Dalton Transactions

PAPER

View Article Online
View Journal | View Issue

Cite this: *Dalton Trans.*, 2014, **43**, 8515

Boosting the salt recognition abilities of L-ornithine based multitopic molecular receptors by harnessing a double cooperative effect†

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Received 24th February 2014,
Accepted 21st March 2014

DOI: 10.1039/c4dt00576g

www.rsc.org/dalton

A family of L-ornithine based salt receptors **1a–f** was synthesized, bearing a cation binding site and multiple anion binding sites (nitrophenylurea and amide groups) that may simultaneously associate with a single anion. The variation in H-bond donor abilities of one of these anion binding sites has relatively little influence on NO_2^- anion binding when the anion is accompanied by a noncoordinating TBA cation. However, in the presence of a sodium cation, which strongly coordinates with the cation binding domain of **1a–f**, the increased H-bond donor abilities of the anion binding group result in a significant enhancement of NO_2^- anion binding. A direct correlation between the anion binding site H-bond donor tendencies and the binding cooperation of sodium cations and nitrite anions was also observed. Cation complexation fixes the nitrophenylurea moiety orientation and exposes that domain to bind anions. This cation and anion cooperation induces a second cooperative effect, namely the simultaneous association of a single anion with both urea and amide binding groups. Receptor **1d** was found to be highly selective for $NaNO_2$ over sodium bromide and nitrate. A transport experiment using a bulky liquid membrane showed that this receptor can effectively transport $NaNO_2$ from the aqueous phase through the organic phase.

Introduction

In both cation and anion binding by monotopic molecular receptors, the complexed ion is accompanied by a counterion. Thus for a receptor to associate with a target ion, it must compete with the counterion. To overcome this problem, the so-called noncompeting counterions are often used in laboratory applications. However, in many real-life applications, the luxury of noncompetitive counterions is not available, and hence inter-ion competition can be significant. The only way to eliminate this problem is through simultaneous binding of both the anion and cation, *i.e.* salt binding.[1] This can be achieved using heteroditopic receptors to simultaneously bind the anion and the cation.[2] A potential advantage to be gained by covalently linking the anion and the cation binding sites is the possibility of positive binding cooperativity, which enhances the selectivity and efficacy of ionic species recognition.[3] Moreover, the complexation of both ions by a ditopic receptor enhances the salt lipophilicity, thus facilitating its solubilization, extraction and membrane transport.[4] However, in spite of their potential applications in various fields, the number of such ion pair receptors remains limited. Among other factors, this is due to the difficulties associated with the synthesis of heteroditopic receptors, which obviously must consist of at least two properly oriented heterotopic binding regions. Moreover, many of the most effective salt receptors have a multi-macrocyclic structure and their synthesis requires the application of high-dilution techniques.[3a–c,g,h,4a,5] Therefore, fine-tuning of the structure, and concurrently the binding properties, of many heteroditopic receptors is very problematic. Furthermore, due to the "closed" structure of these receptors it is difficult to introduce an additional structural element into the system, such as a new binding domain, chromophore/fluorophore or increased solubility/lipophilicity function. Therefore the synthesis of multitopic receptors that can effectively recognize ion pairs and are concurrently prone to structural modification is an important area of interest.

Recently, we reported the synthesis and binding of a heteroditopic salt receptor based on the L-ornithine scaffold.[6] This receptor consists of aza-18-crown-6 (cation binding domain) and nitrophenylthiourea (anion binding domain) appended to the carboxylic and α-amino groups of L-ornithine, respectively. Moreover, the ornithine δ-amino group was converted to a methacrylamide function and used for the

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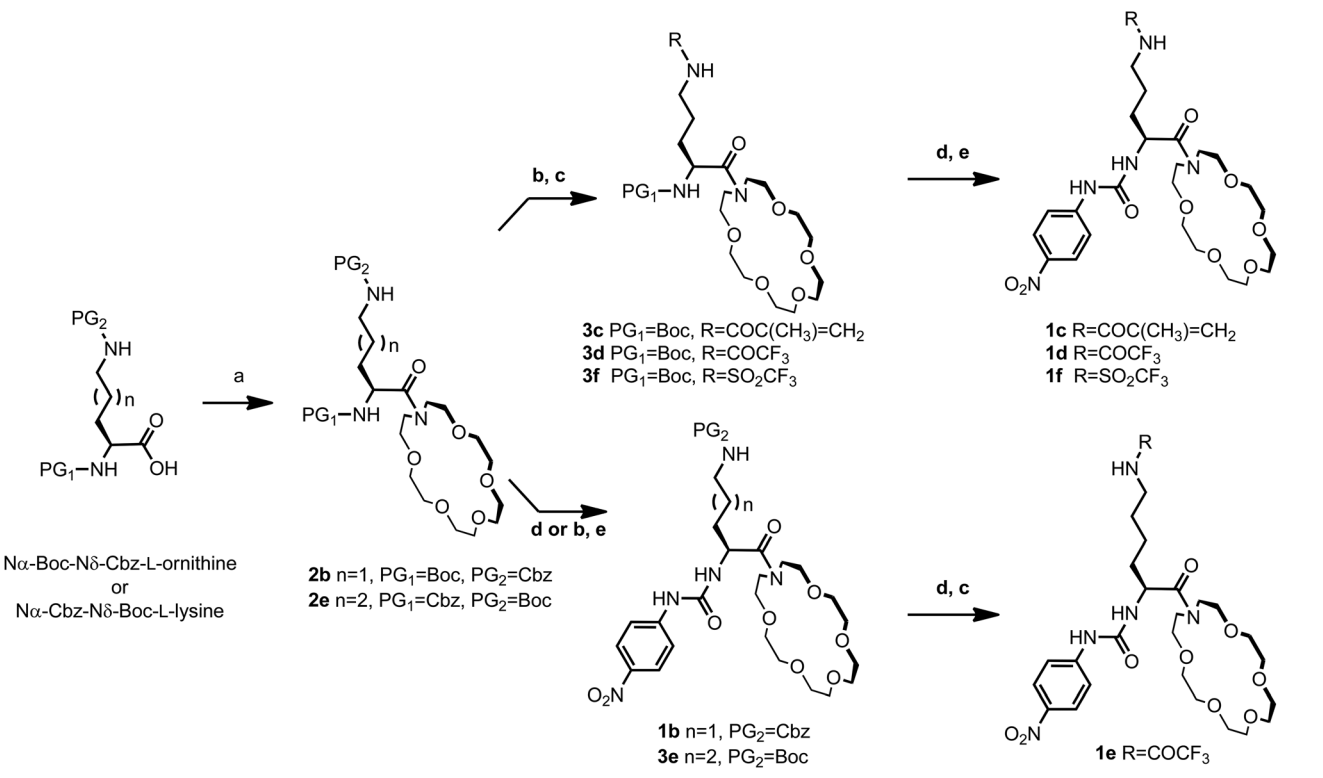
† Electronic supplementary information (ESI) available: Spectroscopic data for all new compounds, as well as experimental procedures for binding and extraction studies. See DOI: 10.1039/c4dt00576g

preparation of copolymers containing the receptor. Further study revealed that this receptor is susceptible to structural changes that alternate its binding propensity. For example, we found that replacing the soft sulfur atom of the nitrophenylthiourea binding domain with a hard oxygen atom (receptor **1c**) reinforced Na^+ cation binding, which affected anion and salt binding.[7] In particular, this modification resulted in an decreased anion binding strength, although an immensely increased salt binding strength and selectivity towards $NaNO_2$ were observed. 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 NH protons. Moreover, we noticed that the methacrylamide group located on the side arm of receptor **1c** provides an additional binding domain for anion recognition and we showed that the strength of anion and salt binding is decreased when this group is not present. Based on this observation we envisioned that introducing a stronger H-bond donor group to the L-ornithine side arm should increase the anion and consequently the salt association strength. Thus, here we report a study concerning the influence of such receptor side arm modifications on the anion and salt binding effectiveness. For the most effective receptor, we also describe a detailed binding study and preliminary extraction and membrane transport experiments.

Results and discussion

Receptors **1b–f** (Scheme 1 and Fig. 1) were prepared starting from commercially available Nα-Boc-Nδ-Cbz-L-ornithine or Nα-Cbz-Nγ-Boc-L-lysine. The DCC-promoted coupling of starting compounds with aza-18-crown-6 leads to crown ether functionalized amino acids **2b** and **2e** with ~90% yield. Subsequent deprotection of the Cbz group of the ornithine derivative **2b** and acylation of the δ-amine function gave compounds **3c**, **3d** and **3f**. Finally, TFA-promoted cleavage of the Boc group followed by acylation of the resulting amines with 4-nitrophenylisocyanate afforded receptors **1c**, **1d** and **1f**. The L-lysine based receptor **1e** was prepared from compound **2e** by deprotection of the Nα-Boc group, acylation with 4-nitrophenylisocyanate and subsequent deprotection of the side arm amine group and its acylation with trifluoroacetyl anhydride. Receptor **1a**, lacking an additional binding domain, was prepared in an analogous manner starting from *N*-Boc-L-leucine.

Since the previously reported receptor **1c** is highly selective for sodium nitrite, we decided to screen the binding ability of receptors **1a–f** for the nitrite anion and its sodium salt. The binding experiments were conducted in CD_3CN using the ^1H NMR titration technique. The addition of tetra-*n*-butylammonium (TBA) nitrite to a 2.6 mM solution of receptor or receptor containing one equivalent of $NaPF_6$ caused nonlinear downfield shifts of both urea protons and amide protons located on



Scheme 1 Synthesis of receptors **1b–f**. *Reagents and conditions*: (a) DCC, 1-aza-18-crown-6, CH_2Cl_2, 0 °C to r.t., 91–92%; (b) H_2, Pd/C, MeOH–THF, r.t., quantitative; (c) **3c**: methacryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to r.t., 50%; **1e** and **3d**: trifluoroacetyl anhydride, Et_3N, CH_2Cl_2, 0 °C to r.t., 73 and 72%; **3f**: trifluoromethanesulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C to r.t., 91%; (d) TFA–CH_2Cl_2 (1 : 1), r.t., quantitative; (e) 4-nitrophenyl isocyanate, Et_3N, THF, **1c**: 75%, **1d**: 60%, **1f**: 72%, **3e**: 81%.

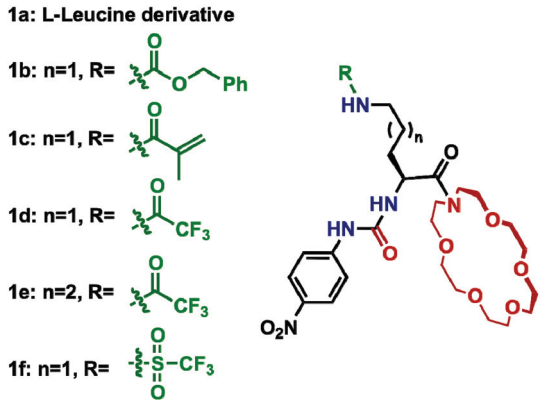


Fig. 1 The structure of amino acid based salt receptors.

Table 1 Association constants (K_a) for interactions of receptors **1a–f** with NO_2^- in the absence or presence of one equivalent of sodium cations[a]

	δ_{NH}Amide	$TBANO_2$	1 eq. $NaPF_6$ $TBANO_2$	K_{Na}/K_{TBA}
1a	—	790	4170	5.3
1b	5.7	795	4250	5.3
1c	6.7	1180	7590	6.4
1d	7.6	1450	19 000	13.1
1e	7.6	1400	8300	5.9
1f	7.9	—	—	—

[a] ^{1}H NMR, solvent CD_3CN, temperature 293 K, [**1**] = 2.6 mM, [$NaPF_6$] = 2.6 mM, [$TBANO_2$] < 20 mM; M^{-1}, errors < 10%.

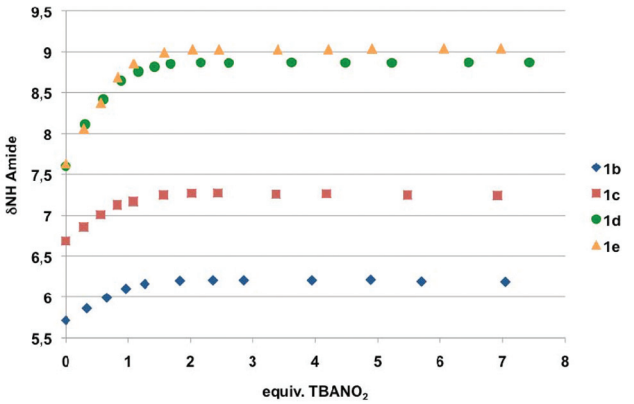


Fig. 2 ^{1}H NMR titrations of receptors **1b–e** with $TBANO_2$ in the presence of 1 equivalent of $NaPF_6$. Profiles based on the chemical shift (δ, ppm) of amide protons.

the amino-acid side arm, if applicable. The association constants calculated by nonlinear regression analysis of the binding isotherms are presented in Table 1.

The receptors listed in Table 1 are arranged in the order of increasing H-bond donor ability of the side arm group, as estimated on the basis of the amide-NH chemical shift of the free receptors (Table 1, Column 2 and Fig. 2).[8] As shown in Table 1, the L-leucine based receptor **1a**, without an additional anion binding domain, and receptor **1b**, possessing a weak H-bond donor HNCbz function, associate with the nitrite anion only moderately. Increasing the hydrogen bond donor ability of the side arm group by introducing methacrylamide **1c** or even the trifluoroacetyl group **1d** did cause an enhancement in $TBANO_2$ association, but this increase was not great, at least not quite twofold. Unfortunately, the most acidic trifluoromethanesulfonamide group is readily deprotonated by an NO_2^- anion, thus **1f** cannot be used for anion and salt binding studies.

There is a much more distinct increase in binding strength with the amplified H-bond donor ability of the side arm domain when the nitrite anion associates with **1**·Na^+ complexes generated by the addition of one equivalent of $NaPF_6$ to the receptor solution. Specifically, while sodium complexes of receptors **1a** and **1b** bound NO_2^- with association constants of approximately 4200 M^{-1}, the association exhibited by **1c**·Na^+ is almost two times stronger, whereas the trifluoroacetyl derivative **1d**·Na^+ was found to bind nitrite with the remarkable association constant value of 19 000 M^{-1}. Therefore, increasing the H-bond donor ability of the side arm anion-binding group results in 4.5 times stronger binding of the $NaNO_2$ salt.

Since the electronic effects of the side arm group of **1** play a very significant role in salt recognition, we decided to investigate how effects associated with the geometrical features of the binding cavity influence $NaNO_2$ binding. Therefore, we prepared the L-lysine based receptor **1e** with the increased distance between the urea and trifluoroacetamide groups. Interestingly, we found that this modification did not influence the strength of $TBANO_2$ binding, although $NaNO_2$ binding is greatly diminished compared to receptor **1d**. These results make it clear that a suitable combination of electronic and geometric factors is necessary for effective recognition of ion pairs.

Positive cooperation (*i.e.* an enhancement of anion binding due to the presence of a cation) can be clearly seen for all the receptors studied, **1a–d** (Table 1, Column 5). The association constants for nitrite binding in the presence of sodium cations considerably increase compared to the association constants for nitrite anions accompanied by non-coordinating TBA cations. The highest cooperativity factor was found for receptor **1d**, whose association with nitrite is over 13 times stronger in the presence of sodium cations. Moreover, inspection of Table 1 revealed that the cooperativity in salt binding correlates well with the H-bond donor tendency of the amide located on the aminoacid side arm. Given that the increased H-bond donor tendency has a relatively small impact on anion binding but a significant influence on anion binding in the presence of sodium cations, we tentatively attributed this phenomenon to cooperative effects.

The cooperativity between sodium and nitrate recognition of receptors **1a–d** could be ascribed to coordination of the urea oxygen atom to the crown ether complexed cation. In particular, the coordination of the urea oxygen atom to Na^+ reduces the electron density of the urea group, which is reflected in the blue shift charge transfer band as well as the downfield shift

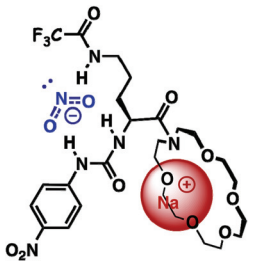


Fig. 3 A tentative sketch of the binding mode in the **1d**·$NaNO_2$ complex.

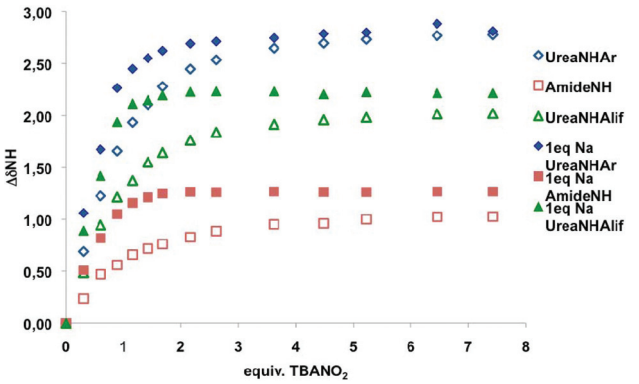


Fig. 4 ^{1}H NMR titration of receptor **1d** with $TBANO_2$ in the presence and absence of 1 equivalent of $NaPF_6$. Open symbols refer to the titration in the absence of sodium cations; full symbols refer to the titration in the presence of sodium cations.

of the urea N–H protons.[7] We assume that this coordination not only increases the acidity of the urea NHs but also fixes the nitrophenylurea moiety orientation and exposes that domain to bind anions together with the amide function (Fig. 3). In consequence, cation and anion cooperation induces a second cooperative effect, namely simultaneous cooperation of both anion binding domains in complexation of a single ion.

After screening the receptors' binding affinity for the NO_2^- anion and $NaNO_2$ salt, the most effective receptor **1d** was further explored in detail. First, its affinity for K^+, NH_4^+ and Na^+ cations in the presence of the non-coordinating PF_6^- anion was established. The addition of cations to a 2.6 mM solution of **1d** caused nonlinear downfield shifts of the crown ether protons. The association constants calculated by nonlinear regression analysis of the binding isotherms revealed that both NH_4^+ and K^+ cations coordinated with the receptor only moderately, with association constant values of K_a = 420 and 740 M^{-1}, respectively. As for the previously reported receptor **1c**, the association constant for Na^+ was found to be higher than 5×10^4, which precluded quantitative K_a determination.[9] Nevertheless, these experiments proved the high selectivity of receptor **1d** for sodium cation recognition. Therefore, the ion-pair binding experiments were carried out in the presence of sodium cations.

The affinity of receptor **1d** towards selected anions and their sodium salts was then examined. Anion addition to **1d** solution caused nonlinear downfield shifts of both urea NH protons and amide protons located on the side arm of the receptor (Fig. 4). Analyzing the complexation induced shifts of all three NH protons of **1d** using the curve fitting program HypNMR enabled the association constants listed in Table 2 to be calculated.

As Table 2 shows, receptor **1d** associates moderately with TBA salts of chloride and nitrite and weakly with bromide and nitrate anions, whereas fluoride anions cause receptor deprotonation. Similar to nitrite anions (see Table 2), the association constant values for other anions are only slightly higher for receptor **1d** than for receptor **1c**.[7] For example, nitrate is bound to receptors **1c** and **1d** with association constants 110 and 150 M^{-1}, respectively. These results further corroborate the findings from NO_2^- binding studies of receptors **1a–e** that even considerable enhancement of the H-bond donor ability of the amide group did not cause a significant increase in anion binding strength. Interestingly, the same trend is observed for anion binding in the presence of sodium cations, with the notable exception of nitrite anions. For example, sodium nitrate is bound to receptors **1c** and **1d** with association constants 850 and 1250 M^{-1}, respectively.[7]

However, the binding ability of the side-arm group has a significant impact on the salt binding selectivity. Specifically, the highest ion pair binding cooperativity was found for sodium nitrite, with a cooperativity factor of 13.1. The cooperativity factors for bromide and nitrate anions in the presence of hard sodium cations are similar for receptors **1d** and **1c**. In consequence, the introduction of a strong H-bond donor group into the side arm of receptor **1d** not only causes great enhancement of $NaNO_2$ binding strength but also makes receptor **1d** more selective towards this salt. This result can be attributed to both the spatial and electronic demand of the binding domains of the receptor. Specifically, we assume that the urea group mainly controls the geometry of the complexed anion, and it is well established that this group preferentially binds Y-shaped coplanar anions like nitrate or nitrite. Moreover, the nitrite anion has the strongest H-bond accepting ability among the anions studied, which can be determined on the basis of its conjugated acid pK_a value.

Table 2 Association constants (K_a) for interactions of receptor **1d** with anions in the absence or presence of 1 equivalent of sodium cations[a]

	TBA^+	Na^+	K_{Na}/K_{TBA}
F^-	—[b]	—[b]	—
Cl^-	3100	—[c]	—
Br^-	390	3450	8.8
NO_2^-	1450	19 000	13.1
NO_3^-	150	1250	8.2

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

Table 3 Solid/liquid extraction experiments data[a]

	δ_{NH}Urea	δ_{NH}Urea	δ_{NH}Amide	**1d**·salt[b] [%]
1d	8.30	7.76	6.93	—
NH_4NO_2	8.88	7.95	7.03	—
KNO_2	9.05	8.07	7.29	—
$NaNO_2$	9.86	8.65	7.83	47.2
NaBr	9.74	8.27	7.60	30.1
$NaNO_3$	9.23	8.18	7.34	40.5
NaCl	8.66	7.93	7.08	26.3

[a] ^{1}H NMR, solvent $CDCl_3$, temperature 293 K, [**1d**] = 3.2 mM. [b] Determined by the sodium content by atomic emission spectroscopy.

To test whether receptor **1d** could be used to affect $NaNO_2$ extraction, preliminary extraction and membrane transport studies were carried out. Specifically, complete solid/liquid salt extraction studies were undertaken using solutions of **1d** in $CDCl_3$ layered over powdered inorganic salts. Based on N–H proton chemical shifts of salt saturated **1d** solutions, the relative content of **1d**·salt complexes in the organic phase could be estimated.[10]

The data collected in Table 3 revealed that under interfacial conditions, the selectivity towards cations of selected nitrite salts is in agreement with solution studies, namely $NH_4^+ < K^+ < Na^+$. Moreover the predisposition of **1d** to preferentially bind nitrite over Cl^-, Br^-, and NO_3^- was also confirmed. This result is further corroborated by the quantitative determination of the sodium cation concentration in the organic phase by atomic emission spectroscopy. These results are in agreement with those from NMR experiments, although lower selectivity between nitrite and nitrate anions is observed.

The ability of receptor **1d** to extract and transport $NaNO_2$ from aqueous solutions was also tested. A 1.5 M solution of $NaNO_2$ in deionized water was layered onto a 14 mM solution of **1d** in $CDCl_3$. The two layers were thoroughly mixed and then separated. The ^{1}H NMR spectrum of the organic phase revealed that NH signals are shifted only slightly. By atomic emission spectroscopy we demonstrated that **1d** is able to transfer sodium cations into chloroform with an extraction efficiency of 3.1%. Encouraged by that result, we carried out a bulky liquid membrane transport experiment.[4e,11] Initially, the source phase consisted of 2 ml of 1 M aqueous $NaNO_2$ solution and 3 ml of the chloroformic liquid membrane contained receptor **1d** at 40 mM. The salt concentration in the receiving phase was determined by conductometric measurements and the initial flux was calculated to be 2.26×10^{-6} mol × (m^{-2} × s^{-1}). Thus extraction and transport experiments demonstrate that receptor **1d** is capable of transporting $NaNO_2$ from the solid state and more importantly from the aqueous solution.

Conclusion

In conclusion we have found that L-ornithine can be used as a convenient molecular platform for the construction of salt receptors. This platform allows for the introduction of cation and anion binding domains and possesses an additional amine group located on the side arm. This functional group can be modified for specific purposes, and in this study we employed it to introduce various anion binding groups with increased H-bond donor abilities. Although enhancement of the H-bond donor ability of the amide group has a relatively small influence on the anion binding strength, this function plays an important role in the salt binding process. We showed that the increased H-bond donor abilities of an additional anion binding group correlated well with the enhanced $NaNO_2$ binding strength. A similar correlation between amide group acidities and ion binding cooperation is also observed. Therefore, we assume that cation complexation fixes the nitrophenylurea moiety orientation and exposes that domain for anion binding. This cation and anion cooperation induces a second cooperative effect, namely simultaneous association of a single anion with both urea and amide binding groups. The highest cooperativity effect is observed for the trifluoroacetamide equipped receptor **1d**, which interacts with $NaNO_2$ with the association constant of 19 000 M^{-1}. Furthermore, receptor **1d** was found to be highly selective for $NaNO_2$ over sodium bromide and nitrate salts. Receptor **1d** proved to be able to extract solid sodium salts of nitrite, nitrate, bromide and chloride in organic solution, exhibiting selectivity for $NaNO_2$ similar to that seen in solution studies. Finally, a transport experiment using a bulky liquid membrane showed that receptor **1d** can effectively transport $NaNO_2$ from the aqueous phase through the organic phase. Thus we have demonstrated that systematic development of the structure and electronic properties of the binding domains of molecular receptors may lead to a very effective and selective salt receptor.

Experimental section

Compounds **1a**, **1c** and **2b** were prepared according to the procedure found in the literature.[6,7] Other reagents and chemicals were of reagent grade quality and purchased commercially. ^{1}H and ^{13}C NMR spectroscopy as well as titration experiments were conducted on a 200 MHz spectrometer. ^{1}H NMR chemical shifts δ are reported in ppm referenced to the tetramethylsilane ($CDCl_3$) or protonated residual solvent signal (CD_3CN).

Compound 2e

To a solution of N_α-Cbz-N_ε-Boc-L-lysine (549 mg, 1.44 mmol) and 1,3-dicyclohexylocarbodiimide (326 mg, 1.58 mmol) in 20 ml of dry dichloromethane, 1-aza-18-crown-6 (380 mg, 1.44 mmol) at 0 °C (ice bath) was added. The reaction mixture was stirred for 30 min and then left at room temperature overnight. The precipitate was filtered off, washed with dichloromethane and the solvent was evaporated. The residue was purified by silica gel column chromatography (2% methanol in chloroform) to give the title product as a colorless oil (820 mg, 91% yield).

HRMS (ESI): calcd for $C_{31}H_{51}N_3O_{10}Na$ $[M + Na]^+$: 648.3472, found: 648.3458.

^1H NMR (200 MHz, $CDCl_3$) δ: 1.28–1.51 (m, 9H + 2H), 1.57–1.79 (m, 2H), 1.80–2.08 (m, 2H), 3.02–3.19 (m, 2H), 3.45–3.85 (m, 24H), 4.61–4.85 (m, 1H + 1H), 5.09 (s, 2H), 5.62 (d, 1H, J = 8.6 Hz), 7.31–7.39 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 22.61, 28.63, 29.80, 33.56, 40.40, 47.08, 49.02, 50.81, 66.97, 69.64, 69.83, 70.61, 70.76, 70.86, 71.09, 79.21, 128.22, 128.68, 136.59, 156.16, 172.43.

Compound 3d

To the degassed solution of **2b** (4.88 g, 7.99 mmol) in 100 ml of THF–MeOH (1 : 4) catalytic amounts of 10% Pd/C were added. The reaction mixture was kept under a H_2 atmosphere (balloon pressure) at room temperature overnight. The catalyst was removed by filtration through a pad of Celite and washed with MeOH. The filtrate was concentrated under reduced pressure to give the crude product in quantitative yield (3.81 g). The amine was used in the next step without further purification. To a solution of amine (2.29 g, 4.8 mmol) in 100 ml of dry dichloromethane, triethylamine (870 µl, 6.24 mmol) was added. The reaction mixture was cooled under an argon atmosphere (0 °C, ice bath) and trifluoroacetyl anhydride (734 µl, 5.28 mmol) was added dropwise. After stirring overnight at room temperature, the reaction mixture was diluted with water. The water layer was separated and extracted with dichloromethane (2×). The organic layers were collected and washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% methanol in chloroform) to give compound **3d** as a colorless oil (1.79 g, 72% yield).

HRMS (ESI): calcd for $C_{24}H_{42}F_3N_3O_9Na$ $[M + Na]^+$: 596.2771, found: 596.2766.

^1H NMR (200 MHz, $CDCl_3$) δ: 1.43 (s, 9H), 1.50–1.85 (m, 4H), 3.30–3.50 (m, 2H), 3.50–3.85 (m, 24H), 4.72 (bs, 1H), 5.35–5.45 (m, 1H), 7.60 (bs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 24.09, 28.51, 31.76, 40.12, 47.16, 49.31, 49.75, 69.51, 69.57, 70.49, 70.73, 70.89, 71.19, 80.06, 172.54.

Compound 3e

To the degassed solution of **2e** (820 mg, 1.32 mmol) in 30 ml of THF–MeOH (1 : 4) catalytic amounts of 10% Pd/C were added. The reaction mixture was kept under a H_2 atmosphere (balloon pressure) at room temperature overnight. The catalyst was removed by filtration through a pad of Celite and washed with MeOH. The filtrate was concentrated under reduced pressure to give the crude product in a quantitative yield (648 mg). The amine was used in the next step without further purification. To the solution of amine (610 mg, 1.24 mmol) in 20 ml of dry THF, 4-nitrophenyl isocyanate (230 mg, 1.4 mmol) was added. After stirring overnight at room temperature, the reaction mixture was concentrated and purified by silica gel column chromatography (2% methanol in chloroform) to give compound **3e** as a pale-yellow oil (660 mg, 81% yield).

HRMS (ESI): calcd for $C_{30}H_{49}N_5O_{11}Na$ $[M + Na]^+$: 678.3326, found: 678.3344.

^1H NMR (200 MHz, $CDCl_3$) δ: 1.26–1.79 (m, 9H + 6H), 2.97–3.16 (m, 2H), 3.55–3.94 (m, 24H), 4.85 (bs, 1H + 1H), 6.96 (bs, 1H), 7.39 (d, 2H, J = 9.2 Hz), 7.97 (d, 2H, J = 9 Hz), 8.35 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.09, 28.63, 29.94, 33.06, 40.20, 47.79, 49.57, 49.88, 69.14, 69.78, 70.86, 71.08, 79.39, 117.69, 125.13, 141.91, 146.05, 154.80, 156.34, 175.00.

Compound 3f

To the degassed solution of **2b** (4.88 g, 7.99 mmol) in 100 ml of THF–MeOH (1 : 4) catalytic amounts of 10% Pd/C were added. The reaction mixture was kept under a H_2 atmosphere (balloon pressure) at room temperature overnight. The catalyst was removed by filtration through a pad of Celite and washed with MeOH. The filtrate was concentrated under reduced pressure to give the crude product in a quantitative yield (3.81 g). The amine was used in the next step without further purification. To an amine solution (500 mg, 1.05 mmol) in 40 ml of dry dichloromethane, triethylamine (160 µl, 1.15 mmol) was added. The reaction mixture was cooled under an argon atmosphere (0 °C, ice bath) and trifluoromethanesulfonyl chloride (111 µl, 1.05 mmol) was added. After stirring overnight at room temperature, the reaction mixture was diluted with water. The aqueous layer was separated and extracted with dichloromethane (2×). The organic layers were collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% methanol in chloroform) to give compound **3f** as a colorless oil (580 mg, 91% yield).

HRMS (ESI): calcd for $C_{23}H_{45}N_3O_{10}SNa$ $[M + Na]^+$: 578.2723, found: 578.2730.

^1H NMR (200 MHz, $CDCl_3$) δ: 1.43 (s, 9H), 1.59–1.83 (m, 4H), 3.19–3.40 (m, 2H), 3.55–4.05 (m, 24H), 4.65–4.84 (m, 1H), 5.47 (d, 1H, J = 8.8 Hz), 7.33 (d, 1H, J = 6.2 Hz).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 20.26, 25.25, 28.53, 30.85, 44.04, 47.11, 49.51, 69.36, 69.45, 70.35, 70.51, 70.66, 77.44, 80.06, 123.30, 155.79, 172.57.

Receptor 1b

Compound **2b** (500 mg, 0.817 mmol) was dissolved in 10 ml of dichloromethane and 2.5 ml of trifluoroacetic acid was added. The reaction mixture was stirred at room temperature until the starting material was consumed (TLC monitoring). The mixture was neutralized with saturated $NaHCO_3$. The water layer was separated and extracted with dichloromethane (2×). The organic layers were collected and washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained amine (395 mg, 95% yield) was used in the next step without further purification. To the solution of amine (395 mg, 0.773 mmol) in 20 ml of dry THF, 4-nitrophenyl isocyanate (126 mg, 0.773 mmol) was added. After stirring overnight at room temperature, the reaction mixture was concentrated and purified by silica gel column chromatography

(2% methanol in chloroform) to give receptor **1b** as a pale-yellow oil (381 mg, 73% yield).

HRMS (ESI): calcd for $C_{32}H_{45}N_5O_{11}Na$ $[M + Na]^+$: 698.3013, found: 698.2982.

^1H NMR (200 MHz, CD_3CN) δ: 1.40–1.80 (m, 4H), 3.00–3.20 (m, 2H), 3.40–3.80 (m, 24H), 4.75–4.85 (m, 1H), 5.02 (s, 2H), 5.75–5.85 (m, 1H), 6.39 (d, 1H, J = 8.2 Hz), 7.20–7.40 (bs, 5H), 7.46 (d, 2H, J = 12.4 Hz), 8.02 (d, 2H, J = 9.4 Hz), 8.06 (s, 1H).

^{13}C NMR (50 MHz, CD_3CN) δ: 26.65, 31.08, 41.35, 47.97, 49.67, 50.62, 66.83, 69.59, 70.40, 71.14, 71.23, 71.28, 71.35, 71.45, 125.88, 128.76, 128.90, 129.51, 147.42, 155.19, 174.37.

Receptor 1d

Compound **3d** (1.4 g, 2.44 mmol) was dissolved in 50 ml of dichloromethane and 10 ml of trifluoroacetic acid was added. The reaction mixture was stirred at room temperature until the starting material was consumed (TLC monitoring). The mixture was evaporated *in vacuo* to yield the crude product as the trifluoroacetate salt in a quantitative yield (1.3 g). The ammonium salt was used in the next step without further purification. To a solution of ammonium salt (1.3 g, 2.44 mmol) in 50 ml of dry THF under an argon atmosphere, triethylamine (850 μl, 6.1 mmol) and 4-nitrophenyl isocyanate (400 mg, 2.44 mmol) were added. After stirring overnight at room temperature, the reaction mixture was concentrated and the residue was partitioned between dichloromethane and water. The aqueous layer was separated and extracted with dichloromethane (2×). The organic layers were collected and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (5% methanol in chloroform) to give receptor **1d** as a pale-yellow oil (860 mg, 60% yield).

HRMS (ESI): calcd for $C_{26}H_{38}F_3N_5O_{10}Na$ $[M + Na]^+$: 660.2468, found: 660.2454.

^1H NMR (200 MHz, $CDCl_3$) δ: 1.62–1.95 (m, 4H), 3.25–3.47 (m, 2H), 3.50–4.12 (m, 24H), 5.04 (bs, 1H), 7.05 (bs, 1H), 7.47 (d, 2H, J = 9 Hz), 7.81 (bs, 1H), 8.05 (d, 2H, J = 9.2 Hz), 8.37 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 25.07, 31.28, 39.98, 47.92, 49.41, 49.94, 68.84, 69.61, 70.72, 70.82, 71.19, 117.79, 125.19, 142.05, 145.92, 154.70, 174.67.

Receptor 1e

Compound **3e** (660 mg, 1.01 mmol) was dissolved in 10 ml of dichloromethane and 2 ml of trifluoroacetic acid was added. The reaction mixture was stirred at room temperature until the starting material was consumed (TLC monitoring). The mixture was evaporated *in vacuo* to yield the crude product as a trifluoroacetate salt in a quantitative yield (675 mg). The ammonium salt was used in the next step without further purification. Next, to a solution of amine (675 mg, 1.01 mmol) in 20 ml of dry dichloromethane, triethylamine (349 μl, 2.5 mmol) was added. The reaction mixture was cooled under an argon atmosphere (0 °C, ice bath) and trifluoroacetyl anhydride (167 μl, 1.2 mmol) was added dropwise. After stirring overnight at room temperature, the reaction mixture was diluted with water. The water layer was separated and extracted with dichloromethane (2×). The organic layers were collected and washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% methanol in chloroform) to give receptor **1e** as a pale-yellow oil (480 mg, 73% yield).

HRMS (ESI): calcd for $C_{27}H_{40}F_3N_5O_{10}Na$ $[M + Na]^+$: 674.2625, found: 674.2637.

^1H NMR (200 MHz, $CDCl_3$) δ: 1.36–1.87 (m, 6H), 3.26–3.40 (m, 2H), 3.50–4.05 (m, 24H), 4.96 (bs, 1H), 7.02 (bd, 1H), 7.29 (bt, 1H), 7.42 (d, 2H, J = 9 Hz), 78.02 (d, 2H, J = 9.4 Hz), 8.33 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 22.83, 28.58, 33.11, 39.82, 47.78, 49.53, 49.73, 68.96, 69.67, 70.66, 70.81, 70.89, 71.16, 117.76, 125.55, 142.01, 145.94, 154.82, 157.40, 158.13, 174.87.

Receptor 1f

Compound **3f** (488 mg, 0.8 mmol) was dissolved in 20 ml of dichloromethane and 5 ml of trifluoroacetic acid was added. The reaction mixture was stirred at room temperature until the starting material was consumed (TLC monitoring). The mixture was evaporated *in vacuo* to yield the crude product as a trifluoroacetate salt in quantitative yield (498 mg). The ammonium salt was used in the next step without further purification. Next, to the solution of ammonium salt (498 mg, 0.8 mmol) in 50 ml of dry THF under an argon atmosphere, triethylamine (279 μl, 2 mmol) and 4-nitrophenyl isocyanate (131 mg, 2.44 mmol) were added. After stirring overnight at room temperature, the reaction mixture was concentrated and the residue was partitioned between dichloromethane and water. The water layer was separated and extracted with dichloromethane (2×). The organic layers were collected and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (2% methanol in chloroform) to give receptor **1f** as a pale-yellow oil (390 mg, 72% yield).

HRMS (ESI): calcd for $C_{25}H_{38}F_3N_5O_{11}SNa$ $[M + Na]^+$: 696.2138, found: 696.2144.

^1H NMR (200 MHz, $CDCl_3$) δ: 1.63–2.05 (m, 4H), 3.22–3.43 (m, 2H), 3.45–4.10 (m, 24H), 5.02 (bs, 1H), 7.11 (bd, 1H, J = 7 Hz), 7.31 (bt, 1H), 7.42 (d, 2H, J = 9 Hz), 8.03 (d, 2H, J = 9 Hz), 8.27 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 26.10, 30.16, 43.98, 47.85, 50.07, 68.96, 70.48, 70.69, 71.12, 117.87, 125.12, 142.09, 145.73, 154.88, 174.63.

Acknowledgements

This work was supported by grant no. DEC-2013/09/B/ST5/00988 from the Polish National Science Center and by a Iuventus grant no. IP2012050572 from the Polish Ministry of Science and Higher Education.

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