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A selective chromogenic chemosensor for carboxylate salt recognition†

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A new heteroditopic chromogenic chemosensor bearing a crown ether substituted at the intraannular position with a nitrophenylthiourea moiety has been synthesized. The binding behavior of this sensor was investigated by ^{1}H NMR spectroscopy and UV-vis spectroscopy. The receptor binds in a cooperative fashion to both a potassium cation and a carboxylate anion whereas a sodium cation sequesters an anion from the anion–receptor complex. The binding events are confirmed by selective color changes of the chemosensor solution.

The simultaneous complexation of alkali metal cations and accompanying anions by heteroditopic molecular receptors has received increasing attention over the past decade. The development of this area of supramolecular chemistry is stimulated by the considerable benefits gained from binding an ion pair. The complexation of both the cation and anion by a ditopic receptor enhances salt lipophility, thus facilitating its solubilization, extraction and membrane transport.[1] Furthermore, the binding of the first ion can affect the subsequent coordination of the counterion. This cooperative effect can significantly increase the binding affinity between the receptor–cation complex and anions which poorly coordinate to monotopic molecular receptors (*i.e.* Br^-, NO_3^-, ClO_4^-).[2]

Although a number of chromogenic chemosensors capable of sensing alkali metal cations or anions are known, systems that are able to detect and differentiate alkali metal salts are rare.[3] The pioneering work in chromogenic sensing of alkali metal ion-pairs was reported by Kim and Hong, who prepared a Zn–porphyrin (anion binding site, chromophore) crown ether (cation binding site) conjugate.[4] This receptor binds in a ditopic fashion selectively to NaCN, resulting in a dramatic color change. Miyaji, Tucker and coworkers have synthesized a ditopic receptor that contains nitrophenylurea and crown ether units linked by a ferrocene moiety.[5] The color change of the receptor solution occurs only in the presence of fluoride, and in the absence of a potassium cation. Similarly, addition of fluoride to the solution of the heteroditopic receptor reported by Yen and coworkers causes the color of the solution to change from light-yellow to orange-red.[6]

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† Electronic supplementary information (ESI) available: Synthesis and characterization data for compound **1**, general procedures used for ^{1}H NMR and UV-vis titration experiments. See DOI: 10.1039/c0cc05537a

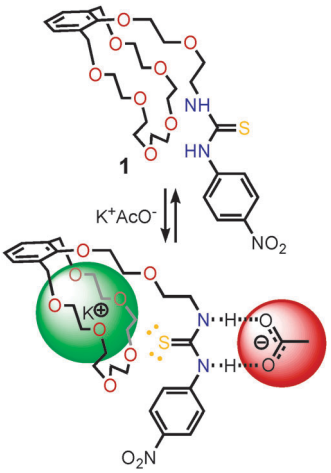


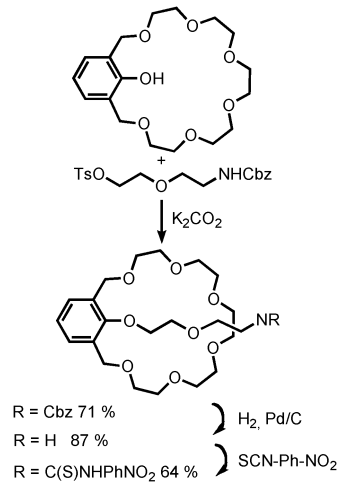
Fig. 1 Proposed binding mode for the complex of **1** and KAcO.

Subsequent addition of Na^+ or Li^+ results in loss of the orange-red color.

We report herein the design, synthesis, salt binding and sensing ability of novel heteroditopic molecular sensor **1** which features both a cation binding site in the form of benzocrown ether and an anion binding site/chromophore in the form of a nitrophenylthiourea moiety (Fig. 1). The most challenging problem in the design of convergent heteroditopic receptors is the proper spatial arrangement of the binding sites. Therefore, to ensure close proximity of the binding domains, the thiourea pendant group was situated at an intraannular position of the benzocrown moiety. Furthermore, the urea and crown ether subunits were linked through a five-atom spacer containing an oxygen atom (an additional cation binding site).

The synthesis of the target receptor was accomplished in three steps starting from known 2-hydroxy-1,3-xylyl-21-crown-6 (Scheme 1).[7] The alkylation of the phenolic group with 2-(2-Cbz-aminoethoxy)ethyl tosylate in the presence of K_2CO_3 and subsequent cleavage of the protecting group gave the amino derivative, which after acylation with nitrophenylthiocyanate led to receptor **1** in 40% overall yield as pale-yellow crystals.

The binding properties of receptor **1** were initially investigated by ^{1}H NMR spectroscopic titration methods in CD_3CN solution. Addition of alkali metal cations to the 2 mM solution of **1** causes small, nonlinear upfield shifts of aliphatic and benzylic protons of the macrocycle, indicating cation binding to the crown ether subunit. Nonlinear regression of the



Scheme 1 The synthesis of compound **1**.

Table 1 Cation association constants data

	Association constants/M^{-1} [a]		
Receptor	Na^+	K^+	TBA^+ [b]
1	70	1270	—[c]

[a] Determined in dry CD_3CN at 295 K by the ^1H NMR technique, errors estimated to be <10%. Cations were added as their hexafluorophosphate salts. [b] TBA—tetra-*n*-butylammonium cation. [c] No binding.

resulting titration curves suggests 1 : 1 complex stoichiometry and the experimental stability constants are listed in Table 1.

Table 1 clearly shows that receptor **1** can effectively bind a potassium cation, whereas binding of a sodium cation is much weaker. No perturbation of the ^1H NMR spectra was observed upon addition of $TBA^+PF_6^-$. Interestingly, alkali cation addition to the solution of **1** leads to significant downfield shifts of both thiourea NH signals ($\Delta\delta \leq 0.3$). This effect may be attributed to breaking of the intermolecular hydrogen bonds between thiourea NH's and ether oxygens of the macrocycle. This may be tentatively attributed to a conformational change of the pendant group upon cation complexation, allowing interaction of the cation with the sulfur lone pair (Fig. 1).

The addition of tetra-*n*-butylammonium acetate or benzoate to a solution of **1** causes dramatic upfield shifts of the thiourea NH signals ($\Delta\delta > 4$ ppm) indicating strong interaction between the receptor and the anions. The anion binding of **1** is too strong to allow quantitative analysis of the ^1H NMR spectroscopic titration binding isotherms to be determined.[8] However, after addition of carboxylate anions to a solution of receptor **1**, the solution changes from colorless to yellow. Thus, anion-binding properties of **1** could be probed by UV-vis spectroscopic analysis.

Upon addition of anions to the 4.8×10^{-5} M solution of **1**, the band centered at 344 nm undergoes a distinct red-shift to 367 nm. This shift is attributed to the hydrogen bond formation between the two thiourea NH groups and the two oxygen atoms of the carboxylate ion. Importantly, no additional absorption band at a longer wavelength is observed. The presence of an absorption band at *ca.* 465 nm is an indication of the anion-induced deprotonation of one of the thiourea NH hydrogen atoms.[9] Moreover, the presence of two sharp isosbestic points at 256 and 350 nm implies that only two species coexist at the equilibrium point. The 1 : 1 binding stoichiometry was verified by a Job plot analysis. The association constants calculated by the nonlinear regression analysis of binding isotherms are presented in Table 2.[10]

Table 2 Anion association constants data

Anion	Cation	K_a/M^{-1} [a]
AcO^-	TBA^+	103 000
	K^+	278 000
$PhCOO^-$	TBA^+	83 000
	K^+	273 000
$H_2PO_4^-$	TBA^+	16 000

[a] Determined at a receptor concentration of 5.8×10^{-5} M in dry CH_3CN at 295 K by UV-vis spectroscopic titration, errors estimated to be <10%. Cations and anions were added as their hexafluorophosphate and tetra-*n*-butylammonium salts, respectively.

The receptor **1** binds strongly to the Y-shaped carboxylate anions, which is a typical feature of thiourea based receptors.[11] The binding of tetrahedral anions, like dihydrogenphosphate, is significantly weaker. No perturbations of the UV-vis spectrum of **1** are observed upon addition of Cl^-, Br^-, NO_2^-, HSO_4^- or BF_6^- ions (tetra-*n*-butylammonium salts) in the presence or absence of metal cation (hexafluorophosphate) salts.

The presence of various alkali metal cations significantly alters the anion binding ability of receptor **1** (Table 2). Specifically, titration of a solution containing receptor **1** and 1 molar equivalent of $NaPF_6$ with acetate provides $K_a \approx 50\,000$ which indicates that the sodium cation lowers the acetate affinity of **1**. Since in the presence of Na^+ some perturbation of the acetate binding isotherm was observed, an analogous titration was conducted in the presence of 5 molar equivalents of $NaPF_6$ (Fig. 2). Addition of the first equivalent of acetate only slightly reduced anion binding affinity. After this point, the binding isotherm initially decreases before rising to a maximum. This clearly indicates that the sodium cation is able to sequester the acetate anion from the receptor which prevents anion–receptor binding.[12] There are likely two factors that contribute to this effect. First, the affinity of receptor **1** for Na^+ is low and hence

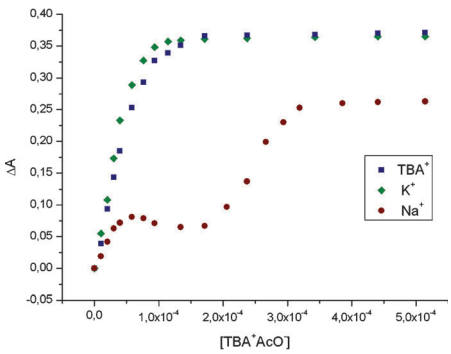


Fig. 2 Titration binding profiles for receptor **1** with acetate (TBA salt) in the presence of various cations (PF_6^- salts). [**1**] = 5.8×10^{-5} M, CH_3CN, T = 295 K, λ = 367 nm.

the concentration of uncomplexed sodium cations is high. Second, the ion-pair association constants for sodium salts in most organic solvents are relatively high (*e.g.* for sodium benzoate K_a = 200 in DMSO), therefore formation of the sodium acetate salt in solution is favored.[13] Similar effects were observed for a benzoate anion whereas dihydrogenphosphate addition resulted in the rapid formation of a precipitate.

In contrast, titration experiments of **1** with acetate and benzoate in the presence of potassium cation showed enhancement of carboxylate affinities (Table 2).[14] The metal-induced enhancement factors (K_{K^+}/K_{TBA^+}) for acetate and benzoate are 2.7 and 3.2 respectively. Such cooperative effects could be rationalized considering the formation of ligand-separated ion pairs where the interactions between the anion and the cation occur through a thiourea group (Fig. 1). On the other hand, such cooperative effects are in agreement with a trend that metal-induced enhancements are moderate for the more basic anions such as carboxylates.[15]

Unfortunately, the addition of alkali cations to the solution of dihydrogenphosphate led to the formation of a precipitate.

Finally, Fig. 3 displays the visual aspects of acetate ion recognition and sensing in the presence of alkali metal cations. Each vial contains a 7.7×10^{-4} M solution of **1** in CH_3CN. The addition of five equivalents of TBAAcO induces the appearance of a bright yellow color (vial b). Subsequent addition of five equivalents of sodium ions to this solution causes disappearance of the yellow color (vial c). As mentioned above, this phenomenon is caused by sequestration of the acetate anion from the receptor to form a more stable ion-pair in solution. Upon addition of potassium cations, however, the initial yellow color substantially fades to a pale yellow color (vial d).[16] This observation supports the proposed salt binding mode illustrated in Fig. 1. The cation interaction with the sulfur lone pair promotes electron density transfer from the anion–**1** complex to the cation, which alters the intensity of the UV-vis spectra.

In conclusion, we have succeeded in preparing a heteroditopic chromogenic ion-pair sensor **1** that is able to bind and optically detect acetate as well as benzoate anions. In the presence of a potassium cation the affinity of **1** for both acetate and benzoate increases, which indicates that the cation and anion are coordinated to the receptor in a cooperative fashion. In contrast, a sodium cation can sequester a carboxylate anion away from receptor **1**. These different modes of cation and anion binding are accompanied by specific color changes of solutions of sensor **1**. Thus, sensor **1** allows for the chromogenic detection and discrimination of tetra-*n*-butyl, sodium and potassium acetates.

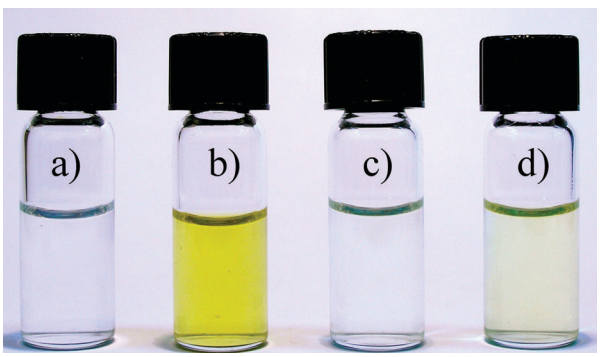


Fig. 3 Changes in the color of 7.7×10^{-4} M solutions of receptor **1** in CH_3CN. (a) **1**; (b) **1** + TBAAcO (5 equiv.); (c) **1** + TBAAcO (5 equiv.) + $NaPF_6$ (5 equiv.); (d) **1** + TBAAcO (5 equiv.) + KPF_6 (5 equiv.).

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