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The Halide Binding Behavior of 2-Carbamoyl-7-ureido-1*H*-indoles: Conformational Aspects

Damjan Makuc,[a] Triyanti,[b] Markus Albrecht,*[b] Janez Plavec,*[a] Kari Rissanen,[c] Arto Valkonen,[c] and Christoph A. Schalley[d]

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Indole-based anion receptors with an carboxamide unit in 2- and an urea in 7-position were prepared and found to bind halides (as well as acetate and nitrate) in chloroform solutions at room temperature. Investigations of the binding behaviour show that the receptor is selective for chloride. Surprisingly, the truncated receptor **3** without the 2-carbamoyl substituent shows the highest affinity for Cl^-. Thorough ^1H, ^{13}C and ^{15}N NMR investigations indicate different binding modes for acetate, nitrate and halides to the receptor **2**. The observation of a major conformational change of this receptor during the binding of the halide ions leads to an understanding of the relative binding affinities of **3** > **4** > **2** for chloride. The results of the NMR study are supported by ab initio calculations. In addition, ESI FTICR MS competition experiments of the indole **2** and the quinoline **1** reveal the "self-aggregation" of the receptors and show that halides have a higher affinity to **2** than to **1**.

Introduction

Specific host-guest chemistry of substrates and appropriate receptors is an important task since the days of Emil Fischer and Paul Ehrlich.[1] Following the lock-and-key principle, the "shape" of receptor and substrate should be highly complementary in a geometric as well as electronic sense. However, in many natural (biological) or artificial systems the receptor adopts its shape to the need of the substrate ("induced fit"). Therefore flexibility of the receptor is required for binding.[2]

In this respect, anion receptor chemistry is a very attractive field of research.[3] The vivid growth in this area of supramolecular chemistry has been stimulated by many roles played by anions.[4] Inorganic and biotic anions such as halides, acetates and phosphates are essential in the activity of enzymes, transport of hormones, protein synthesis and DNA regulation. They are indispensable in the areas of medicine and catalysis. On the other hand, they can be found in noxious processes, like pollutant anions in eutrophication of rivers and carcinogenesis. As a result, a great variety of anion hosts has been synthesized and studied over the last years.[5]

Recently, a new kind of anion receptors based on the 2-carbamoyl-8-ureidoquinoline derivative **1** was introduced. This receptor is very rigid. Intramolecular hydrogen bonding between the internal urea and the carboxamide NH to the quinoline nitrogen fixes the geometry[6] of the compound and provides a cleft which is specific for the binding of fluoride anions over the other halides, nitrate or benzoate.[7]

In a more recent study, the quinoline moiety was substituted by indole[8] and the new receptor **2** was introduced by us and Gale.[9] This one shows some features related to **1**. However, **2** possesses one more hydrogen-bond donor NH unit and there is no internal fixation of the geometry by hydrogen bonding. Probably H-bond donors are blocked by hydrogen bonding to carbonyl oxygen atoms. X-ray structural investigations indicated that (even upon interaction with anions) the conformer **B** is favored in the solid state.[9] In contrast to this, our initial proposal was that in the presence of anions the conformer **A** should become more dominant (Figure 1).

In order to show this in solution, we performed sophisticated NMR studies with the indole receptors **2** in the absence and in the presence of halides and supported our interpretations by ab initio calculations. In addition the hydrogen binding sites were reduced by detaching the 2-amide

[a] Slovenian NMR Center, National Institute of Chemistry and Faculty of Chemistry and Chemical Technology, University of Ljubljana,
Hajdrihova 19, 1000 Ljubljana, Slovenia
E-mail: janez.plavec@ki.si
[b] Institut für Organische Chemie, RWTH Aachen,
Landoltweg 1, 52074 Aachen, Germany
E-mail: markus.albrecht@oc.rwth-aachen.de
[c] Nanoscience Center, Department of Chemistry, University of Jyväskylä,
P. O. Box 35, 40014 Jyväskylä, Finland
[d] Institut für Chemie und Biochemie, Organische Chemie, Freie Universität Berlin,
Takustr. 3, 14195 Berlin, Germany

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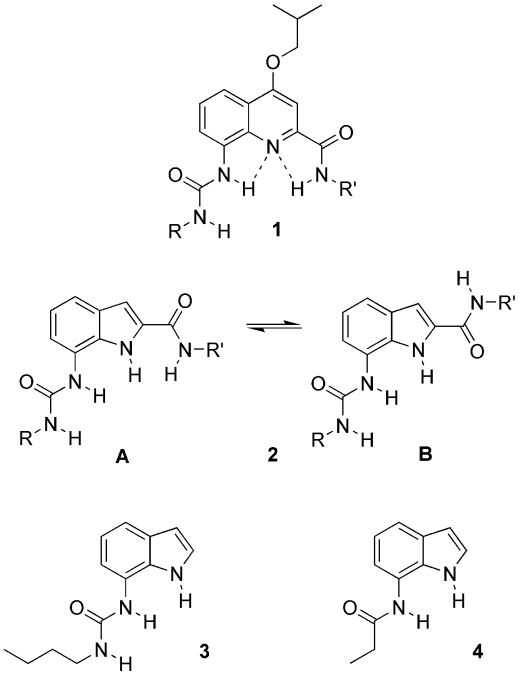


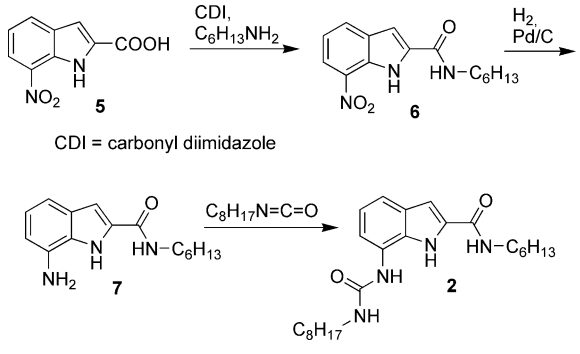
Figure 1. Quinoline derivative **1** and indoles **2** (in this study: R = *n*-octyl, R′ = *n*-hexyl), **3** and **4**. The conformational flexibility of the indole–carboxamide bond is indicated.

3 and by reducing the urea to an amide **4**. In order to compare the anion receptor behavior of hosts **1** and **2** we investigated their binding competition by ESI FT-ICR MS.

Results and Discussion

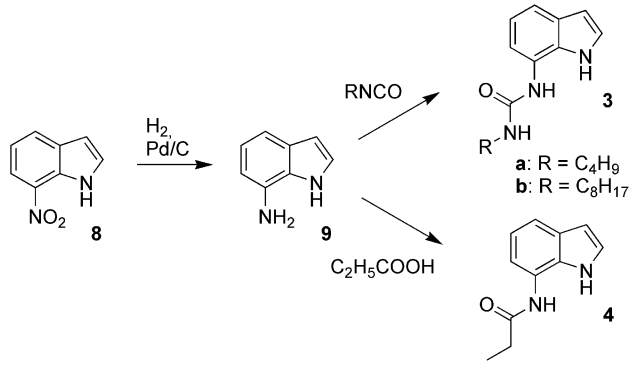
Preparation of Receptors 2–4

The indole receptor **2** was prepared starting from 7-nitroindole-2-carboxylic acid **5**. The acid is transformed to the amide **6** by reaction with *n*-hexylamine in the presence of carbonyl diimidazole as activator. The nitro compound **6** is reduced to the amine **7** to obtain the desired compound **2** after coupling with *n*-octylisocyanate (Scheme 1).[9]



Scheme 1. Preparation of the 2-amide-7-ureidoindole **2**.

The simpler receptors **3** and **4** are obtained in reaction sequences starting with 7-nitroindole **8**. After reduction with hydrogen at palladium on carbon, reaction with isocyanates affords the urea derivatives **3a/b**, while coupling with propionic acid in the presence of diisopropylamine and HBTU [2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate][10] results in the formation of the amide **4** (Scheme 2).



Scheme 2. Preparation of the 7-ureido- **3a/b** and 7-carbamoyl-substituted indoles **4**.

Anion Binding Behaviour of Receptors 2–4

The anion binding behaviour of the receptors **2**–**4** was studied by NMR spectroscopy at room temperature in $CDCl_3$. Initially, the stoichiometry of interactions between the receptors **2**, **3a** and **4** and halide anions were determined to be 1:1 by Jobs technique of continuous variation.[11] Figure 2 shows as a representative example the Job plots of receptor **2** with the anions fluoride, chloride and bromide and nitrate (added as their tetrabutylammonium salts).[12]

Subsequently, NMR titrations were performed in which successively anion tetrabutylammonium salt was added to a solution of the receptor at room temperature in [D]chloroform and the titration curve was recorded for the change of chemical shifts. Non-linear regression afforded binding constants for the receptor–anion interaction.[11]

Figure 3 shows as a representative example the titration curve for the titration of receptor **2** with tetrabutylammonium chloride in $CDCl_3$ at room temperature. The data which were extracted from the titration curves[11] with receptors **2**, **3a** and **4** and fluoride, chloride or bromide anions are summarized in Table 1.

Table 1 reveals that the indole receptor **2** possesses the highest binding constant with chloride and the lowest with fluoride (the determined fluoride binding constants are probably too low due to the observation of CH instead of NH signals. The latter cannot be observed because of fast exchange processes and line broadening).[13] The anion selectivity trends of the "truncated" receptor **3a** is roughly comparable to that of **2**. Surprisingly, much higher binding affinities are observed for this smaller receptor. Further reduction of the hydrogen-bond donor abilities leads to the indole-carboxamide **4**. As expected, the substitution of the urea by an amide unit results in the reduction of K_a.

The observed binding constants show that the indole receptors under study are most appropriate binders for chloride over the other halide anions. However, at first sight,

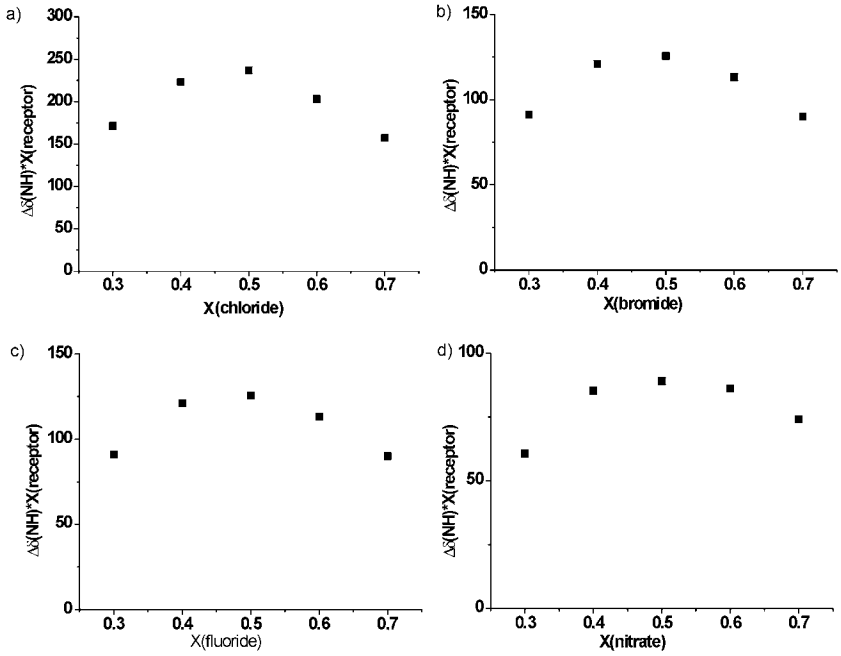


Figure 2. Job-plots for the interaction of indole **2** with chloride (a), bromide (b), fluoride (c), and nitrate (d).

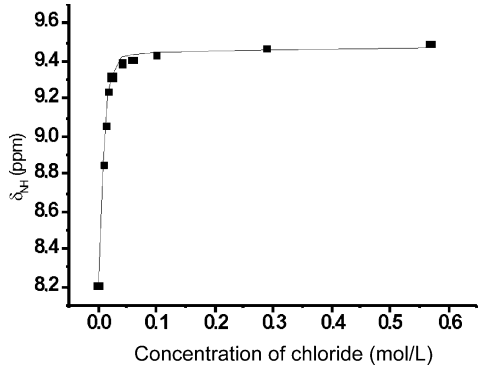


Figure 3. NMR titration curve for the addition of tetrabutylammonium chloride to receptor **2** (concentration 0.0149 M) in $CDCl_3$ at room temperature.

the increase of the binding affinity by reduction of hydrogen-bond donors from receptor **2** to **3a** seems to be highly surprising. This effect can be expected to be due to conformational properties of the receptors which possess rotatable bonds between the indole platform and the urea as well as the amide. The preferred receptor conformations need to be investigated more closely in order to understand the unusual binding behavior and to check whether the conformation and not e.g. solvation effects are responsible for it.

Table 1. Binding constants K_a [M^{-1}] for the 1:1 binding of various halide anions (as tetrabutylammonium salts) with receptors **2**, **3a** and **4**.[a]

Anion	**2**	**3a**	**4**
Fluoride	(230)	13.300	9.200
Chloride	9.000	442.000	230.000
Bromide	5.600	10.000	7.500
Nitrate[b]	1.600		

[a] Binding constants were determined by ^1H NMR in $CDCl_3$ at a concentration of 0.0149 M and 296 K. All data are the result of at least two independent measurements. Errors are estimated to be <25%. All titrations are obtained by detection of the NH protons with the exception of the data for fluoride which are obtained following aromatic CH resonances. Therefore the latter are expected to be highly inaccurate (error > 25%). The error of the data with $K_a > 100.000\ M^{-1}$ might be higher than 25% due to the inaccuracy of NMR to determine such high binding constants. [b] The focus in this study is on halide anion binding. However, some selected data are added for other anions.

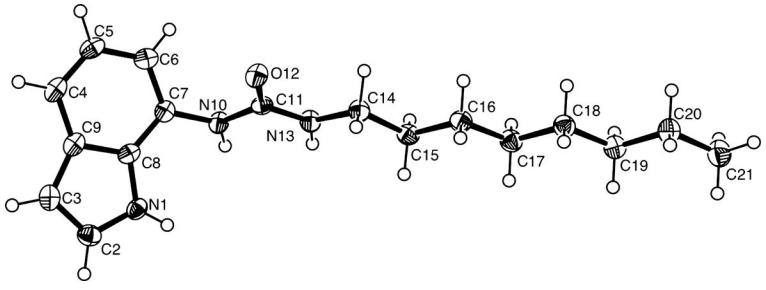


Figure 4. The molecular structure of **3b** as found in the solid state.

X-ray Crystal Structure Analysis of 3b

We were able to obtain an X-ray crystal structure of compound **3b**, which is shown in Figure 4. The urea unit reveals the expected *syn* orientation of the NH bonds. It is twisted out of plane of the indole platform with a dihedral angle C8–C7–NH-(C=O) of –118.3°. This twist is enforced by hydrogen-bonding between neighboring urea units in addition to π–π stacking of the indoles. CH-π interactions of indole moieties occur between H-bonded "urea rods". Therefore, in the solid phase conformation of **3b** the urea and the indole NH are not in an ideal orientation for an effective interaction with anions. The urea first has to rotate in-plane. In order to investigate the conformation of the receptor **2** (which possesses the urea as well as the amide unit) in solution we performed thorough NMR studies.

Solution Studies by NMR Spectroscopy

NMR Signal Assignment of the Indole-Based Anion Receptor 2

Assignment of ^{1}H, ^{13}C and ^{15}N NMR resonances of **2** was achieved through inspection of chemical shifts and respective integrals in the 1D spectra, from the observed through-bond connectivities in the 2D COSY spectra as well as ^{13}C-^{1}H and ^{15}N-^{1}H correlations in 2D HSQC and HMBC spectra. NH protons of **2** were well resolved in the wide chemical shift range between 6.0 and 11.2 ppm.

Conformational Analysis

Conformational properties of anion receptor **2** were assessed in acetone solution where intermolecular interactions were negligible as verified by dilution experiments. The potential π-stacking interactions of indole rings that could be reflected in chemical shift changes and NOE enhancements were greatly reduced in this quite polar solvent. Four major energetically preferred conformations are expected to be observed with respect to rotations across C2–C2α and C7–N7α bonds (Figure 5). The *syn-syn* orientation appears to be predisposed for the most effective binding of anions. On the other hand, without an H-bond acceptor present it is expected to be disfavored with respect to the other three rotamers. The *anti-syn* conformer was shown to be favorable in the solid state in the absence of anions.[9]

Conformational preorganization and conformational equilibria of indole based receptors were studied by 1D difference NOE experiments. The indole H1 proton with its central position in the receptor is surrounded by carboxamide and ureido NH protons. Figure 6 shows 1D difference NOE spectra of **2**, where all four NH protons are well resolved and thus enable unambiguous quantification of

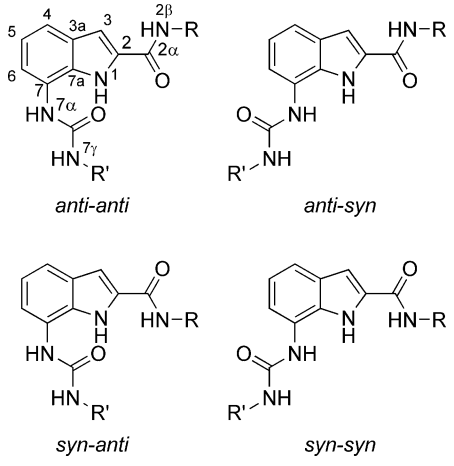


Figure 5. Major possible conformers of the 2-carbamoyl and 7-ureido substituents in indole anion receptor **2**. The first notation refers to the orientation across C2–C2α and the second across C7–N7α bond with the respective torsion angles θ_2 [N1–C2–C2α–N2β] and θ_7 [C6–C7–N7α–C7β].

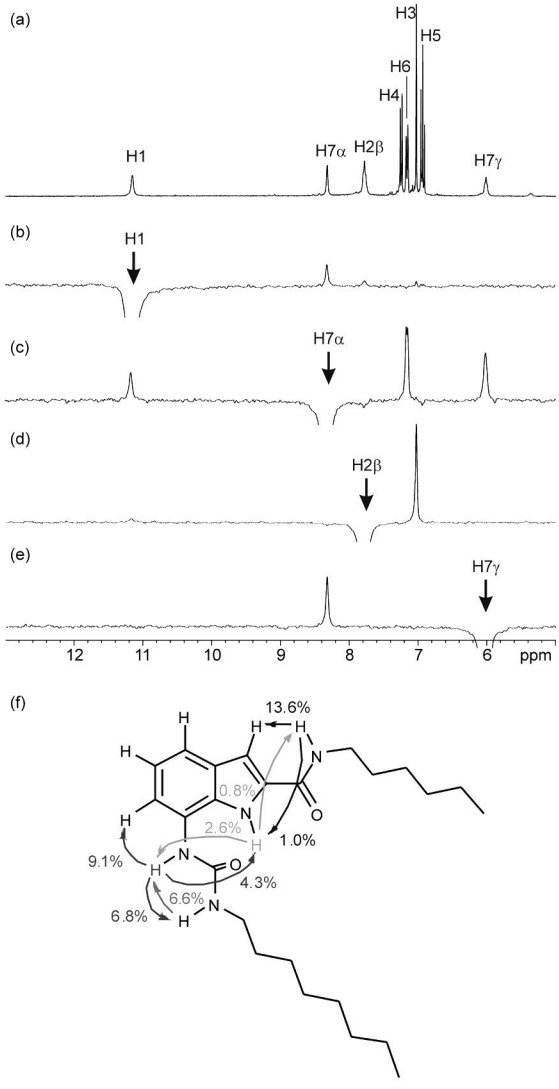


Figure 6. Partial 1D difference NOE spectra of **2** upon saturation of H1 (b), H7α (c), H2β (d) and H7γ (e) at 298 K. Saturated signals are truncated for clarity. The ^{1}H NMR spectrum in panel (a) is shown for reference. (f) The predominant *anti-anti* conformation of **2** in acetone as determined by NOEs where arrows and numbers indicate NOE enhancements.

NOE enhancements. The saturation of the ureido H7α gave strong NOE enhancement at H6 (9.1%) and H7γ (6.8%, Figure 3, c). The saturation of carboxamide H2β proton resulted in strong NOE enhancement of 13.6% at H3 (Figure 6, d). Small NOE interactions among H1 and H7α were also observed which suggest conformational freedom across C7–N7α bond. Nevertheless, the major NOE enhancements suggest that **2** predominantly adopts the *anti-anti* conformation in acetone (Figure 6, f).

Changes of NMR Parameters Induced by Interaction with Anions

Interactions between the receptor and anions were monitored initially through ^{1}H NMR chemical shift changes. Spherical halides were the first anions to be studied. Upon addition of one equivalent of Cl^- to receptor **2** broadening of all NH signals was observed (Figure 7, a and b). The signals of H1 and H7α protons shifted downfield considerably which indicates their strong interaction with chloride anions.

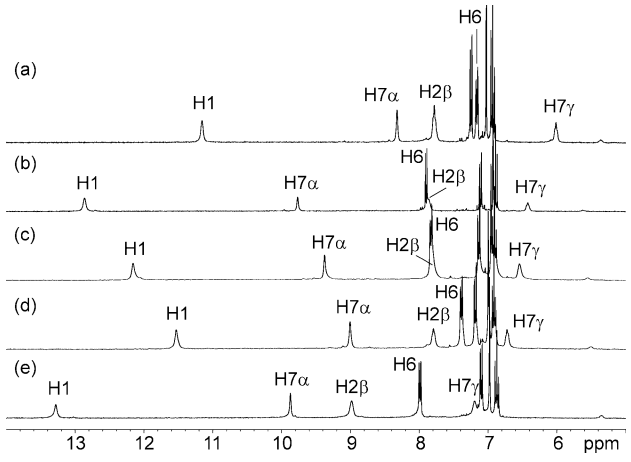
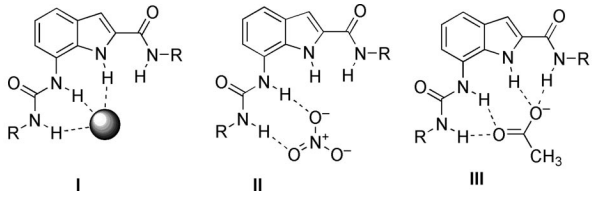


Figure 7. Partial ^{1}H NMR spectra showing chemical shift changes for **2** upon addition of one equivalent of the following anions: chloride (b), bromide (c), nitrate (d) and acetate (e) at 298 K. The spectrum in panel (a) without anions is shown as a reference.

The proposed formation of hydrogen bonds between anion and NH protons of **2** is further supported by downfield shift of H7γ proton. In addition, considerable $\Delta\delta$ values of H6 protons were observed. Although H6 protons are most probably not directly involved in anion-receptor interactions, their downfield chemical shifts indicate clear changes of their shielding environment, which suggest conformational changes along C7–N7α bond upon anion binding. Additionally, the larger spherical bromide anion as well as Y-shaped nitrate and acetate oxoanions were studied. Perusal of Figure 7 shows that different anion species result in significant differences in spectra which are in agreement with their distinct binding affinities with **2**.

Addition of one equivalent of bromide and nitrate anions to **2** results in smaller chemical shift changes for H1 and H7α in comparison to chloride anion which is in agreement with their lower basicity. In contrast, a small increase of the H7γ chemical shift changes was observed upon interaction with one equivalent of bromide or nitrate anions with respect to chloride which could be attributed to the bigger size of bromide and favorable geometric properties of trigonal planar nitrate anion. Interestingly, there seems to be weak or no interaction between chloride, bromide and nitrate anions with carboxamide H2β proton as implied by its small chemical shift changes. It is noteworthy that according to $\Delta\delta$ values binding of chloride and bromide anions to **2** occurs primarily to H1 and H7α protons, whereas nitrate anion favors interaction with H7α and H7γ. Furthermore, large downfield shifts of all four NH protons were induced by addition of acetate anion which indicates interaction of larger and more polarized acetate anion with all available donor groups of **2** (Figure 7). Y-shaped nitrate and acetate anions induced larger $\Delta\delta$ values of H7γ protons for **2** with respect to halide anions which suggest their favorable interaction with urea diprotic NH donor groups. Size, geometry, electronegativity and polarization of anions play important role in interaction with receptors. Smaller chloride in comparison to larger bromide anion has been shown to interact strongly with receptor **2**. Bidentate nitrate and acetate anions can interact through two hydrogen bond-acceptor oxygen atoms which result in even stronger interaction and larger chemical shift changes of all four donor NH groups. However, addition of nitrate anions was shown to induce minor chemical shift changes which indicate its weaker binding to receptor **2** in comparison to the other anions. NMR spectroscopic data are in complete agreement with the lower basicity and weaker polarization of charge distribution of nitrate anion. On the other hand, the higher basicity and stronger polarization of the acetate anion increase its interaction with donor groups of receptor **2**, which is in accordance with the larger chemical shift changes of NH protons. Following those results, we propose tentatively three different dominating modes **I**–**III** (**I** = halide, **II** = nitrate, **III** = acetate) for the binding of the anions.



Interactions inferred from analyses of proton chemical shift changes are corroborated by ^{15}N NMR spectroscopic data (Figure 8). The largest $\Delta\delta$ values in **2** upon addition of chloride and bromide anions were observed for N7α. Signals for N2β and N7γ are also deshielded upon interaction with anions. Interestingly, N1 is deshielded upon addition of one equivalent of spherical chloride and bromide anions, and shielded in the presence of trigonal planar nitrate and acetate anions.

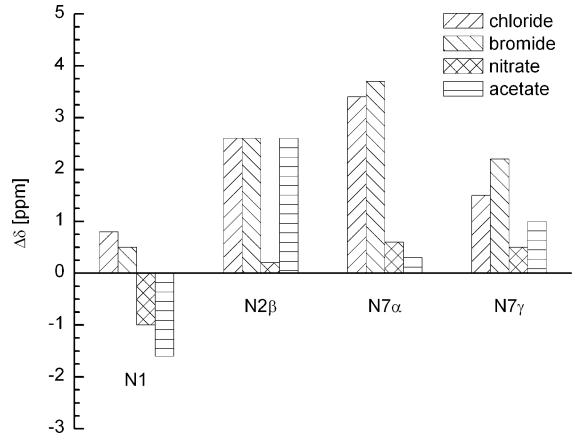


Figure 8. ^{15}N NMR chemical shift changes, $\Delta\delta = \delta$(in the presence of anions) – δ(in the absence of anions), induced by addition of one equivalent of anions to receptor **2**.

Conformational Changes upon Interactions with Anions

1D difference NOE spectra of **2** upon addition of one equivalent of Cl^- anions showed interesting conformational changes induced by anion binding. The saturation of the H1 proton resulted in strong NOEs at H2β and H7α protons (Figure 9, b). Furthermore, the saturation of H7α proton showed strong response at H7γ and H1 protons (Figure 9, c). NOE enhancements shown in Figure 9 (f) are in agreement with *syn-syn* conformation. In the **2**·Cl^- complex, all NH protons are spatially close together and their repulsion is minimized by interactions with the anion.

Comparison of NOE enhancements in the absence and in the presence of anions reveals conformational changes of receptors **2** induced by complexation of anions. The {H2β}–H3 NOE decreased significantly upon addition of chloride anion, while NOEs at H2β and H7α upon the saturation of H1 increased considerably (Table 2). These results are in agreement with the observed $\Delta\delta$ values and confirm the interaction of chloride anions with H1, H7α and H7γ through hydrogen-bond formation. The observed changes in NOEs at H3 upon saturation of H2β could not be attributed to the binding of a chloride anion to H2β, but is most probably due to the repulsion between anion and the polarized C2α carbonyl group. Similar changes of {H1}–H2β, {H1}–H7α and {H7α}–H1 NOE enhancements were observed in case of **2**·Br^- and **2**·AcO^- complexes. Addition of NO_3^- anions to receptor **2** induced very small changes in comparison to other anions. Furthermore, strong NOEs were observed between H2β and H3 protons, as well as H7α and H6 which implies the absence of conformational changes upon addition of nitrate anions.

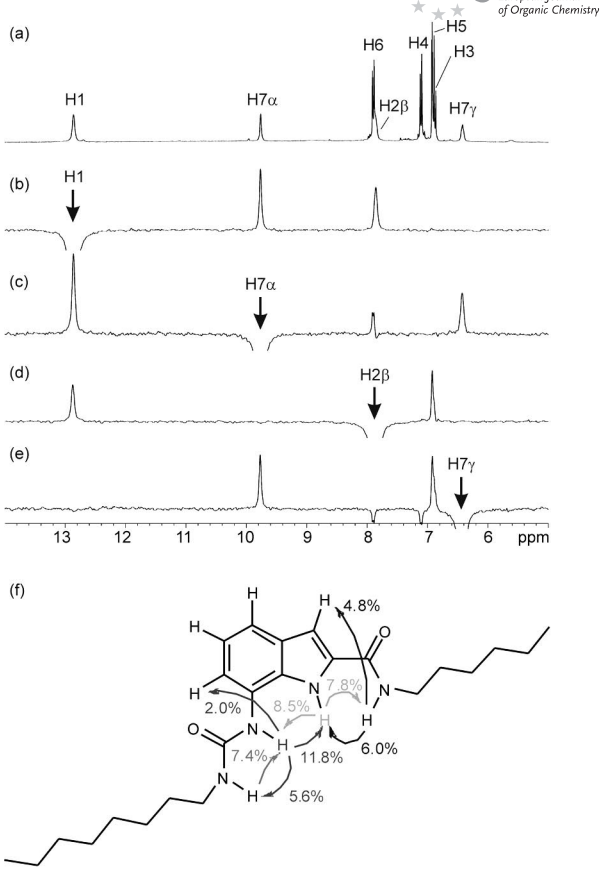


Figure 9. Partial 1D difference NOE spectra of **2**·Cl^- complex upon saturation of H1 (b), H7α (c), H2β (d) and H7γ (e) at 298 K. Saturated signals are truncated for clarity. The ^{1}H NMR spectrum in panel (a) is shown as a reference. (f) The predominant *syn-syn* conformation of **2**·Cl^- complex in acetone as determined by NOEs where arrows and numbers indicate NOE enhancements.

Conformational Analysis by Ab Initio Calculations

Our observations of conformational preorganization and changes upon anion binding were complemented by quantum mechanical calculation at HF and B3LYP levels of theory using Gaussian 03.[14] Structure calculations were

Table 2. The key NOE enhancements (%) observed for **2** in the absence and in the presence of one equivalent of anions.

Saturated	H2β		H3	H1		H7α			H7γ	H6
Enhanced	H3	H1	H2β	H2β	H7α	H1	H7γ	H6	H7α	H7α
Without anion	13.6	1.0	3.4	0.8	2.6	4.3	6.8	9.1	6.6	1.6
Cl^-	4.8	6.0	3.5	7.8	8.5	11.8	5.6	2.0	7.4	0.3
Br^-	_[a]	_[a]	_[a]	5.8	6.2	7.0	7.5	3.4	6.7	_[a]
NO_3^-	11.5	2.9	2.2	2.4	3.1	4.4	3.7	9.4	6.4	1.5
OAc^-	3.6	5.4	0.2	8.5	4.8	3.8	4.1	2.2	4.5	0.2

[a] ^{1}H signals were overlapped and pairwise enhancements could not be quantified unequivocally.

Table 3. Comparison of relative energies, torsion angles and hydrogen bond lengths for the four major conformers.

		Relative energy[a]		θ_2	θ_7	$d_{H1\text{-}Cl^-}$	$d_{H2\beta\text{-}Cl^-}$	$d_{H7a\text{-}Cl^-}$	$d_{H7\gamma\text{-}Cl^-}$
Anion	Conformer	HF	B3LYP						
without	*anti-anti*	0.00	0.00	178.8	133.9	–	–	–	–
	syn-anti	1.66	1.40	–11.8	138.0	–	–	–	–
	anti-syn	1.93	2.70	185.9	0.0	–	–	–	–
	syn-syn	5.74	7.49	16.3	–11.5	–	–	–	–
chloride	*anti-anti*	63.23	59.34	153.4	133.9	2.29	4.74	5.27	4.38
	syn-anti	33.68	20.51	–0.4	138.0	2.26	2.27	4.77	3.92
	anti-syn	10.41	10.06	206.9	6.8	2.50	6.26	2.29	2.50
	syn-syn	0.00	0.00	0.0	–11.5	2.27	2.61	2.45	2.73

[a] Relative energies are reported in kcal/mol with respect to the lowest energy (arbitrarily set to 0.00 kcal/mol) in the absence and in the presence of chloride anion. Geometry optimizations were carried out at B3LYP/6-311+G(d,p) level, and energy calculations using both HF and B3LYP levels of theory using the same basis set.

performed on a model compound with methyl groups attached to the amide and ureido substituents (R = R′ = Me, Figure 1) in order to reduce calculation time with respect to the analyzed indole systems **2**. Initial energy minimizations were performed without any constraints for the four major conformational structures shown in Figure 5. Their respective energies and optimized structural properties are summarized in Table 3. Two torsion angles θ_2 [N1–C2–C2α–N2β] and θ_7 [C6–C7–N7α–C7β] were defined to follow energetic changes induced by reorientation of substituents across C2–C2α and C7–N7α bonds. The *anti-anti* conformer with the lowest energy was chosen as the starting structure in energy profile calculations that were carried out at B3LYP/6-311+G(d,p) level.

Indole aromatic ring represents the rigid part of anion receptor. The energy profile for torsion angle θ_2 with 15° resolution shows that conformer with the lowest energy is in the *anti* region. The minimum in the *syn* region exhibits 1.4 kcal/mol higher energy (Figure 10, a). The energy barrier for rotation along torsion angle θ_2 is 6.4 kcal/mol with the highest energy at θ_2 = 90°. Taking the optimized θ_2-*anti* structure as a starting structure, the orientation of the C7 substituent was scanned and the global minimum was found for *anti-anti* conformer (Figure 10, b). The rotation energy barrier of 3.3 kcal/mol along torsion angle θ_7 was found at θ_7 = 60°. The global minimum in *anti-anti* region is in agreement with our NOE experimental data. Furthermore, relatively small energy barrier supports the experimentally inferred conformational freedom along C7–N7α bond.

Energy profiles were also computed for complexes of chloride, bromide and acetate anions with the model receptor molecule. Few energy minima were found for each anion-receptor pair (Figure 10, a). The lowest energies for torsion angle θ_2 were found in *syn* region. The local minima in *anti* region of θ_2 conformational space were characterized with significantly higher energies (>8 kcal/mol) in contrast to energy preferences in the absence of anions. The energy barriers between the two regions were 12.1, 11.6 and 13.2 kcal/mol for complexes with chloride, bromide and acetate anions, respectively (Figure 10, a). In further energy profile calculations, torsion angle θ_2 was retained in *syn* conformation but was free to optimize, while torsion angle θ_7 for chloride-receptor complex was fixed at the selected value. The lowest energy was obtained for *syn* conformer which was the only energy minimum in this calculation (Figure 10, c). The energy barrier for θ_7 reorientation from *syn* to *anti* conformation for chloride-receptor complex was found to be 20.5 kcal/mol. Representative models of the two lowest energy structures of model receptor alone and in the presence of chloride anion demonstrate that interaction with anion is coupled with conformational change from *anti-anti* into *syn-syn* orientation (Figure 11). It is noteworthy, that the θ_2 and θ_7 energy profiles and the energies of the local minima are in agreement with conformational preferences established through NMR measurements.

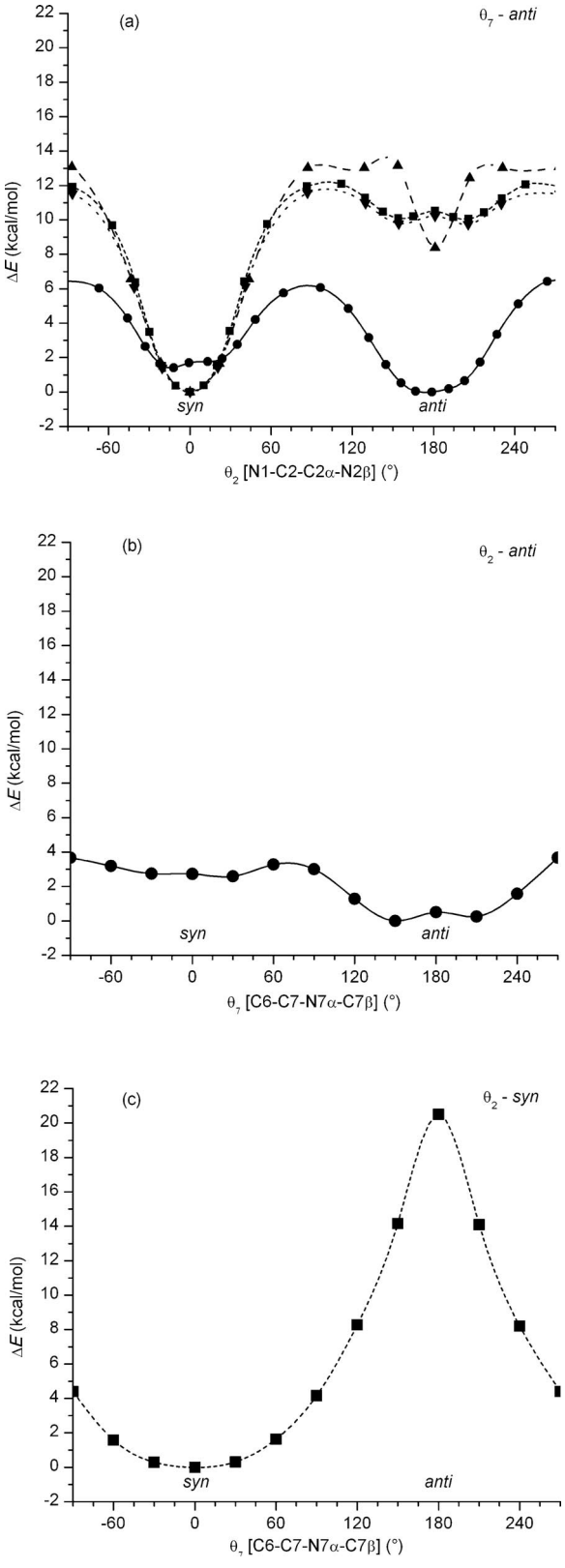


Figure 10. Relative potential energy [kcal/mol] of model receptor (●) and its complexes with anions (■ chloride, ▼ bromide and ▲ acetate) calculated at B3LYP/6-311+G(d,p) level as a function of torsion angle θ_2 with a step sizes of 15° and 30° and θ_7 in *syn* orientation (a), and for torsion angle θ_7 while θ_2 was placed in *anti* (b) and *syn* conformation (c). For each energy profile the lowest energy was arbitrarily set at 0.0 kcal/mol.

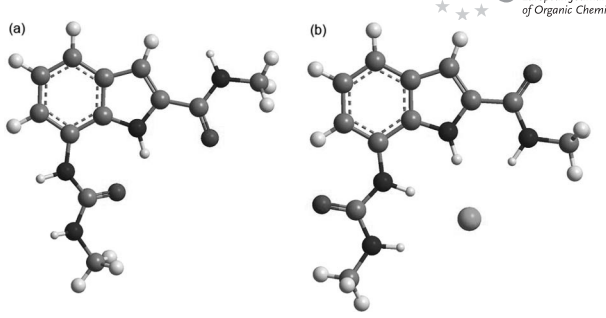


Figure 11. Two lowest energy structures of model indole receptor alone in *anti-anti* conformation (a) and in complex with chloride anion in *syn-syn* conformation (b). Both conformations are the result of completely free optimizations at B3LYP/6-311+G(d,p) level in vacuo.

Anion Binding Competition of 1 and 2

In order to study the anion binding properties of indole receptor **2** in competition to the earlier described quinoline **1**, we performed a series of ESI-FTICR MS measurements.[15] In chloroform, **1** shows some selectivity for fluoride over chloride over bromide binding. Concentration-dependent NMR measurements of the receptor **1** in the absence of anions reveal, that self-aggregation takes place,[6] which according to X-ray structure analyses of related compounds should occur between the hydrogen bonding donor site and a carbonyl (either amide or urea) of a further molecule as hydrogen-bond acceptor (see Figure 12).[16]

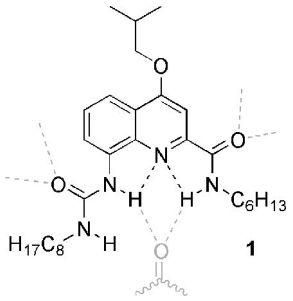


Figure 12. A possible mode for receptor aggregation is indicated for the quinoline derivative **1** (printed in grey).

For comparison, we chose the derivatives **1** and **2** with similar substituents at the urea and at the amide for our studies. Due to intramolecular hydrogen bonding the quinoline possesses a well preorganized N–H arrangement for the binding of anions. The indole, on the other hand, bears an additional hydrogen-bond donor. No intramolecular hydrogen bonds fix the N–H units in a preoriented arrangement. As discussed above, the amide and urea moieties undergo a conformational rearrangement prior to the binding of anions.

The self-aggregation behaviour of quinoline **1** is documented by negative ESI-FTICR measurements of the compound in the presence of tetrabutylammonium chloride (sprayed from chloroform). The quinoline/chloride adduct **1**·Cl^- is observed at m/z = 533 besides the signals of higher

oligomers at *m*/*z* = 1031 ($\mathbf{1}_2$·Cl⁻), 1530 ($\mathbf{1}_3$·Cl⁻), 2028 ($\mathbf{1}_4$·Cl⁻), 2526 ($\mathbf{1}_5$·Cl⁻), and 3025 ($\mathbf{1}_6$·Cl⁻). The high degree of aggregation indicates on one hand that it is not merely unspecific binding. Furthermore, it shows oligomerization to take place by interaction between the receptors and not by binding of several receptors to the anion. The species at *m*/*z* = 1530 ($\mathbf{1}_3$·Cl⁻) and 2082 ($\mathbf{1}_4$·Cl⁻) were isolated in the gas phase and were submitted to a CID experiment (collision-induced decay) in the FTICR cell. The MS/MS spectra show successive losses of quinoline molecules (see Figure 13) from the oligomer. Similar results on the oligomerization of the receptors in the presence of anions were obtained for the indole **2** and for mixtures of **2** and **1**.

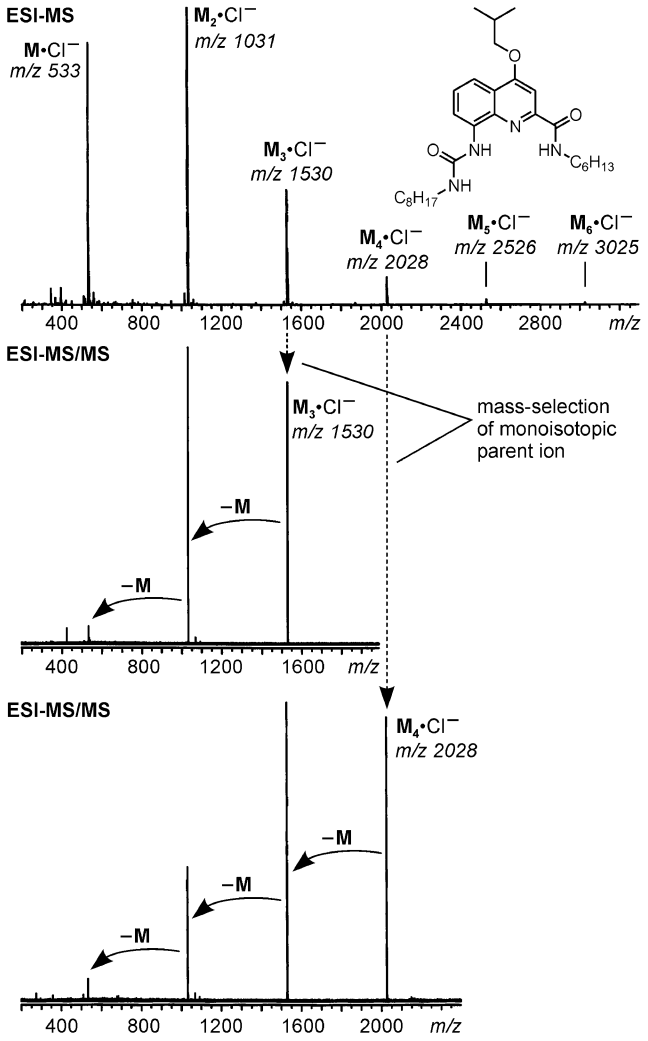


Figure 13. ESI-FTICR MS experiments of receptor **1** (denoted as M) in the presence of Cl⁻ showing the self-aggregation of the receptor as well as the binding of the anion. Mass selection of monoisotopic ions followed by collision-induced decay show the sequential loss of quinolines from the oligomers.

In further studies, **1** and **2** were introduced as competitors for the halide anions F⁻, Cl⁻ and Br⁻ and MS/MS measurements were performed. The spectra are shown in Figure 14.

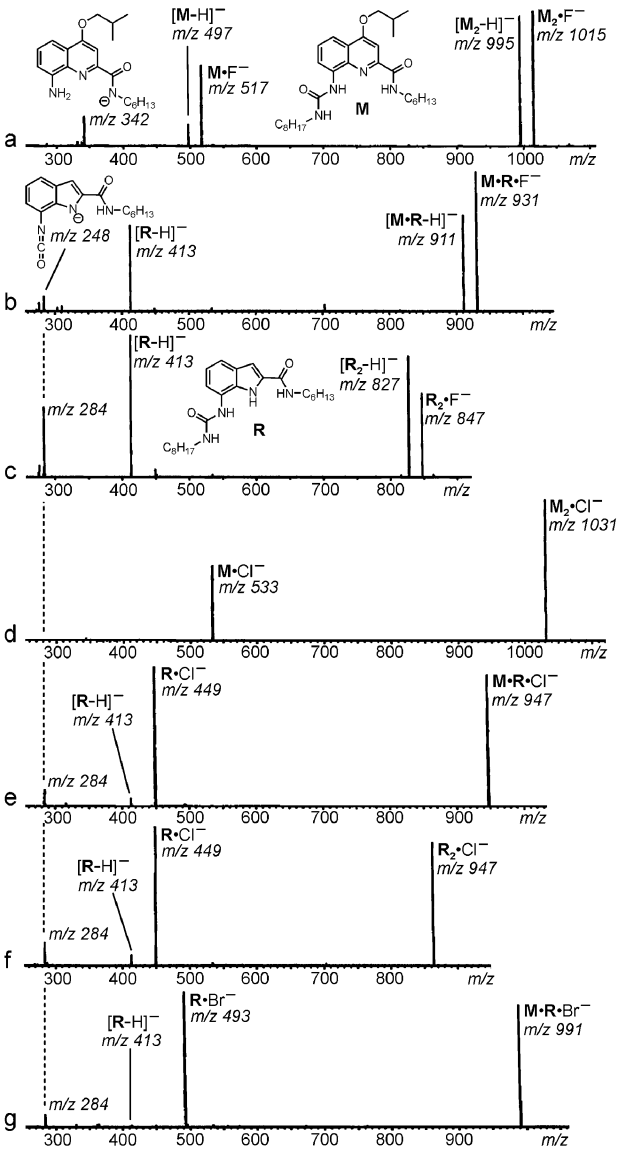


Figure 14. ESI FT-ICR MS CID experiments of receptors **1** (**M**) and **2** (**R**) showing the fragmentation of the isolated peaks $\mathbf{1}_2F^-$ (a), **1·2**F⁻ (b), $\mathbf{2}_2F^-$ (c), $\mathbf{1}_2Cl^-$ (d), **1·2**Cl⁻ (e), $\mathbf{2}_2Cl^-$ (f), and **1·2**Br⁻ (g).

Figure 14 depicts the results obtained with KF/18C6 in methanol (due to the poor solubility of the salt, the crown ether was added). Isolation of $\mathbf{1}_2$·F⁻ at *m*/*z* = 1015 and CID experiments leads to the loss of HF, of **1** and of **1**·HF (Figure 14, a). This is due to the high basicity of the fluoride anion in the gas phase (proton affinities: F⁻ 1529 kJ/mol, Cl⁻: 1373 kJ/mol, Br⁻: 1331 kJ/mol),[17] leading to deprotonation at the receptor. In case of the indole derivative, fragmentation of the "dimer" $\mathbf{2}_2$·F⁻ is observed with fragments corresponding to HF and **2**·HF losses (Figure 14, c). Part b of Figure 14 shows the competition experiment, in which a mixture of both receptors is reacted with fluoride (1:1:1) and the heterodimer **1·2**·F⁻ is isolated and fragmented. Again, the loss of HF from the aggregate is observed leaving a detectable anion [**1·2**-H]⁻. In addition, dissociation of the neutral species M·HF from the parent or the loss of M from [**1·2**-H]⁻ is found with the remaining

anion [**2**-H]$^-$. No peaks can be detected, which show an interaction of indole with fluoride in this competitive system, indicating a significantly higher affinity of the quinoline for fluoride as compared to the indole.[18] We assume that in a species with two receptors and one anion, only one of the receptors binds to the anion, while the second coordinates to a carbonyl of the first.

Performing related experiments with tetrabutyl ammonium chloride or bromide in chloroform does not lead to deprotonation. CID of the peak of mass-selected **1**$_2$·Cl$^-$ (Figure 14, d) or **2**$_2$·Cl$^-$ (Figure 14, f) results in the dissociation of one of the receptor molecules in each case. The same is observed with the mixed species **1·2**·Cl$^-$ (Figure 14, e). However, detection of only the chloride adduct of the indole **2**·Cl$^-$ indicates a higher affinity of chloride to **2** than to the quinoline **1**. Bromide behaves the same way and thus only the MS/MS experiment for the CID of **1·2**·Br$^-$ is shown in Figure 14 (g).

These ESI FT-ICR MS measurements strongly support the NMR spectroscopic findings. An oligomerization of the receptors is observed which can be detected by MS due to introduction of a negative charge by binding of an anion (probably to the terminus of a chain of oligomers). In case of fluoride, deprotonation of the receptor occurs and can be made visible by a CID experiment in the gas phase through the corresponding HF loss side products. In competition experiments using mixtures of the two receptors M and R (1 equiv. each) and one equivalent of halide, a preference of fluoride for the quinoline receptor and of chloride and bromide for the indole is found. This resembles closely the data obtained for the binding of halides by the two receptors, which were obtained by solution studies.

Conclusions

Studies towards the anion binding by indole-type receptors were described. Based on preliminary work with derivatives like **2** which bear a carboxamide unit in 2- and a urea moiety in 7-position, we investigated the importance of the two substituents for the binding of the guest. The urea moiety as well as the indole NH seem to be crucial for the binding of anions. Only in binding studies with nitrate interactions preferentially occur with the urea only. However, the amide in 2-position is essential for the binding of acetate. With halides, small shift effects are observed for this CO–NH and an orientation towards the anion can be shown by NOE. Calculations support an interaction of all four hydrogen-bond donors with the anion in the gas phase. However, this interaction in solution seems to destabilize the binding event either due to steric repulsion, unfavorable dipoles in the receptor, or the loss of entropy. Thus, in the series investigated here the truncated receptor **3** with the indole and urea unit only is the superior receptor for halides.

ESI-MS experiments show, that in solution a competition of anion binding and oligomerization of the receptor takes place which allows the investigation of relative binding affinities by this technique.

In summary, we presented a study towards the optimization of anion binding by substituted indole receptors and found a system **3** which shows high affinities and good selectivities for the chloride anion over the other halides.

Experimental Section

General: NMR spectra are recorded on a Varian Mercury 300, and Inova 300 and 400 spectrometers. FT-IR spectra are recorded on a Perkin–Elmer FT IR 1760 spectrometer (KBr). MS spectra were measured on a Varian MAT 212 spectrometer. Elemental analyses are obtained with a Heraeus CHN-O-Rapid analyzer. Melting points: Büchi B-540 (uncorrected). Fluorescence measurements were performed on a Perkin–Elmer LS 50-B spectrofluorometer.

Ab Initio Calculations: Initial structures were generated by Chem3D Pro 10.0 software and energy minimization was performed without any constraints for four major conformational structures using Gaussian 03.[14] Ab initio calculations of model receptor and their 1:1 Cl$^-$, Br$^-$ and AcO$^-$ binding complexes were carried out. The structures were optimized, and the total electronic energies were calculated with the HF and hybrid B3LYP functional and a polarized 6-311+G(d,p) basis. Frequency calculations verified that the optimized geometries were stable points on the potential energy surface. The one with the lowest energy was chosen as the starting structure used in the following two-step systematic searching of two torsion angles carried out in vacuo. In each step of the systematic searching, potential energy surface was built for the molecule with all the coordinates relaxed except the target torsion angle, which was varied in step size of 15° and 30°. In case of anion-receptor complexes, anion was placed close to NH protons so that could form hydrogen bonds (distance between NH and anion was ca. 1.9 Å). The anion-receptor complex structures were optimized and followed by systematic searching of energy potential in same way as for receptor molecule without anion.

Crystallography: Data were recorded with a Bruker-Nonius Kappa APEX II diffractometer using graphite-monochromatized Mo-K_α radiation [λ = 0.71073 Å] and at 123.0(1) K. The data were processed with Denzo-SMN v0.95.373[19] and the structure was solved by direct methods.[20] Renements based on F^2 were made by full-matrix least-squares techniques.[21] No absorption correction was applied. The hydrogen atoms were calculated to their idealized positions with isotropic temperature factors (1.2 or 1.5 times the C and N temperature factor) and rened as riding atoms.

(Tandem) Mass Spectrometric Experiments: ESI mass spectra and MS/MS spectra were recorded on a Bruker APEX IV Fourier-transform ion cyclotron resonance (FT-ICR) mass spectrometer with an Apollo electrospray ion source equipped with an off-axis 70° spray needle. Typically, chloroform served as the spray solvent and ca. 30–50 μM solutions of the analytes were used. In order to solubilize the anions in this apolar solvent, tetrabutylammonium salts have been utilized. Analyte solutions were introduced into the ion source with a syringe pump (Cole-Parmers Instruments, Series 74900) at flow rates of ca. 3–10 μL/min. Ion transfer into the first of three differential pump stages in the ion source occurred through a glass capillary with 0.5 mm inner diameter and nickel coatings at both ends. Ionization parameters – some with a significant effect on signal intensities – were adjusted as follows: capillary voltage: +3.8 to +4.4 kV; endplate voltage: +2.5 to +3.5 kV; capexit voltage: –50 to –80 V; skimmer voltages: –8 to –10 V; temperature of drying gas: 40 °C. The flow of the drying gas was kept in a medium range (ca. 20 psi), while the flow of the nebulizer gas was rather low (ca.

5 psi). The ions were accumulated in the instruments hexapole for 2–4 s, introduced into the FT-ICR cell which was operated at pressures below 10^{-10} mbar and detected by a standard excitation and detection sequence. For each measurement 16 to 128 scans were averaged to improve the signal-to-noise ratio.

For MS/MS experiments, the whole isotope pattern of the ion of interest was isolated by applying correlated sweeps, followed by shots to remove the higher isotopes. After isolation, argon was introduced into the ICR cell through a pulsed valve at a pressure of ca. 10^{-8} mbar. The ions were accelerated by a standard excitation protocol and detected after a 2 s pumping delay. A sequence of several different spectra was recorded at different excitation pulse attenuations in order to get at least a rough and qualitative idea of the effects of different collision energies.

***N*-Hexyl-7-nitro-1*H*-indole-2-carboxamide (6):** A solution of 7-nitro-1*H*-indol-2-carboxylic acid (**5**; 0.60 g, 2.91 mmol, 1.0 equiv.) and carbonyl diimidazole (0.61 g, 3.75 mmol, 1.3 equiv.) in chloroform (20 mL) was heated at reflux for 1.5 h under an atmosphere of Ar. A solution of *n*-hexylamine (0.31 g, 3.00 mmol, 1.0 equiv.) in chloroform (2 mL) was added and the mixture was heated at reflux for an additional 2 d. After cooling to room temperature, the organic phase was washed with water and dried ($MgSO_4$). The solvent was removed in vacuo. After column chromatography (silica gel, CH_2Cl_2) **6a** was obtained in 91% (0.77 g) as a yellow solid; m.p. 153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.57 (s, 1 H, NH), 8.23 (dd, J = 2.0, 8.0 Hz, 1 H, H_{ar}), 7.97 (d, J = 8.0 Hz, 1 H, H_{ar}), 7.24 (t, J = 8.0 Hz, 1 H, NH), 7.06 (d, J = 2.0 Hz, 1 H, H_{ar}), 6.59 (s, 1 H, H_{ar}), 3.54 (m, 2 H, CH_2), 1.65 (m, 2 H, CH_2), 1.35 (m, 6 H, 3 CH_2), 0.92 (t, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3 (C), 133.7 (C), 133.5 (C), 131.4 (C), 130.0 (C), 129.2 (CH), 121.4 (CH), 119.9 (CH), 102.9 (CH), 39.9 (CH_2), 38.7 (CH_2), 31.5 (CH_2), 29.6 (CH_2), 22.6 (CH_2), 14.0 (CH_3) ppm. MS (EI70 eV): *m*/*z* (%) = 289 (46) [M^+, $C_{15}H_{19}N_3O_3^+$], 271 (22) [$C_{15}H_{17}N_3O_2^+$], 205 (34) [$C_9H_7N_3O_3^+$], 189 (100) [$C_9H_5N_2O_3^+$], 172 (24) [$C_9H_2NO_3^+$], 143 (21) [$C_8HNO_2^+$], 100 (3) [$C_8H_4^+$], 56 (3) [$C_4H_{10}^+$]. IR (KBr): $\tilde{\nu}$ = 3459 (s), 3359 (s), 3310 (s), 3111 (w), 2925 (s), 2856 (s), 1638 (vs), 1564 (vs), 1508 (m), 1477 (s), 1441 (m), 1405 (m), 1290 (vs), 1256 (s), 1155 (w), 1120 (m), 985 (m), 883 (w), 831 (m), 762 (m), 728 (s), 633 (m), 546 (m), 467 (m) cm^{-1}. $C_{15}H_{19}N_3O_3$ (289.33): calcd. C 62.27, H 6.62, N 14.52; found C 62.23, H 6.81, N 14.55.

7-Amino-*N*-hexyl-1*H*-indole-2-carboxamide (7): A mixture of the nitro precursor **6** (0.2 g, 0.69 mmol) dissolved in EtOAC (20–30 mL) and 10% Pd/C was stirred at ambient temperature under 5 bar atmosphere of hydrogen for 4 h. The solution was filtered through Celite, and the solvent was evaporated; yield 0.153 g (0.59 mmol, 85%); m.p. 191 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.09 (s, 1 H, NH), 7.05 (d, J = 7.9 Hz, 1 H, H_{ar}), 6.95 (t, J = 7.9 Hz, 1 H, H_{ar}), 6.82 (s, 1 H, NH), 6.58 (d, J = 7.9 Hz, 1 H, H_{ar}), 6.35 (s, 1 H, H_{ar}), 4.36 (s, 2 H, NH_2), 3.45 (m, 2 H, CH_2), 1.63 (m, 2 H, CH_2), 1.35 (m, 6 H, 3 CH_2), 0.89 (t, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7 (C), 133.1 (C), 130.0 (C), 128.5 (C), 127.6 (C), 121.6 (CH), 111.6 (CH), 108.2 (CH), 102.8 (CH), 40.1 (CH_2), 31.5 (CH_2), 29.6 (CH_2), 26.7 (CH_2), 22.6 (CH_2), 14.0 (CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 259 (59) [M^+, $C_{15}H_{21}N_3O^+$], 158 (100) [$C_9H_6N_2O^+$], 130 (6) [$C_8H_6N_2^+$], 104 (4) [$C_6H_4N_2^+$], 77 (1) [$C_5H_3N^+$]. IR (KBr): $\tilde{\nu}$ = 3410 (s), 3349 (s), 3290 (vs), 3053 (w), 2928 (s), 2857 (m), 1558 (s), 1519 (m), 1426 (s), 1331 (m), 1288 (m), 1256 (m), 814 (m), 781 (m), 731 (m), 690 (m), 607 (w), 547 (w), 510 (w) cm^{-1}. $C_{15}H_{21}N_3O$ (259.35): calcd. C 69.47, H 8.16, N 16.20; found C 68.49, H 8.72, N 16.02.

***N*-Hexyl-7-(3-octylureido)-1*H*-indole-2-carboxamide (2):** Carboxamide **7** (0.48 g, 1.84 mmol, 1.0 equiv.) and *n*-octyl isocyanate (0.43 g, 2.76 mmol, 1.5 equiv.) in chloroform were refluxed for 3 h. After cooling to room temperature the solvent was removed in vacuo. **1** was obtained in 93% (0.71 g, 1.71 mmol) as a black solid; m.p. 127 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.1 (s, 1 H, NH), 8.29 (s, 1 H, NH), 7.42 (d, J = 7.5 Hz, 1 H, H_{ar}), 7.36 (d, J = 7.5 Hz, 1 H, H_{ar}), 7.06 (t, J = 7.8 Hz, 1 H, H_{ar}), 6.86 (s, 1 H, NH), 6.59 (s, 1 H, H_{ar}), 5.44 (s, 1 H, NH), 3.44 (m, 2 H), 3.26 (m, 2 H, CH_2), 1.55 (m, 4 H, 2 CH_2), 1.25 (m, 16 H, 8 CH_2), 0.86 (m, 6 H, 2 CH_3) ppm. ^{15}N NMR ([D$_6$]acetone): δ = 137.8 (N1), 113.0 (N2β), 104.3 (N7α), 90.1 (N7γ) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.9 (C), 156.9 (C), 131.1 (C), 129.1 (C), 124.3 (C), 120.9 (C), 117.7 (CH), 116.3 (CH), 103.2 (CH), 40.5 (CH_2), 39.9 (CH_2), 31.8 (CH_2), 31.5 (CH_2), 30.1 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 14.1 (2 × CH_3), 14.0 (CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 414 (78) [M^+, $C_{24}H_{38}N_4O_2^+$], 285 (100) [$C_{15}H_{21}N_3O^+$], 259 (53) [$C_{15}H_{21}N_3O^+$], 184 (80) [$C_9H_{18}N_3O^+$], 158 (50) [$C_9H_7N_2O^+$], 130 (18) [$C_8H_6N_2^+$], 100 (7) [$C_8H_4^+$], 57 (3) [$C_4H_9^+$]. IR (KBr): $\tilde{\nu}$ = 3304 (vs), 2927 (vs), 2856 (s), 2271 (w), 1675 (m), 1623 (s), 1560 (s), 1437 (s), 1378 (w), 1314 (s), 1252 (m), 1048 (w), 825 (m), 735 (m), 605 (w), 552 (w) cm^{-1}. $C_{24}H_{38}N_4O_2 \cdot 1/4\ H_2O$ (419.08): calcd. C 68.78, H 9.26, N 13.37; found C 68.71, H 8.99, N 14.07.

7-Amino-1*H*-indol (9): A mixture of 7-nitro-1*H*-indole (**8**) (0.2 g, 1.23 mmol) dissolved in EtOAC (20–30 mL) and 10% Pd/C were stirred at ambient temperature under 10 bar atmosphere of hydrogen for 24 h. The solution was filtered through Celite, and the solvent was evaporated. **9** was obtained in 90% (0.18 g, 1.36 mmol) as a grey solid; m.p. 97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (br. s, 1 H, NH), 7.20 (dd, J = 1.0, 8.0 Hz, 1 H, H_{ar}), 7.09 (t, J = 7.4 Hz, 1 H, H_{ar}), 6.96 (t, J = 7.4 Hz, 1 H, H_{ar}), 6.59 (dd, J = 1.0, 8.0 Hz, 1 H, H_{ar}), 6.52 (d, J = 3.0 Hz, 1 H, H_{ar}), 3.43 (br. s, 2 H, NH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 130.9 (C), 129.0 (C), 127.0 (C), 124.0 (CH), 120.6 (CH), 112.8 (CH), 108.7 (CH), 103.4 (CH) ppm. MS (EI, 70 eV): *m*/*z* (%) = 132 (100) [M^+, $C_8H_8N_2^+$], 104 (27) [$C_6H_4N_2^+$], 77 (6) [$C_5H_3N^+$]. IR (KBr): $\tilde{\nu}$ = 3369 (s), 3305 (m), 3217 (m), 3053 (w), 3003 (w), 2924 (w), 2857 (w), 1582 (s), 1498 (m), 1442 (s), 1386 (w), 1352 (m), 1300 (m), 1259 (m), 1234 (m), 1172 (w), 1114 (m), 1048 (m), 877 (m), 794 (vs), 728 (vs), 667 (m), 602 (m), 542 (m), 476 (m) cm^{-1}. $C_8H_8N_2$ (132.16): calcd. C 72.70, H 6.10, N 21.20; found C 72.68, H 5.99, N 20.71.

1-Butyl-3-(1*H*-indol-7-yl)urea (3a): 7-Amino-1*H*-indole (**9**) (0.1 g, 0.76 mmol, 1.0 equiv.) and *n*-butyl isocyanate (0.11 g, 1.14 mmol, 1.5 equiv.) in chloroform were refluxed for 24 h. After cooling to room temperature the solvent was evaporated. **3a** was obtained in 91% (0.16 g, 0.69 mmol) as a black solid; m.p. 137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.1 (s, 1 H, NH), 7.50 (d, J = 7.7 Hz, 1 H, H_{ar}), 7.23 (s, 1 H, NH), 7.07 (t, J = 7.7 Hz, 1 H, H_{ar}), 6.94 (d, J = 7.4 Hz, 1 H, H_{ar}), 6.55 (d, J = 7.4 Hz, 2 H, H_{ar}), 5.17 (s, 1 H, NH), 3.26 (t, J = 7.1 Hz, 2 H, CH_2), 1.50–1.42 (m, 2 H, CH_2), 1.35–1.28 (m, 2 H, CH_2), 0.89 (t, J = 7. 1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7 (C), 129.9 (2 × C), 124.8 (CH), 122.4 (CH), 119.6 (C), 118.0 (CH), 115.2 (CH), 102.5 (CH), 40.3 (CH_2), 32.1 (CH_2), 20.0 (CH_2), 13.7 (CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 231 (39) [M^+, $C_{13}H_{17}N_3O^+$], 158 (9) [$C_{10}H_{10}N_2^+$], 132 (100) [$C_8H_8N_2^+$], 104 (13) [$C_6H_4N_2^+$], 77 (3) [$C_5H_3N^+$]. IR (KBr): $\tilde{\nu}$ = 3392 (s), 3254 (m), 3167 (w), 3100 (w), 3048 (w), 2957 (m), 2930 (m), 2863 (m), 1653 (vs), 1625 (s), 1562 (vs), 1435 (s), 1349 (m), 1306 (m), 1258 (m), 789 (m), 764 (m), 726 (s), 512 (w), 463 (m) cm^{-1}. $C_{13}H_{17}N_3O$ (231.29): calcd. C 67.51, H 7.41, N 18.17; found C 66.93, H 7.41, N 17.84.

3-(1*H*-Indol-7-yl)-1-octylurea (3b): 7-Amino-1*H*-indole (**9**) (0.15 g, 1.13 mmol, 1.0 equiv.) and octyl isocyanate (0.26 g, 1.70 mmol, 1.5 equiv.) in chloroform were refluxed for 24 h. After cooling to room temperature the solvent was removed in vacuo. The receptor was purified by filtration in MeOH and followed by several washes with MeOH. **3b** was obtained in 58% (0.19 g, 0.66 mmol) as a yellow solid; m.p. 137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.13 (s, 1 H, NH), 7.49 (d, J = 8.0 Hz, 1 H, H_{ar}), 7.23 (d, J = 2.0 Hz, 1 H, H_{ar}), 7.07 (t, J = 8.0 Hz, 1 H, H_{ar}), 6.93 (d, J = 7.4 Hz, 1 H, H_{ar}), 6.55 (d, J = 2.0 Hz, 1 H, H_{ar}), 5.18 (s, 1 H, NH), 3.26 (t, J = 7.4 Hz, 2 H, CH_2), 1.55–1.44 (m, 12 H, 6 CH_2), 0.87 (m, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9 (C), 129.9 (2 × C), 124.8 (CH), 122.4 (CH), 119.6 (C), 117.9 (CH), 115.2 (CH), 102.5 (CH), 40.6 (CH_2), 31.7 (CH_2), 30.0 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 287 (41) [M^+, $C_{17}H_{25}N_3O^+$], 132 (100) [$C_8H_8N_2^+$]. IR (KBr): $\tilde{\nu}$ = 3388 (vs), 3306 (vs), 3099 (w), 2925 (vs), 2854 (s), 1695 (w), 1630 (vs), 1566 (s), 1469 (m), 1431 (m), 1380 (w), 1341 (m), 1240 (s), 1104 (w), 1050 (w), 1019 (m), 808 (m), 777 (m), 720 (s), 626 (s), 509 (s), 469 (w) cm^{-1}. $C_{17}H_{25}N_3O$·1/4 CH_3OH (300.40): calcd. C 70.17, H 8.81, N 14.24; found C 69.77, H 9.18, N 13.36.

Crystal Data for 3b: $C_{17}H_{25}N_3O$, crystal size 0.30 × 0.28 × 0.18 mm, monoclinic, space group *P*c, a = 16.3756(6) Å, b = 4.6787(1) Å, c = 10.1995(4) Å, β = 91.120(2)°, V = 781.30(5) Å^3, Z = 2, D_{calc} = 1.222 g/cm^{-3}, μ = 0.077 mm^{-1}, 4416 reections measured ($2\theta_{max}$ = 25°), 1388 independent, 1305 with $I > 2\sigma(I)$, number of parameters 199, R_{int} = 0.0480, R = 0.0328 [$I > 2\sigma(I)$], wR^2 = 0.0751 [all data], GOF = 1.114. Maximum and minimum peaks in the difference map, 0.140 and –0.146 e Å^{-3}.

CCDC-729713 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

***N*-(1*H*-Indol-7-yl)propionamide (4):** 1.23 g of HBTU (3.24 mmol, 1.2 equiv.) was added to a solution of propionic acid (0.20 g, 2.70 mmol, 1.0 equiv.) and diisopropylethylamine (0.38 g, 2.97 mmol, 1.1 equiv.) in acetonitrile (20 mL). Then 0.36 g (2.70 mmol, 1.0 equiv.) of 7-amino-1*H*-indole was added. The mixture was strirred at room temp. for an additional 18 h. The solvent was removed in vacuo and the solid phase was dissolved in ethyl acetate. This organic phase was washed with ammonium chloride, sodium hydrogen carbonate, water und sodium chloride solution and dried ($MgSO_4$). After removing the solvent in vacuo and after recrystallization from MeOH **4** was obtained in 59% (0.3 g, 1.59 mmol) as a grey solid; m.p. 160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.05 (s, 1 H, NH), 7.48 (d, J = 8.0 Hz, 1 H, H_{ar}), 7.27 (s, 1 H, NH), 7.24 (t, J = 2.8 Hz, 1 H, H_{ar}), 7.01 (t, J = 7.7 Hz, 1 H, H_{ar}), 6.76 (d, J = 7.7 Hz, 1 H, H_{ar}), 6.58 (t, J = 2.8 Hz, 1 H, H_{ar}), 2.57 (q, J = 7.7 Hz, 2 H, CH_2), 1.37 (t, J = 7.7 Hz, 3 H, CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 188 (74) [M^+, $C_{11}H_{12}N_2O^+$], 132 (100) [$C_8H_8N_2^+$], 104 (24) [$C_6H_4N_2^+$], 77 (9) [$C_5H_3N^+$], 57 (13). IR (KBr): $\tilde{\nu}$ = 3746 (w), 3428 (s), 3309 (vs), 3078 (w), 2981 (w), 2364 (m), 2344 (m), 1646 (vs), 1552 (vs), 1433 (s), 1381 (w), 1342 (m), 1260 (m), 1068 (m), 843 (m), 795 (w), 726 (s), 556 (m) cm^{-1}. $C_{11}H_{12}N_2O$ (188.23): calcd. C 70.19, H 6.43, N 14.88; found C 69.83, H 6.51, N 14.45.

Supporting Information (see also the footnote on the first page of this article): Table S1: Cartesian coordinates for the B3LYP/6-311+G(d,p) optimized model receptor structures and model receptor·Cl^- complexes.

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[1] a) E. Fischer, *Ber. Dtsch. Chem. Ges.* **1894**, *28*, 2985–2993; b) P. Ehrlich, *Studies on immunity*, Wiley, New York, **1906**.
[2] T. Steitz, *New Scientist* **1968**, *38*, 568–570.
[3] a) A. Bianchi, K. Bowman-James, E. Garcia-España (Eds.), *Supramolecular Chemistry of Anions*, Wiley-VCH, New York, **1997**; b) K. Kavallieratos, S. R. deGala, D. J. Austin, R. H. Crabtree, *J. Am. Chem. Soc.* **1997**, *119*, 2325–2326; c) K. Kavallieratos, C. M. Bertao, R. H. Crabtree, *J. Org. Chem.* **1999**, *64*, 1675–1683; d) P. D. Beer, P. A. Gale, *Angew. Chem.* **2001**, *113*, 502–532; *Angew. Chem. Int. Ed.* **2001**, *40*, 486–516; e) K. Bowman-James, *Acc. Chem. Res.* **2005**, *38*, 671–678; f) J. L. Sessler, P. A. Gale, W. S. Cho, *Anion Receptor Chemistry*, Royal Society of Chemistry, Cambridge, **2006**; g) R. Vilar, *Eur. J. Inorg. Chem.* **2008**, 357–367.
[4] a) J. W. Pflugrath, F. A. Quiocho, *J. Mol. Biol.* **1988**, *200*, 163–180; b) B. L. Jacobson, F. A. Quiocho, *J. Mol. Biol.* **1988**, *204*, 783–787.
[5] a) F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, *97*, 1609–1646; b) P. A. Gale, *Coord. Chem. Rev.* **2000**, *199*, 181–233; c) P. A. Gale, *Coord. Chem. Rev.* **2001**, *213*, 79–128; d) P. A. Gale, *Coord. Chem. Rev.* **2003**, *240*, 191–221; e) C. R. Bondy, S. J. Loeb, *Coord. Chem. Rev.* **2003**, *240*, 77–99; f) P. A. Gale, R. Quesada, *Coord. Chem. Rev.* **2006**, *250*, 3219–3244; g) S. O. Kang, R. A. Begum, K. Bowman-James, *Angew. Chem.* **2006**, *118*, 8048–8061; *Angew. Chem. Int. Ed.* **2006**, *45*, 7882–7894; h) F. P. Schmidtchen, *Coord. Chem. Rev.* **2006**, *250*, 2918–2928; i) P. A. Gale, *Acc. Chem. Res.* **2006**, *39*, 465–475; j) P. A. Gale, S. E. Garcia-Garrido, J. Garric, *Chem. Soc. Rev.* **2008**, *37*, 151–190.
[6] a) Y. Hamuro, S. J. Geib, A. D. Hamilton, *Angew. Chem.* **1994**, *106*, 465–467; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 446–448; b) C. A. Hunter, L. D. Sarson, *Angew. Chem.* **1994**, *106*, 2424–2426; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2313–2316; c) A. Affeld, G. M. Hübner, C. Seel, C. A. Schalley, *Eur. J. Org. Chem.* **2001**, 2877–2890; d) S.-Y. Chang, H. S. Kim, K.-J. Chang, K.-S. Jeong, *Org. Lett.* **2004**, *6*, 181–184.
[7] a) M. Albrecht, Triyanti, M. de Groot, M. Bahr, E. Weinhold, *Synlett* **2005**, 2095–2097; b) M. Albrecht, Triyanti, S. Schiffers, O. Osetska, G. Raabe, T. Wieland, L. Russo, K. Rissanen, *Eur. J. Org. Chem.* **2007**, 2850–2858.
[8] a) K.-J. Chang, D. Moon, M. S. Lah, K.-S. Jeong, *Angew. Chem.* **2005**, *117*, 8140–8143; *Angew. Chem. Int. Ed.* **2005**, *44*, 7926–7929; b) K. J. Chang, B. N. Kang, M. H. Lee, K. S. Jeong, *J. Am. Chem. Soc.* **2005**, *124*, 12214–12215; c) K.-J. Chang, M. K. Chae, C. Lee, J.-Y. Lee, K.-S. Jeong, *Tetrahedron Lett.* **2006**, *47*, 6385–6388; d) J. L. Sessler, D. G. Cho, V. Lynch, *J. Am. Chem. Soc.* **2006**, *128*, 16518–16519; e) T. H. Kwon, K.-S. Jeong, *Tetrahedron Lett.* **2006**, *47*, 8539–8541; f) F. M. Pfeffer, K. F. Lim, K. J. Sedgwick, *Org. Biomol. Chem.* **2007**, *5*, 1795–1799; g) J.-Y. Lee, M.-H. Lee, K.-S. Jeong, *Supramol. Chem.* **2007**, *19*, 257–263; h) T. Zielinski, P. Dydio, J. Jurczak, *Tetrahedron* **2008**, *64*, 568–574.
[9] G. W. Bates, Triyanti, M. E. Light, M. Albrecht, P. A. Gale, *J. Org. Chem.* **2007**, *72*, 8921–8927.
[10] M. Bodanszky, A. Bodanszky, *The Practice of Peptide Synthesis*, Springer, Berlin, **1984**.
[11] a) C. S. Wilcox, in: H.-J. Schneider, H. Dürr (Eds.), *Frontiers in Supramolecular Chemistry and Photochemistry*, VCH, Weinheim, Germany, **1991**, p. 123; b) K. A. Connors, *Binding Constants*, Wiley, New York, **1987**.

[12] For the role of halide binding in nature see, for example: K. H. G. Verschueren, F. Seljee, H. J. Rozeboom, K. H. Kalk, B. W. Dijkstra, *Nature* **1993**, *363*, 693–698.
[13] a) M. Boiocchi, L. Del Boca, D. E. Gomez, L. Fabbrizzi, M. Licchelli, E. Monzani, *J. Am. Chem. Soc.* **2004**, *126*, 16507; b) V. Amendola, D. Esteban-Gomez, L. Fabbrizzi, M. Licchelli, *Acc. Chem. Res.* **2006**, *39*, 343–353.
[14] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzales, J. A. Pople, *Gaussian*, Inc., Pittsburgh PA, **2003**.
[15] a) C. A. Schalley, *Int. J. Mass Spectrom.* **2000**, *194*, 11–39; b) C. A. Schalley, *Mass Spectrom. Rev.* **2001**, *20*, 253–309.
[16] M. Albrecht, K. Witt, E. Wegelius, K. Rissanen, *Tetrahedron* **2000**, *56*, 591.
[17] Data taken from: H. Y. Afeefy, J. F. Liebman, S. E. Stein, *Neutral Thermochemical Data*, in: *NIST Chemistry WebBook*, NIST Standard Reference Database Number 69 (Eds.: P. J. Linstrom, W. G. Mallard), June **2005**, National Institute of Standards and Technology, Gaithersburg MD, 20899, USA (http://webbook.nist.gov).
[18] This is a further indication for the inaccuracy of the determination of the **2**·F^- binding constant (Table 2).
[19] Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307–326.
[20] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467–473.
[21] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.
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