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A new heteroditopic receptor and sensor highly selective for bromide in the presence of a bound cation

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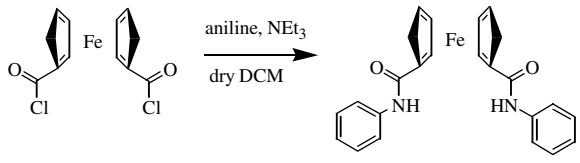
Abstract—The heteroditopic receptor **2** containing a crown ether and amidoferrocence groups was synthesized and the binding abilities with various anions are reported in the presence and absence of metal cations. In the presence of Na^+, **2** showed positive cooperative binding towards Br^- with the binding affinity K_{ass} = 16,096 M^{-1}. Therefore, receptor **2** showed a switched-on binding for Br^- in the presence of Na^+ and a switched-off binding in the absence of Na^+. Compound **2** was also found to sense Cl^- and Br^- electrochemically.

Anion recognition and sensing by synthetic anion receptors and sensors have received increasing attention over the past few years.[1] Heteroditopic receptors, a class of supramolecular compounds, show simultaneous binding of cationic and anionic guests by multi-site receptors. These compounds operate with cooperative and allosteric behaviour. The binding affinity of one species is induced by the other due to electrostatic interactions and conformational effects.[2] A guest binding at one site can result in a negative[3] or positive[4] effect on a different guest binding at the remote second site. Such positive binding systems have a potential for selective extraction of nuclear waste products[5] and zwitterionic amino acids.[6] The extraction or solubilization[7] of metal salts and transportation affinities through lipophilic membranes have also been reported.[8]

Smith and co-workers have recently reported syntheses and properties of macrocyclic ion pair receptors based on diazacrown ether and amide units.[9] Smith's system showed positive binding of anions in the presence of alkali metal ions. The amidoferrocene function was found to act as a good anion receptor and sensor.[10] We report herein the synthesis of a new macrocyclic receptor and sensor based on a crown ether, the cationic binding site, covalently linked to amidoferrocene, the anion binding and sensing unit.

The diaza crown ether was synthesized according to methods described in the literature.[11] Receptor **1** can be prepared in one-step by coupling bis(chlorocarbonyl) ferrocene with aniline using NEt_3 as the base in dry dichloromethane. Compound **1** was obtained in 75% yield as an orange solid (Scheme 1).[12] Receptor **2** was synthesized by coupling the diaza crown ether **3** with 3,nitrobenzyl chloride, in the presence of Na_2CO_3, in acetonitrile yielding compound **4** in 98% yield. Reduction of **4** by $NaBH_4$ and Pd/C in 4:1 THF/MeOH resulted in diamine **5** in 95% yield. This compound was further reacted with bis(chlorocarbonyl)ferrocene in dichloromethane using NEt_3 as the base to give receptor



Scheme 1. Synthesis of receptor **1**.

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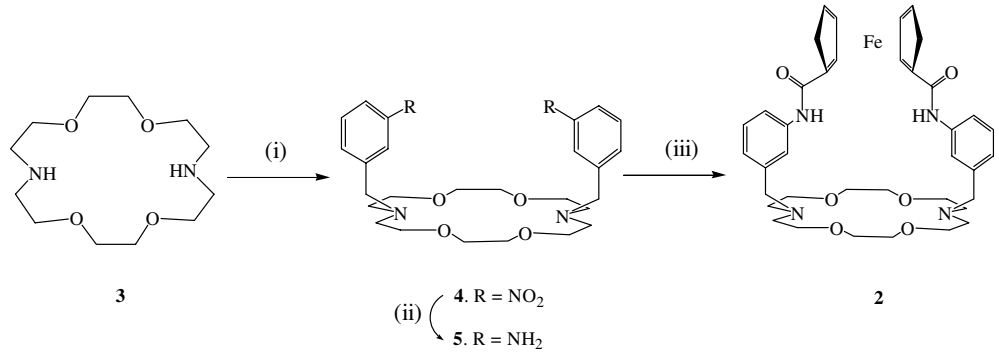

Scheme 2. Synthesis of receptor **2**. Reagents and conditions: (i) 3-nitrobenzyl chloride, Na_2CO_3, NaI, acetronitrile, reflux, N_2, 15 h, 98%; (ii) $NaBH_4$, Pd/C, THF/MeOH (4:1), 20 min, N_2, 95%; (iii) ferrocene diacid chloride, NEt_3, dichloromethane, room temperature, 3 h, 33%.

2 as a yellow-orange solid[13] after purification by Al_2O_3 column chromatography in 33% yield (Scheme 2).

In order to compare with the results reported by Smith and colleagues, DMSO-d_6 should be the solvent of choice for our system. Unfortunately, compound **2** was found to decompose in DMSO-d_6. Therefore, NMR experiments were carried out using mixed solvents. The quantitative evaluation of the cation binding ability of compound **2** was obtained by ^{1}H NMR titration experiments in 5% $CD_3CN/CDCl_3$.[14] In the presence of metal cations, complexation occurred under slow exchange conditions. Therefore, both complexes and free species were distinguishable in ^{1}H NMR spectra. Binding constants were determined by direct integration of the host and complex resonances in the ^{1}H NMR spectra as described by Macomber.[15] Binding constants of **2** towards Na^+ and K^+ are presented in Table 1.

Anion affinities were evaluated by adding aliquots of tetrabutylammonium salts to a solution of **2** in the presence and absence of 1 M equiv of sodium and potassium ions. In the absence of metal ions, the addition of tetrabutylammonium chloride, bromide and iodide to the solution of receptors **2** resulted in slightly downfield shifts of the NH amide protons, which indicated that anion binding occurred via hydrogen bonding to the NH amide protons.[16] The control compound **1** was also titrated with the three halide salts. Data from all titration experiments correlated well with titration curves calculated by EQNMR[17] using a 1:1 binding model and gave stability constants as shown in Table 2. From these results, receptor **2** binds chloride more weakly than the control receptor **1**, probably due to the more rigid structure of receptor **2**.

Table 1. Binding constants of receptor **2** towards Na^+ and K^+ in 5% $CD_3CN/CDCl_3$

Metal cations	K (M^{-1})
Na^{+a}	764
K^{+b}	387

[a] The counter anion is perchlorate.
[b] The counter anion is hexafluorophosphate.

Table 2. Binding constants for halide anions binding with receptors **1**, **2**, [**2**+Na^+] and [**2**+K^+] in 5% $CD_3CN/CDCl_3$

Host	K[a] (M^{-1})		
	Cl^-	Br^-	I^-
1	60	–[b]	–[b]
2	35	–[b]	–[b]
[**2**+Na^+][c]	–[d]	16,096	93
[**2**+K^+][c]	–[d]	–[d]	39

[a] Maximum error estimated to be ±10%.
[b] Values are very small and errors are more than 10%.
[c] The alkali metal cations were added as their perchlorate or hexafluorophosphate salts.
[d] Cannot be calculated due to ion-pair formation between bound metal cations and added anions.

However, addition of tetrabutylammonium halides in the presence of 1 equiv of sodium and potassium ions gave interesting results.[18] In the systems of [**2**+Na^+]/Cl^-, [**2**+K^+]/Cl^- and [**2**+K^+]/Br^-, the NH amides shifted insignificantly upon addition of less than 1 equiv of anion. Further addition of anions resulted in a large shift of the NH amide protons as shown in Figure 1. This signifies that these anions do not bind NH amide protons but form stable ion pairs with bound Na^+ as

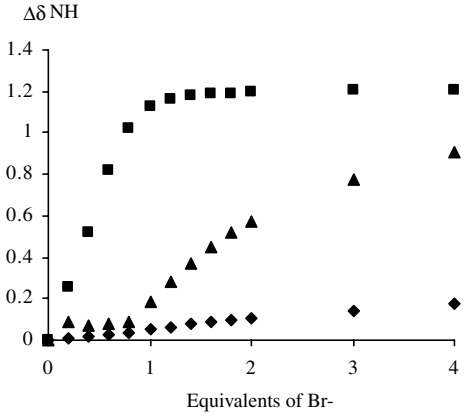

Figure 1. Change in NH chemical shift (ΔNH) of receptor **2** as a function of increasing equivalents of TBA bromide, (♦) indicates absence of Na^+, (■) presence of Na^+ (1 equiv) and (▲) presence of K^+ in 5% $CD_3CN/CDCl_3$.

described by Al-Sayah and Branda[19] and Tumcharern et al.[20] These results are different from those reported by Smith and co-workers where the similar crown macrobicycles were used.[9] Both Smith and co-workers carried out NMR titrations of their compounds in DMSO-d_6 and no ion pair from bound cations with added anions were observed. This is obviously the solvent effect.

In the [**2**+Na^+]/Br^-, [**2**+Na^+]/I^- and [**2**+K^+]/I^- systems, upon addition of anions the NH amide protons significantly shifted downfield. The induced shifts were consistent with the NH amide hydrogen bonding with the anions. The binding affinities of Br^- and I^- anions were markedly enhanced in the presence of Na^+. The association constant of [**2**+Na^+] and Br^- was found to be 16,096 M^{-1}, a large increase from the undetermined binding constant without Na^+. However, in the presence of K^+, only iodide binding affinity was enhanced. Therefore, the presence of alkali metal ions in receptor **2** switches on bromide and iodide binding.

Single crystals of [**2**·NaCl]·2$CHCl_3$ were obtained by the slow evaporation of a $CHCl_3$ solution of **2** saturated with NaCl.[21] Receptor **2** binds NaCl as a contact ion pair (Fig. 2). Na^+ was encapsulated in the crown ether cavity and Cl^- bound two NH amide protons via hydrogen bonding. The two Cp rings are nearly eclipsed, while

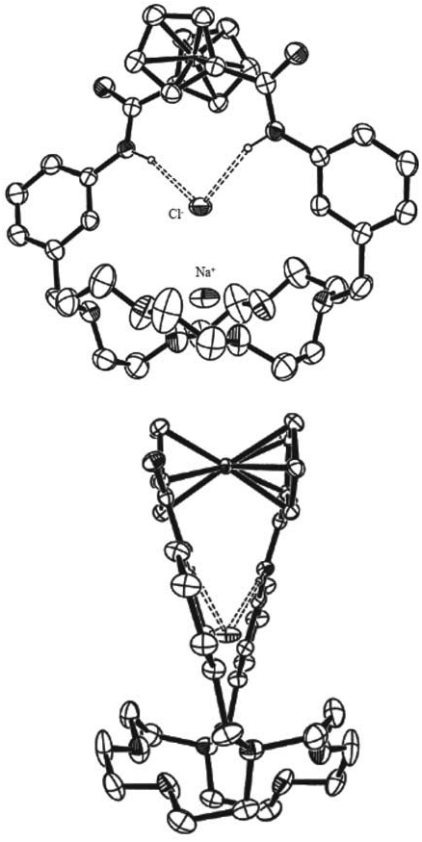

Figure 2. Front and side views of the X-ray crystal structures of [**2**·NaCl]·2$CHCl_3$, showing only relevant protons. $CHCl_3$ was omitted for clarity.

Table 3. Extraction percentage of halide salts by **2** into $CDCl_3$ within 1 h

Anions	% Extraction	
	Na^+	K^+
Cl^-	18	40
Br^-	74	23
I^-	100	25

the average distance of Fe from the cyclopentadienyl rings is 2.03 Å. The Na–Cl distance, 2.624 Å, is shorter than the Na–Cl distance in crystalline sodium chloride (2.81 Å).[22] The Cl–N distance (3.396 Å) is larger than that of other heteroditopic receptors, which showed positive co-operative Cl^- binding.[9] Moreover, the average distance from the four diazacrown ether oxygen donors to the Cl^- is 4.053 Å, which is markedly closer to Cl^- than that observed in the analogous compounds reported by Smith and co-workers[9] and can cause ion-dipole repulsion between the diazacrown ether and Cl^-. This may result in the ion-pair formation between bound Na^+ and added Cl^- found in NMR titration experiments.

Solid/liquid extraction studies were carried out by allowing a solution of **2** in $CDCl_3$ to stand over an excess of an alkali metal salt, NaX or KX (X = Cl, Br and I).[23] The relative amount of complexes formed were determined on the basis of the integration of the ^1H NMR signals of the aromatic protons of the complex and free ligand. The extraction percentage of metal salts by **2** is shown in Table 3. Surprisingly, receptor **2** can solubilize NaI completely within 1 h. This result is probably due to the more covalent characteristic of NaI and its solubility in $CDCl_3$.

Cyclic voltammograms of **1** and **2** showed reversible redox couples of ferrocene/ferrocenium at $E_{1/2}$ of 0.411 and 0.473 mV, respectively. Addition of Na^+ and K^+ to **2** results in a slight anodic shift of the CV wave. In the light of ^1H NMR titrations, Cl^- and Br^- were subjected to electrochemical investigation. Upon addition of Bu_4NCl to a solution of **1** and **2**, a new oxidation wave appeared at a less positive potential (cathodic shift) and the original Fc/Fc^+ redox wave disappeared. The ion-pairing associations were accompanied by adsorption phenomena on the electrode surface leading to the loss of reversibility of the Fc/Fc^+ redox couple (Fig. 3). The differences between Epa (free receptor) and Epa (complex) of **1**, **2**, [**2**+Na^+] and [**2**+K^+] are shown in Table 4. The presence of metal ions leads to increase of cathodic shift of the redox potential of **2** upon binding anions.

In summary, we have synthesized a new heteroditopic receptor based on a crown ether and amidoferrocene, which exhibits high selectivity for bromide in the presence of sodium. Compound **2** showed the ability to sense Cl^- and Br^- by a shift of the redox wave to a less positive potential. The presence of metal ions resulted in the more cathodic shift of the redox potential upon binding anions.

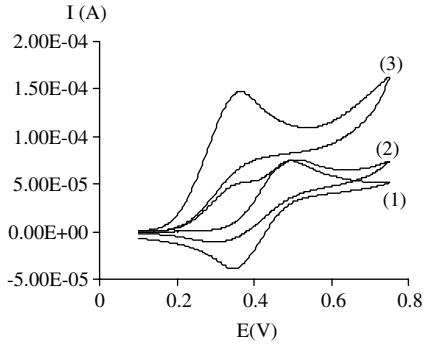

Figure 3. Cyclic voltammograms of [**2**+K^+] titrate with Bu_4NCl (1) free **2**, (2) [**2**+K^+] + 1.0 equiv of Cl^- and (3) [**2**+K^+] + 4.0 equiv of Cl^-.

Table 4. Electrochemical recognition data (ΔE)[a] for receptors **1** and **2** towards Cl^- and Br^- in 40:60 CH_3CN/CH_2Cl_2 with 0.1 M $TBAPF_6$ at scan rate 100 mV/s

	ΔE (mV)	
	Cl^-	Br^-
1	58	10
2	107	28
[**2**·Na^+][b]	122	46
[**2**.K^+][c]	153	–[d]

[a] ΔE is defined as E_{pa}(free receptor) − E_{pa}(complex).
[b] Added as sodium perchlorate.
[c] Added as potassium hexafluorophosphate.
[d] Precipitation occurred.

Crystallographic data for [**2**·NaCl]·$2CHCl_3$ are available upon request from the Cambridge Crystallographic Data Base (CCDC 239522).

Acknowledgements

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12. Compound **1**: ^1H NMR (400 MHz, $CDCl_3$): 4.42 (s, 4H), 4.63 (s, 4H), 7.05 (t, 2H, J = 7.2 Hz), 7.29 (t, 4H, J = 8.4 Hz), 7.72 (d, 4H, J = 8 Hz), 8.95 (s, 2H). Anal. Calcd for $C_{24}H_{20}FeN_2O_2$: C, 67.95; H, 4.72; N, 6.61. Found: C, 67.85; H, 4.63; N, 6.51.
13. Compound **2**: ^1H NMR (400 MHz, $CDCl_3$): 3.01 (s, 8H), 3.59 (s, 8H), 3.67 (t, 8H, J = 5.2 Hz), 3.93 (s, 4H), 4.53 (s, 4 H), 4.71 (s, 4H), 7.21 (d, 2H, J = 7.6 Hz), 7.33 (t, 2H, J = 7.6 Hz), 7.58 (d, 2H, J = 8 Hz), 7.97 (s, 2H), 8.68 (s, 2H). Anal. Cald for $C_{38}H_{46}FeN_4O_6$: C, 64.24; H, 6.48; N, 7.89. Found: C, 64.37; H, 6.52; N, 7.56.
14. Solutions of **2** (5×10^{-3} M) in 5% $CD_3CN/CDCl_3$ were prepared. To a solution of the ligand in each NMR tube was added 0.0–1.0 equiv of a 0.024 M of a metal salt solution.
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16. Solutions of **1** and **2** (5×10^{-3} M) in 5% $CD_3CN/CDCl_3$ were prepared. To a solution of a ligand in each NMR tube was added 0.0–4.0 equiv of a 0.05 M tetrabutylammonium salt solution of an anion.
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21. Crystal data for [**2**·NaCl]·$2CHCl_3$: $C_{40}H_{48}Cl_7N_4O_6FeNa$, M_r = 1007.81, T = 293(2) K, orthorhombic, space group

Pbcn, $a = 16.7080(4)$, $b = 19.0500(8)$, $c = 14.8950(8)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 4740.9(3)$ Å^3, $\rho_{calcd} = 1.412$ g cm^{-3}, $\mu = 0.769$ mm^{-1}, $Z = 4$, reflections collected: 5479, independent reflections: 2918 ($R_{int} = 0.0254$), final R indices [$I > 2\sigma I$]: $R1 = 0.0733$, $wR2 = 0.2102$, R indices (all data): $R1 = 0.1014$, $wR2 = 0.2383$ (CCDC 239522).

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23. Solutions of **2** (5×10^{-3} M) in $CDCl_3$ were prepared. To a solution of the ligand in each NMR tube was added the solid form of a metal salt. Spectra were recorded after 1 h.