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Selective $NaNO_2$ recognition by a simple heteroditopic salt receptor based on L-ornithine molecular scaffold†

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This paper describes the development of a simple heteroditopic salt receptor consisting of aza-18-crown-6 (a cation binding domain), nitrophenylurea (an anion binding domain) and an additional metacrylamide group appended to the carboxylic, α-amine and δ-amino groups of L-ornithine. Detailed binding studies showed that this receptor is capable of effectively and selectively binding $NaNO_2$ salt.

Nitrite is a naturally occurring anion that is a part of the nitrogen cycle and is of biological, environmental, and synthetic significance.[1] Nitrite is not stable and does not usually accumulate in the environment, but it can be transformed rapidly into nitrosamines, which are potent carcinogens.[2] Although drinking water levels of nitrite are usually low, it is extensively used as a food preservative, especially for curing meat. Excessive nitrite levels in the human body result in methemoglobinemia, also known as "blue baby syndrome", and have been linked to heightened risk of gastrointestinal cancer.[3] Given the significant influence of nitrite on the environment and on human health, it is advantageous to control and regulate its concentration.

Interestingly, nitrate coordination is rarely included in studies of anion recognition by monotopic molecular receptors.[4] In such studies, noncompetitive tetra-*n*-butylammonium (TBA) salts are often used. However, the luxury of noncompetitive counterions is not available in real-life applications; hence inter-ion competition can be significant.[5] Therefore, the design and synthesis of effective and selective molecular receptors able to bind nitrite salts of hard countercations is a field of great interest.[6]

In this context, Smith *et al.* proposed a heteroditopic salt receptor that consists of 1,10-diaza-18-crown-6 and 1,3-phenylenedicarboxamide subunits that cooperatively associate with alkali chlorides as a contact ion pair.[7] Although a single crystal X-ray structural analysis revealed that this receptor is also able to bind sodium nitrite, unfortunately no quantitative solution binding study was performed.[8] We recently reported the synthesis of a heteroditopic macrotricyclic ammonium salt receptor capable of strongly complexing ammonium nitrite in highly competitive solvent.[9] That receptor is able to extract ammonium nitrite from the aqueous to organic phase. Fabbrizzi and co-workers reported a heteroditopic receptor based on aza-crown thioether linked through ethylene-spacer to a nitrophenylurea/thiourea moiety.[10] Studies in acetonitrile demonstrated that as opposed to the TBA cation, in the presence of soft Ag^+ cations the binding of nitrite anions is enhanced by nearly 10^3-fold. Herein, we describe an amino acid-based heteroditopic receptor that effectively and selectively associates with sodium nitrite (Fig. 1).

Recently we described the design, synthesis and binding studies of heteroditopic salt receptor **2**. This receptor consists of aza-18-crown-6 (cation binding domain) and nitrophenylthiourea (anion binding domain) appended to the carboxylic and α-amine groups of L-ornithine, respectively. The

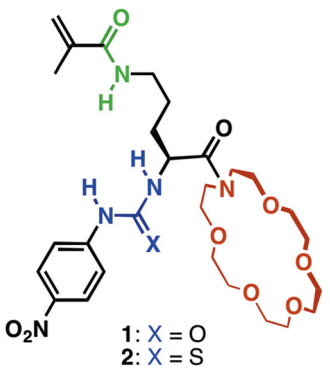

Fig. 1 The structures of receptors **1** and **2**.

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ornithine δ-amino group was converted to a metacrylamide function, used for the preparation of copolymers containing **2**.[11] Receptor **2**, in the presence of soft, noncoordinating TBA cations, strongly associates with acetates and less strongly with chlorides, whereas nitrates are bound only weakly. However, when the hard sodium cation is present, the binding of acetate and chloride is greatly suppressed, whereas the strength of nitrate binding increases. We ascribed the cooperativity of $NaNO_3$ binding to the formation, inside the receptor, of the thiourea group separated ion pair. We assumed that the coordination of the sodium cation to the crown ether moiety is supported by its interaction with the thiourea sulfur atom, whereas the anion is bound by thiourea NHs. Therefore, we envisioned that replacing the soft sulfur atom with a hard oxygen atom should increase the Na^+ binding strength.[12] Thus, we report here a detailed binding study of the urea group containing heteroditopic salt receptor **1**. The influence of receptor **1** subunits on cation, anion, and salt recognition is also presented.

The cation binding properties of receptors **1** and **2** were probed in CD_3CN by the ^1H NMR titration method. The addition of sodium and potassium PF_6^- salts to a 2.7 mM solution of the receptor caused variation of ^1H NMR chemical shifts of the signals corresponding to crown ether $-O-CH_2$ protons. Analysis of the binding isotherm so obtained revealed that receptor **2**, containing a thiourea group, coordinates to the sodium cation with the association constant value of K_a = 6460 M^{-1}. However, receptor **1**, incorporating a urea group, binds the sodium cation so strongly that the association constant value cannot be accurately determined using the ^1H NMR spectroscopic titration method (>50 000 M^{-1}). The dramatic increase in cation binding abilities of receptor **1** as compared to **2** can be attributed to the coordination of the urea oxygen atom to the crown ether complexed cation. The interaction of the Na^+ with an oxygen lone pair reduces the electron density on the urea oxygen atom and consequently the whole urea group. This effect has been confirmed experimentally. In particular, the addition of $NaPF_6$ to the receptor **1** solution causes a downfield shift of the urea N–H protons, indicating that sodium coordination increases the acidity of urea NHs (Fig. S1, ESI†).[13] Furthermore, the presence of sodium cations induced a blue shift of the charge transfer bands in the UV-vis spectrum of **1**, another assumption of the proposed sodium-binding mode. The metacrylamide NH of the receptor side arm is not affected by Na^+ cation addition, suggesting no participation of methacrylamide C=O in cation recognition.

Quantitative information about the binding ability of receptor **1** toward anions was obtained by ^1H NMR titration experiments in CD_3CN. First, we verify that no perturbation of NMR spectra was observed upon addition of $TBAPF_6$, which suggests no interaction of these ions with receptor **1**. The addition of TBA anion salts caused a considerable downfield shift of both urea NHs. Additionally, a less pronounced downfield shift was also observed for methacrylamide NH. This behavior could be ascribed to the formation of hydrogen bonding interactions involving anions and urea and amide groups. Analyzing the complexation induced shifts of all three NH protons of **1** using the curve fitting program HypNMR enabled the association constants listed in Table 1, to be calculated.

Table 1 Association constants (K_a) for the interactions of **1** with anions in the absence or presence of 1 equivalent of sodium cations[a]

	TBA^+	Na^+	K_{Na}/K_{TBA}
AcO^-	10 700	2340	0.22
Cl^-	2040	930	0.46
Br^-	320	3310	10.34
NO_2^-	1180	7590	6.43
NO_3^-	110	850	7.73
HSO_4^-	490	690	1.41

[a] ^1H NMR, solvent CD_3CN, temperature 293 K, [**1**] = 2.6 mM, [$NaPF_6$] = 2.6 mM, anions added as TBA salts [TBAX] < 20 mM; M^{-1}, errors < 10%.

A number of trends may be observed in these data. First, as expected, the urea containing receptor **1** binds anions (in the form of TBA salts) more weakly than the thiourea analogue **2**.[14] For example, chloride is bound to receptors **1** and **2** with association constants 2040 and 13 990 M^{-1}, respectively. Second, the association constants of the oxoanions examined are in agreement with the common trend observed for thiourea and urea based anion receptors.[15]

The affinity of receptor **1** for anions in the presence of the hard sodium cation was then established. As can be seen from the data collected in Table 1 and Fig. 2, two different trends are observed. In the presence of sodium cations the association constants of the strongly coordinated anions such as acetate and chloride decrease considerably. This can be explained in terms of the formation of strong ion-pairs outside the receptor. On the other hand, the association constants of anions that TBA salts bind to the receptor **1** less strongly are greatly enhanced in the presence of cobound Na^+ cations. The largest positive cooperativity factor, K_{Na}/K_{TBA} = 10.3, is observed for the simultaneous binding of sodium and bromide ions. However, the enhancement of nitrate and nitrite anion binding is also significant (7.7 and 6.4 respectively). It is noteworthy that in the case of triourea analogue **2**, moderate

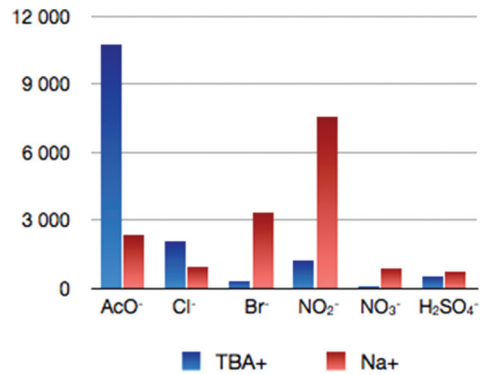

Fig. 2 Comparison of receptor **1** selectivity in the absence or presence of 1 equivalent of Na^+.

positive cooperativity (~2.7) was achieved only for bromide and nitrate binding. To assure that this positive cooperativity effect originates from ion pair formation inside the receptor, we performed a binding study of an analog of receptor **1** lacking the crown ether moiety (receptor **3**, ESI†). The K_a of complexes of that analog with $TBANO_2$ is 600 M^{-1}, whereas the presence of sodium cations induces ion-pair formation outside the receptor and salt precipitation. This clearly manifests the significance of the cation binding domain in salt recognition.

The coordination of the sodium cation to receptor **1** dramatically alters the anion binding selectivity. As can be seen in Table 1 and Fig. 2, in the absence of Na^+, receptor **1** preferentially binds the most basic acetate anions. However, in the presence of cobound sodium cations the combination of negative and positive cooperative effects causes receptor **1** to strongly and selectively bind nitrate anions. This shows that heteroditopic receptors could be used for the effective binding of salts of hard cations and anions that usually poorly coordinate to monotopic receptors.

As mentioned above, the addition of anions to free **1** or the **1**·Na^+ complex results in downfield shifts of the metacrylamide NH resonance ($\Delta\delta$ 0.15–1.34). This suggests that the side arm group of receptor **1** can support the anion binding. To evaluate the influence of this group on anion binding strength, ^{1}H NMR titration was carried out with a lysine based salt receptor (receptor **4**, Scheme S2, ESI†). Interestingly, the absence of amide group in the receptor side arm results in a considerable decrease in $TBANO_2$ complex stability (K_a = 790 M^{-1}). However, in the presence of sodium cations the association constant of the lysine based receptor for the nitrate anion is nearly half that of receptor **1** (K_a = 4170 *vs.* 7590 M^{-1}). Hence, the additional anion-binding domain located on the receptor side arm is of particular importance for effective ion pair binding.

To gain a better understanding of the mechanisms of cation, anion, and salt binding by receptor **1**, density functional theory calculations were performed. Free receptor **1** displays numerous accessible low-energy structures, which is consistent with a conformationally flexible molecule. However, the **1**·Na^+ complex shows one low-energy conformation. In this structure, sodium cation is coordinated to crown ether oxygen atoms (the average O···Na^+ distance is 2.44 Å), but not to the nitrogen atom. As expected, Na^+ binding is supported by the interaction of Na^+ with the urea oxygen atom (C═O···Na^+ distance is 2.23 Å). This coordination fixes the nitrophenylurea moiety orientation and exposes the NH groups to the outside of the molecule. Thus, the results of solution binding studies and molecular modeling unanimously suggest that the coordination of the urea C═O group to the cation complexed by the crown ether is responsible for the enhancement of anion binding and consequently for the cooperativity effect. The calculated structure of the **1**·$NaNO_2$ complex reveals a sodium cation binding coordination mode very similar to the **1**·Na^+ complex (Fig. 3). As anticipated, the NO_2^- anion oxygen atoms form hydrogen bonds to both urea NHs (O···H–N distance ~2.94 Å). Moreover, anion binding is supported by the additional metacrylamide–NH hydrogen bond (O···H–N distance is 2.91 Å). Additionally, we have calculated the Mulliken partial charges on the urea hydrogen atoms and detected a small increase of the partial charge from 0.49 to 0.51 (average value for both protons) after cation coordination, which corresponds to an increased acidity of these protons. Thus, solution-binding studies assisted by molecular modeling show the importance of participation of the side arm group in the anion binding event.

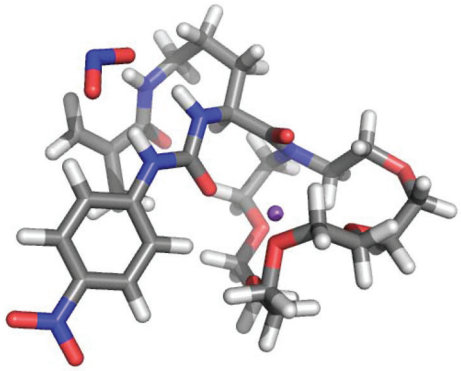

Fig. 3 The calculated structure of the **1**·$NaNO_2$ complex.

In conclusion, we have developed a simple heteroditopic salt receptor based on the L-ornithine molecular scaffold. This receptor is capable of highly effective and selective association with nitrate anions in the presence of the hard sodium cation, as judged from ^{1}H NMR titration experiments. Detailed solution binding studies supported by molecular modeling revealed that urea C═O group coordination to the crown ether complexed sodium cation is responsible for the reinforcement of anion binding to urea NHs. The metacrylamide group located at the side arm of receptor **1** provides an important additional binding domain for anion recognition.

Acknowledgements

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