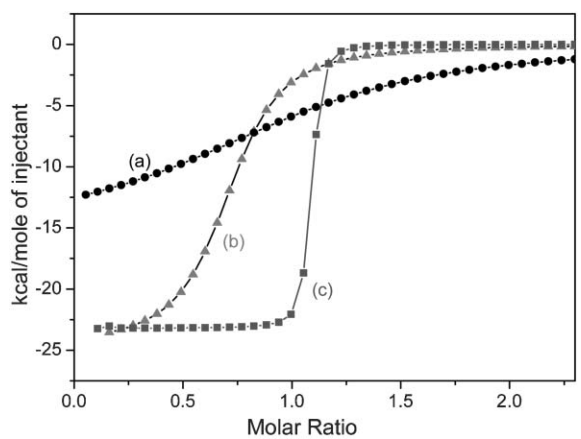

Fig. 2 ITC plots of (a) receptor **2** with acetate **3**, (b) ditopic receptor **1** with dicarboxylate **5** and (c) ditopic receptor **1** with dicarboxylate **6** in CH_3CN at 303 K.

Table 1 Thermodynamic data for host–guest complexation determined by isothermal titration calorimetry[a]

Host	Guest[b]	$\Delta H^{\circ c}$	$-T\Delta S^{\circ c}$	$\Delta G^{\circ c}$	K^d	n^e
1	**3**	−20.9	14.5	−6.4	3.0×10^4	[f]
		5.9	−11.8	−5.9	1.9×10^4	
1	**5**	−24.7	17.1	−7.6	2.8×10^5	0.70
1	**6**	−23.2	13.2	−10.0	1.6×10^7	1.06
2	**3**	−15.4	9.4	−6.0	2.1×10^4	1.00

[a] Determined in CH_3CN at 303 K. [b] Bu_4N^+ salts. [c] Unit: kcal/mol. [d] Unit: M^{-1}. [e] Host–guest stoichiometry. [f] Sequential binding.

corresponds to the (1 : 1) host–guest stoichiometry suggested by the Job plot.‖ Ditopic receptor **1** binds dicarboxylate **6** strongly, with a larger ΔG° value (−10.0 kcal mol^{-1}) compared to other cases. It binds with dicarboxylate **6** about 760 times more strongly than receptor **2**.

The electrochemical behavior of receptors **1** and **2** with the carboxylates present was investigated by cyclic voltammetry in CH_3CN at a receptor concentration of 1.0 mM (ESI). As shown in Fig. 3a, ditopic receptor **1** shows a reversible redox process centered at $E^{\circ\prime}$ = +0.984 V (*vs.* Ag/AgCl), which was obtained from $E^{\circ\prime} = (E_{pa} + E_{pc})/2$. Significantly, the addition of one equivalent of the dicarboxylate **6** to the solution resulted in a large negative shift of −153 mV (Fig. 3c). No further change was observed after the addition of more than one equivalent of the guest, consistent with the formation of a strong ditopic complex with a (1 : 1) stoichiometry. Indeed, the ^1H NMR spectrum at this equivalence point showed almost 100% complexation. In the presence of 0.5 equivalent of dicarboxylate **6**, two anodic peaks and broad cathodic peaks appeared (Fig. 3b). Obviously, 50% of the free host and 50% of the complex exist at this stage. The cathodic peak for the (1 : 1) adduct becomes featureless. In the presence of 0.7 equivalent of dicarboxylate **6**, the cathodic peak of the host was reduced and another cathodic peak of the complex appeared more clearly, and the shift in formal potential $\Delta E^{\circ\prime} = E^{\circ\prime}_{complex} - E^{\circ\prime}_{host}$ was also estimated to be −153 mV (see ESI).

As control experiments, cyclic voltammetric experiments on the receptors **1** and **2** with acetate **3** were also carried out. Receptor **2**

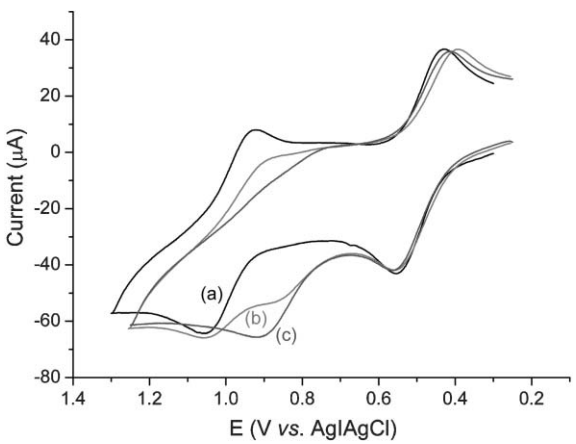

Fig. 3 Cyclic voltammograms of receptor **1** (1.0 mM in CH_3CN): (a) in the absence of dicarboxylate **6**, (b) in the presence of 0.5 equivalent of dicarboxylate **6** and (c) in the presence of 1.0 equivalent of dicarboxylate **6**. Note that the first redox peaks at ~0.5 V *vs.* Ag/AgCl correspond to the authentic Fc^+/Fc pair used as an internal reference.

Table 2 Electrochemical data of compounds **1** and **2** detailing the shift in the formal electrode potential, $\Delta E^{\circ\prime}$ (mV), upon addition of guests **3** and **6**[a]

Receptor	**3** (2.0 equiv)	**3** (4.0 equiv)	**6** (1.0 equiv)
1	−122	−149	−153
2	−40	−40	—

[a] In CH_3CN (1.0 mM) at 298 K.

gave a formal potential at $E^{\circ\prime} = +0.710$ V (*vs.* Ag/AgCl), showing a lower formal potential than that of ditopic receptor **1**. In the presence of one equivalent of acetate **3**, the cathodic peaks of receptor **1** (and also **2**) became broad because both free host and complex are present. After addition of two equivalents of acetate **3**, the complex peaks became clearer and the shifts in the formal potential ($\Delta E^{\circ\prime}$) were estimated; they are listed in Table 2. The receptor **2** gave a negative shift of −40 mV toward acetate **3**. The ditopic receptor, **1**, gave a large negative shift of −122 mV in the presence of two equivalents of acetate **3**. At this stage, a mixture of a (1 : 2) host–guest complex and a (1 : 1) host–guest complex seems to be present. However, when four equivalents of acetate **3** were added to ditopic receptor **1**, almost all complexes became a (1 : 2) host–guest species and gave a large negative shift of −149 mV. These results indicate that anionic complexes cause negative shifts,[9] especially di-anionic species cause large negative shifts for the ferrocene-centered redox potentials. Only one equivalent of dicarboxylate **6** was enough to cause the largest negative shift of ditopic receptor **1**, which again indicates that the strong cooperative binding process effectively introduces di-anionic charges to the ferrocene redox centre.

Based on the binding modes supported by the Job plots, ITC and cyclic voltammetry data, a plausible host–guest complex structure between ditopic receptor **1** and dicarboxylate **6** is modeled and shown in Fig. 4.** The distance between the two trifluoroacetyl units seems to fit the two carboxylate ends, which results in the cooperative (1 : 1) host–guest complex formation.

In conclusion, we have demonstrated that the redox-active ditopic receptor **1** selectively recognizes and senses the dicarboxylate **6** *via* cooperative formation of a (1 : 1) host–guest adduct. Work on the recognition and sensing of a specific guest by related ferrocene receptors is currently under way and will be reported in due course.

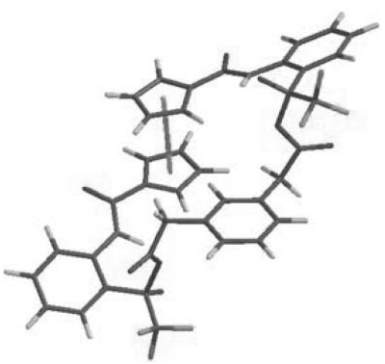

Fig. 4 A modeled structure of the cooperative adduct between ditopic receptor **1** and dicarboxylate **6**, in which the hydrogen bonding stabilization has not been incorporated.

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Notes and references

§ Tetrabutylammonium salts were prepared according to the literature (see T. R. Kelly and M. H. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 7072). Attempts to prepare the tetrabutylammonium salts of terephthalic acid were not successful. Tetrabutylammonium acetate **3** was purchased from Aldrich.

¶ A minor complex, presumably a (2 : 1) host : guest complex, appeared with different chemical shifts, which was not counted in the Job plot of Fig. 1.

‖ A (1 : 1) binding mode that is not a chelated adduct but an open structure may exist in a negligible amount if at all, because the association constant observed greatly exeeds that of the (1 : 1) acetate adduct formation, which involves a similar open structure. In fact, we could not observe any other minor peaks in the ^{1}H NMR spectrum of the (1 : 1) host–guest complex.

** Semiempirical computations were performed using Spartan '04 Windows from Wavefunction, Inc. The computation used the AM1 parameters, and an isolated and equilibrium ground state geometry was obtained.

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