

Anion-induced conformational changes in 2,7-disubstituted indole-based receptors

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The conformational preorganization and anion-induced conformational changes of indole-based receptors functionalized with amido group at C2 and a variety of amido, urea and thiourea moieties at C7 have been studied by the means of NMR spectroscopy. NOE experiments showed that *anti-anti* orientation across C2–C2 α and C7–N7 α bonds is preferred for receptors **1-4** in acetone solution in the absence of anions. Anion-receptor interactions have been evaluated through ¹H and ¹⁵N chemical shift changes. In bis-amido 2,7-functionalised indoles the interaction with chloride and bromide anions primarily occurs at H1 proton. The formal introduction of urea and thiourea moieties increases the number of hydrogen bond donor sites which manifests itself in distribution of halide-receptor interactions among H1, H7 α and H7 γ protons. Acetate anions also interact strongly with indole and urea NH donor groups, whereas nitrate anions interact solely with H7 α and H7 γ urea/thiourea protons. NOE enhancements in the presence of anions revealed that anion-receptor complexes favor *syn-syn* conformation of C2 and C7 substituents.

Introduction

The development of unique anion receptors, sensors and transporters is an area of intense research activity.¹⁻⁵ Potential applications in the separation and extraction of anionic species, in the development of new sensing systems and in the design of new compounds that may have potential biological activity has driven the synthesis of a plethora of receptors containing amides and thioamides, pyrroles and indoles, ureas and thioureas, ammonium, guanidinium and imidazolium moieties.^{6, 7}

Indole is employed by Nature in sulfate binding protein⁸ and in the enzymatic active site of haloalkane dehalogenase⁹ to bind anions, however research in area of indole-based anion receptors¹⁰⁻²⁰ is still at an early stage compared to the range of anion receptors based on pyrrole.²¹ The recognition and sensing properties of indole can be effectively regulated by appending additional hydrogen bond donors to the indole skeleton. Amides have been widely used as hydrogen bond donor groups to bind anionic species²², whilst urea and thiourea moieties have been as well extensively employed as receptors for Y-shaped oxo-anions through two directional hydrogen bonds.^{23, 24}

In this study we have analysed the potential conformational preorganization and conformational changes of four previously synthesized bis-amido and mono-amido-mono-urea 2,7-functionalised indoles²⁵ in the presence of a diverse range of anionic guests with anions using NMR techniques. The indoles have a variety of substituents in the 7-position including secondary amides, urea and thiourea groups (Figure 1) and a carboxamidophenyl substituent in the 2-position. Crystal structure elucidation of solid-state complexes of these species with anions and solution stability constant determinations in DMSO-*d*₆/0.5% water have been conducted

previously.²⁵

Results

NMR assignment

NMR spectroscopy has been used to evaluate and correlate structural and conformational properties of anion receptors **1-4** in acetone-*d*₆ to their preorganization for interaction with anions. As a first step, ¹H, ¹³C and ¹⁵N resonances of **1-4** have been assigned based on the analysis of 1D proton and carbon spectra as well as ¹³C-¹H and ¹⁵N-¹H correlations in 2D HSQC and HMBC spectra. The selected ¹H and ¹⁵N NMR chemical shifts are reported in Table 1, with the full list including ¹³C NMR data available in the Experimental.

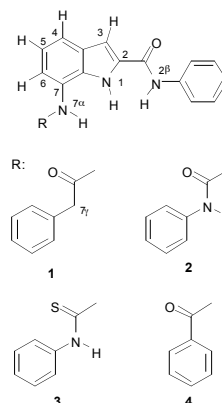


Figure 1. Anion receptors **1-4** and atom numbering.

Table 1. Selected ^1H and ^{15}N NMR Chemical Shifts for **1-4**.^a

	H1	H2 β	H7 α	H7 γ	H6	N1	N2 β	N7 α	N7 γ
1	10.87	9.59	9.61	3.86	7.53	136.5	128.2	131.8	–
2	10.91	9.59	8.43	8.26	7.28	136.2	128.2	106.1	110.4
3	10.75	9.61	9.07	9.16	7.37	133.8	128.4	125.4	133.1
4	10.91	9.62	9.80	–	7.64	136.6	128.3	126.4	–

^a Reported chemical shifts (in ppm) correspond to NMR spectra acquired in acetone- d_6 at 298 K. The complete set of ^1H and ^{13}C NMR chemical shifts is available in the Experimental.

The different physicochemical properties of C7-substituents in 2,7-bisfunctionalized indoles **1-4** are reflected in NMR parameters and in particular in the chemical shielding of their inherent H-bond donors. Receptor **1** with its phenylacetamido group exhibits H7 α and N7 α chemical shifts of 9.61 and 131.8 ppm, respectively. The introduction of urea moiety in **2** manifests itself in the considerable upfield shifts of H7 α and N7 α to 8.43 and 106.1 ppm, respectively. Additional nitrogen atom N7 γ in **2** exhibits chemical shift of 110.4 ppm with the corresponding H7 γ proton resonating at 8.26 ppm. Substitution of oxygen atom in **2** with sulfur in **3** causes considerable deshielding of H7 α , H7 γ , N7 α and N7 γ which is in agreement with the more acidic nature of thiourea moiety (Table 1). Moderate deshielding of H7 α in **4** with respect to **1** has been attributed to its benzoylamido group. On the other hand, N7 α in **4** is shielded by 5.4 ppm with regard to **1**. Considerable changes of H7 α and N7 α chemical shifts in **1-4** correspond to variations in the electron donating/withdrawing nature of N7 α -substituents. The minute alterations of chemical shifts of H2 β and N2 β are in agreement with invariant C2 substituent. The ^{13}C chemical shifts changes are insignificant and do not reflect that different groups have been attached to C7 atom (Experimental).

^1H NMR chemical shift changes in **1-4** upon anion interactions

The chemical shift values changed upon addition of one equivalent of chloride, bromide, nitrate and acetate ions added as tetrabutylammonium salts to receptors **1-4**. The anion-receptor interactions induced a significant change in the chemical shielding of ^1H and ^{15}N NMR resonances and only minor changes in ^{13}C resonances. Figure 2 illustrates ^1H chemical shift changes in **2** upon interaction with different anions. Significant deshielding of H1, H7 α and H7 γ protons was observed upon addition of chloride or bromide anions to solution of **2** (Figures 2a-c). Interaction of nitrate anions with **2** resulted in relatively smaller downfield shifts of the urea H7 α and H7 γ protons (Figure 2d). The significant deshielding of all four NH protons of **2** indicated a strong interaction with acetate anions (Figure 2e).

A comparison of proton $\Delta\delta$ values induced upon addition of one equivalent of the four anions to receptors **1-4** is shown in Figure 3. The chemical shift of H1 shows the greatest change among all NH protons in **1** upon interaction with chloride (Figure 3a). Moderate chemical shift changes of H2 β and H7 α

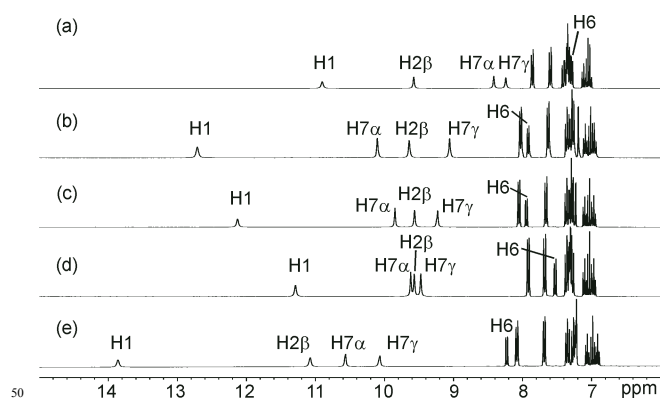


Figure 2. ^1H NMR spectra of **2** in the absence of anions (a) and upon addition of one equivalent of the following anions: chloride (b), bromide (c), nitrate (d) and acetate (e). All spectra were recorded at 298 K.

were observed for the **1**·Cl⁻ complex, while the methylene H7 γ

shows only a negligible change. The significantly larger $\Delta\delta$ values for both the urea H7 α and H7 γ protons in **2**·Cl⁻ should be noted vs. **1**·Cl⁻, whereas the H2 β chemical shift change is smaller. However, the $\Delta\delta$ value for indole H1 is the largest ^1H chemical shift change upon formation of **2**·Cl⁻. A similar trend was observed for **3**·Cl⁻, where strong deshielding of H7 α and H7 γ protons is in accordance with the higher acidity of thiourea group. Interestingly, a significant chemical shift change of H6 was observed in **3**·Cl⁻ which is most probably the result of conformational changes and will be discussed later. In contrast to the other three receptors, the smallest $\Delta\delta$ value for H7 α and greatly increased deshielding of H1 and H2 β protons upon formation of **4**·Cl⁻ complex can be attributed to the benzoylamido substituent at C7 (Figure 3a).

The addition of bromide anions resulted in a slightly smaller downfield chemical shift changes in all four receptors in comparison to chloride anions (*cf.* Figures 3a and 3b). As both anions are spherical, the main reason for these differences can be attributed to their different size and basicity. H1 showed significant downfield shifts in **1**·Br⁻ and **4**·Br⁻ complexes, whereas **2**·Br⁻ and **3**·Br⁻ exhibited considerable deshielding of H1, H7 α and H7 γ . The latter suggested that all mentioned protons participate in the interaction with bromide anions.

Notably smaller chemical shifts changes were observed upon addition of nitrate to **1-4** compared to the other anions studied. Receptors **1** and **4** which lack urea or thiourea moieties show relatively small $\Delta\delta$ values below 0.4 ppm, which lead us to suggest only minor nitrate-receptor interactions are occurring in this case (Figure 3c). On the other hand, in **2** and **3** deshielding of both H7 α and H7 γ protons by up to 1.3 ppm was observed upon addition of nitrate anions.

Significant $\Delta\delta$ values of up to 3.3 ppm of NH protons in all four studied receptors occurred upon addition of acetate anions to **1-4** (Figure 3d) consistent with the formation of strong complexes.²⁵

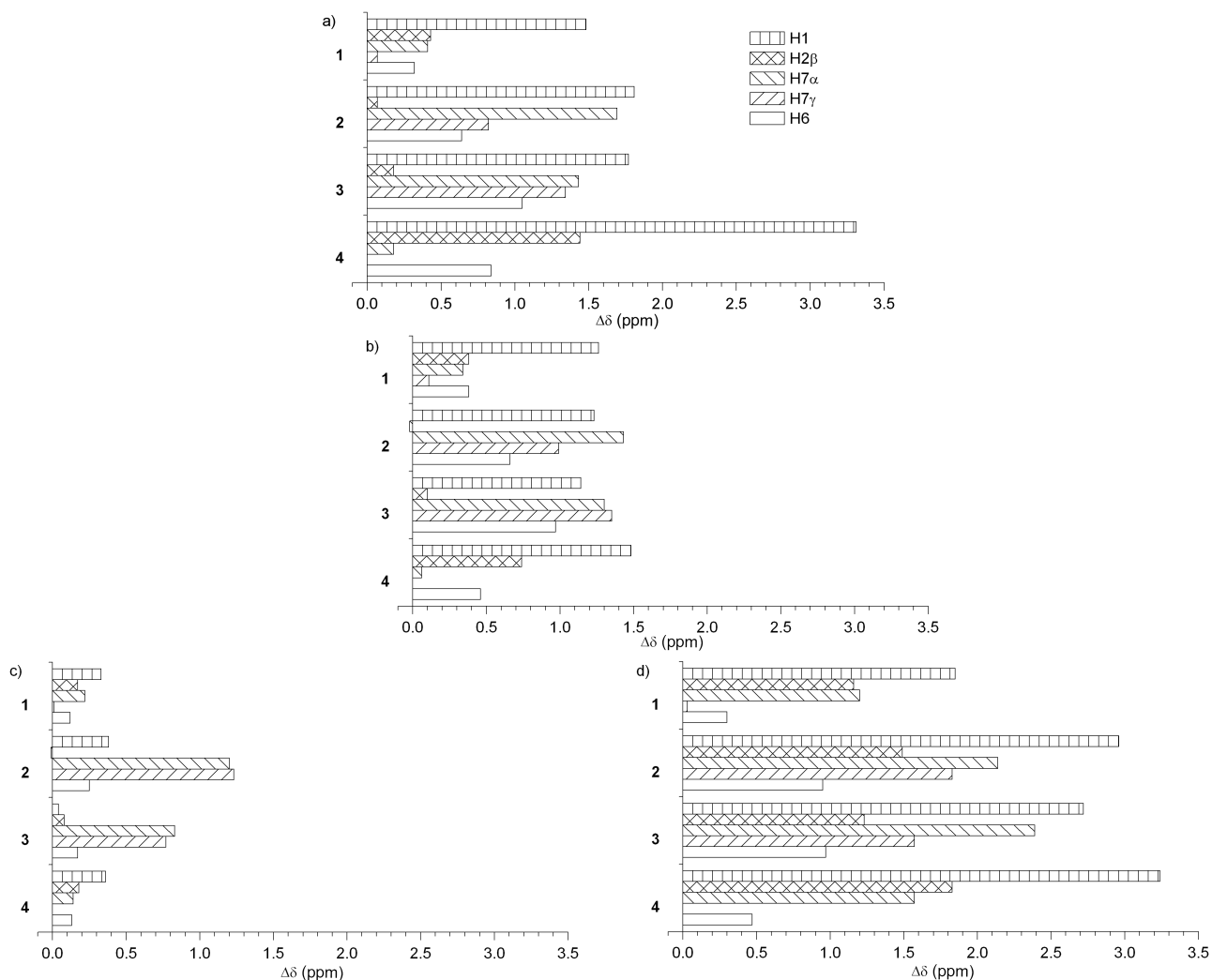


Figure 3. ¹H NMR chemical shift changes, $\Delta\delta = \delta(\text{in the presence of anions}) - \delta(\text{in the absence of anions})$, induced by addition of one equivalent of chloride (a), bromide (b), nitrate (c) and acetate (d) anions to receptors 1-4. Note, there is no H7 γ proton in 4.

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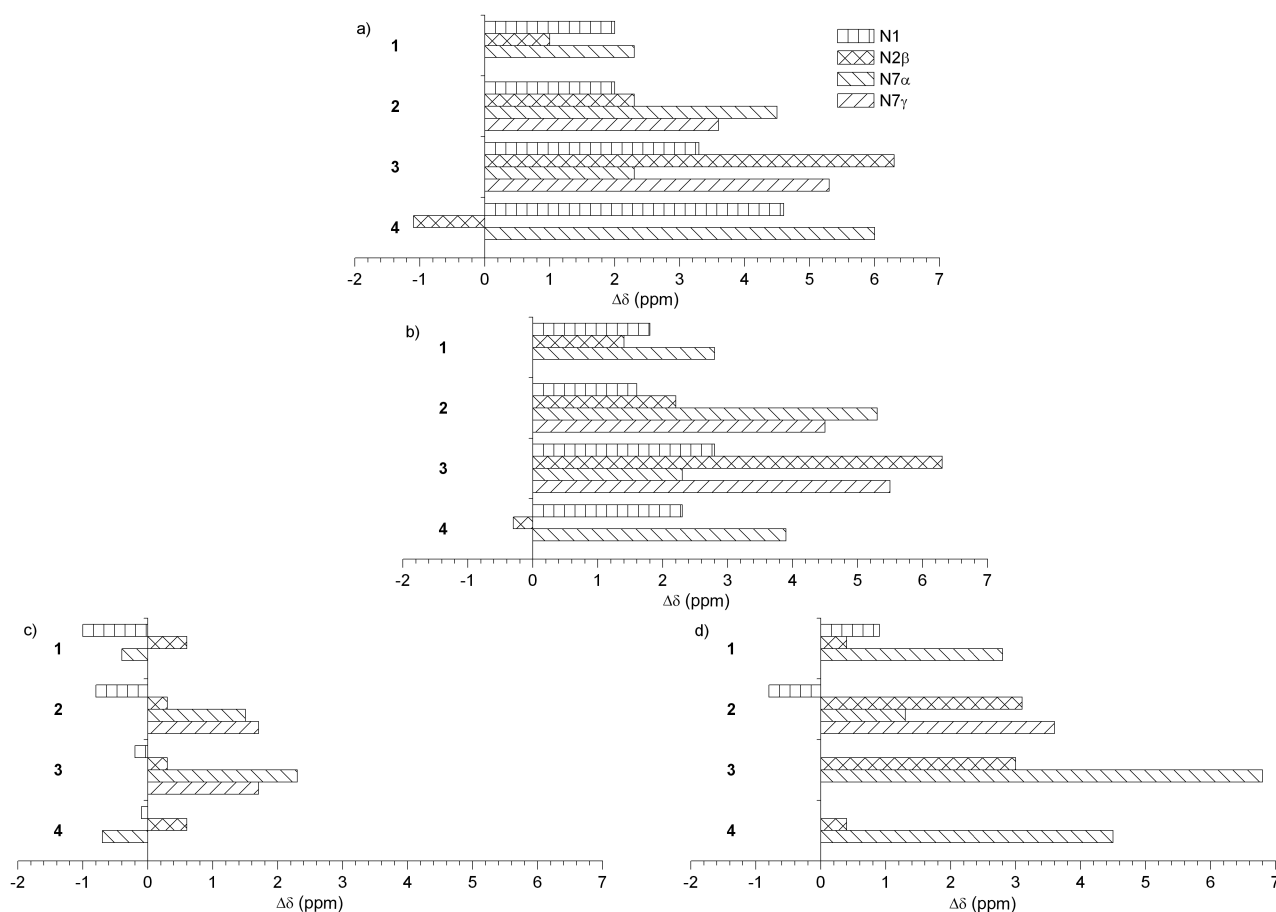


Figure 4. ¹⁵N NMR chemical shift changes, $\Delta\delta = \delta(\text{in the presence of anions}) - \delta(\text{in the absence of anions})$, induced by addition of one equivalent of chloride (a), bromide (b), nitrate (c) and acetate (d) anions to receptors 1-4. Note, ¹⁵N chemical shifts could not be determined for some atoms due to signal broadening after addition of acetate to 3 and 4. There is no N7 γ in 1 and 4.

¹⁵N NMR chemical shift changes induced by anion interactions

Anion-receptor interactions evaluated through ¹H chemical shift changes have been supported by ¹⁵N NMR data (Figure 4). The largest $\Delta\delta$ values in 1, 2 and 4 upon addition of chloride and bromide anions were observed for N7 α , whereas in 3 chemical shifts of N2 β atom changed the most (Figures 4a and 4b). N2 β and N7 γ atoms in 2 and 3 were also deshielded upon interaction with Cl⁻ and Br⁻. Interestingly, N1 was deshielded upon addition of one equivalent of chloride and bromide anions, and shielded in the presence of nitrate anions in 1-4 (Figures 4a-c). The substitution of methylene H7 γ in 1 with the NH group in 2 leads to increased deshielding of N2 β upon addition of chloride, bromide and acetate anions. The change was magnified even further with $\Delta\delta$ values up to 6.8 ppm when urea (2) was swapped for thiourea moiety (3). A similar increase of N7 γ deshielding ($\Delta\delta$ up to 5.5 ppm) in the presence of chloride and bromide was observed in 3 with respect to 2. The interaction of Cl⁻ with 4 leads to deshielding of N1 and N7 α by up to 4.6 and 6.0 ppm, respectively, whereas N2 β is shielded in 4•Cl⁻ complex (Figure 4a). Analogous albeit smaller chemical shift changes were observed in 4•Br⁻ complex (Figure 4b). Addition of nitrate anions results in lower $\Delta\delta$ values. The largest ¹⁵N chemical shift changes of up to 2.5 ppm were observed for

N7 α and N7 γ atoms in 2 and 3 (Figure 4c).

Conformational properties of receptors 1-4 in the absence and in the presence of anions

Conformational equilibria of 2,7-functionalized indole receptors have been studied with the use of 1D difference NOE experiments. As an example, a 1D difference NOE spectra of 2 in the absence and upon addition of Cl⁻ ions are shown in Figure 5. Four well resolved NH protons have enabled unequivocal quantification of NOE enhancements. The predominant orientation of 2-phenylcarboxamide group in 2 has been established by the strong NOE enhancement of 14.5% at H3 upon saturation of the carboxamide H2 β proton (Figure 5e). In full agreement, the saturation of H2 β has resulted in a very weak NOE at H1 (0.5%). The orientation along C7–C7 α bond in 2 has been established through NOE enhancements among H1, H6 and H7 α . Relatively strong {H7 α }-H6 (7.3%) and weaker {H1}-H7 α NOEs (2.9%) have suggested the predominant conformation with H7 α pointing away from indole H1 proton (Figures 5c and 5g). A considerable decrease of {H2 β }-H3 and {H7 α }-H6 NOE enhancements to 7.5% and 2.7% was observed upon addition of chloride anions, respectively (Figures 5f and 5h). Furthermore, observation of NOE enhancements among H1-H2 β and H1-H7 α lead us to suggest conformational changes

occur in **2** upon interaction with chloride anions (*cf.* Figures 5c-d, 5e-f and 5g-h).

The key NOE enhancements for **1-4** in the absence and in the presence of one equivalent of anions are presented in Table 2. Relatively strong {H2 β }-H3 NOE (8.5%) in **1** is evidence to support the spatial proximity of H2 β and H3 protons. Such orientation across C2-C2 α bond is in accordance with weak NOEs between H2 β and H1 (\leq 1.0%). The saturation of H7 α has resulted in weak NOE enhancement at H1 (\leq 1.0%), whereas stronger NOE was observed at H6 (3.2%). The saturation of H1 yields a weak overall NOE at H2 β and H7 α protons (Table 2). Although the H2 β and H7 α signals overlap in **1**, differences in overall NOE values in the absence and in the presence of anions have turned out to be very informative in the assessment of conformational properties. Addition of one equivalent of chloride to **1** has altered several NOE enhancements. The saturation of H2 β and H7 α has resulted in an increase of NOE at H1 from \leq 1.0% to 6.9%, and a decrease of {H2 β }-H3 NOE from 8.5% to 4.9% and {H7 α }-H6 NOE from 3.2% to 2.1% (Table 2). Furthermore, the saturation of H1 has caused major increase of overall NOE at H2 β and H7 α (13.0%). Addition of bromide to **1** has triggered very similar changes which lead us to suggest an analogous predominant conformation as established for **1**·Cl⁻ complex (Table 2). In contrast, addition

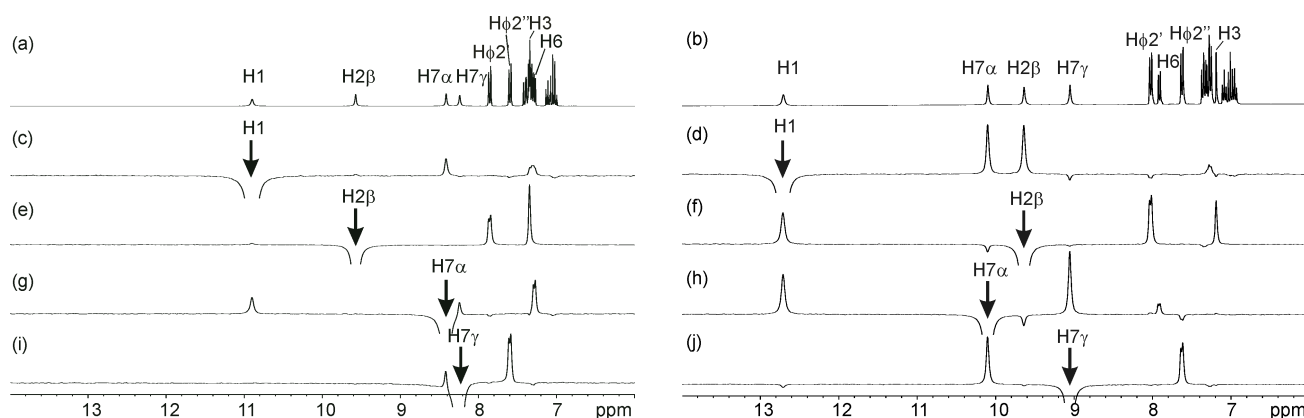


Figure 5. ¹H NMR spectra of **2** in the absence (a) and in the presence of Cl⁻ ions (b), and corresponding 1D difference NOE spectra upon saturation of H1 (c-d), H2 β (e-f), H7 α (g-h) and H7 γ protons (i-j). All spectra were recorded at 298 K.

of nitrate anions to **1** has resulted in strong {H2 β }-H3 NOE and moderate increase of {H7 α }-H6 NOE which indicated negligible conformational changes in **1** upon interaction with NO₃⁻ (Table 2). The decrease of {H2 β }-H3 and {H7 α }-H6 NOEs for **1**·AcO⁻ complex is in agreement with conformational changes across C2-C2 α and C7-N7 α bonds. Unfortunately, negative values of other key NOEs due to proton exchange prevented more detailed conclusions regarding conformational changes of **1** upon interaction with acetate anions.

The interaction of bromide anions with **2** resulted in increase of {H2 β }-H1, {H1}-H2 β , {H1}-H7 α and {H7 α }-H1 NOEs (Table 2). Changes of NOE enhancements are analogous to those observed in **2**·Cl⁻, evidence for comparable conformational changes in **2** upon interaction with bromide anions. Strong {H2 β }-H3 and {H7 α }-H6 NOEs of 10.0% and 6.8%, respectively, suggest only minor conformational

Table 2. The key NOE enhancements observed for **1-4** in the absence and in the presence of one equivalent of anions.

Saturated: Enhanced:	H2 β		H1		H7 α		H6
	H3	H1	H2 β	H7 α	H1	H6	H7 α
without	8.5	\leq 1 ^a	1.2 ^a	\leq 1 ^a	3.2	0.6	
chloride	4.9	6.9 ^a	13.0 ^a	6.9 ^a	2.1	0.9	
bromide	4.1	6.7 ^a	11.5 ^a	6.7 ^a	1.6	0.9	
nitrate	9.9	2.5 ^a	5.2 ^a	3.6 ^a	4.4	1.9	
acetate	4.5	- ^b	- ^b	- ^b	2.5	0.1	
without	14.5	0.5	0.2	2.9	5.0	7.3	1.0
chloride	7.5	12.0	13.6	12.9	13.8	2.7	0.9
bromide	8.2	9.7	12.0	10.7	11.4	3.7	0.7
nitrate	10.0	4.7	3.0	5.2	6.3	6.8	2.9
acetate	1.5	12.9	15.8	10.2	8.8	0.9	0
without	15.2	0	0.1	1.0	1.0 ^c	2.5 ^c	- ^d
chloride	7.1	7.2	6.4	5.7	3.6 ^c	1.1 ^c	0.5
bromide	6.9	5.8	5.3	4.4	3.8 ^c	1.4 ^c	0.2
nitrate	15.3	1.4	1.1	0	0 ^c	2.8 ^c	0.7
without	15.3	0	0	0.9	1.5 ^a	6.5	0.6 ^d
chloride	1.1	8.0	8.0	5.3	5.6	- ^d	0.3 ^d
bromide	7.3	8.2	6.8	5.4	5.9	3.9	0.5 ^d
nitrate	13.1	2.5 ^a	1.3	2.3	3.9 ^a	5.9	1.0 ^d

^a H2 β and H7 α were saturated simultaneously or integrated together due to small $\Delta\delta$ values. ^b Negative NOEs due to proton exchange. ^c Both H7 α and H7 γ were saturated simultaneously or integrated together due to small $\Delta\delta$ values. ^d ¹H signals were overlapped and pair-wise enhancements could not be quantified unequivocally.

{H2 β }-H3 and {H7 α }-H6 NOE values to 1.5% and 0.9%, respectively (Table 2). Strong NOEs between H1 and H2 β , and likewise between H1 and H7 α in **2**·AcO⁻ complex indicate major conformational changes along C2-C2 α and C7-N7 α bonds.

Receptor **3** with its 7-thiourea moiety exhibited strong {H2 β }-H3 NOE (15.2%) which indicated conformational preorganization along C2-C2 α bond. The predominance of the conformer of **3** with H2 β and H3 being spatially close is further supported by negligible NOEs between H1 and H2 β protons ($<$ 0.1%). The weak NOEs between H1 and H7 α (1.0%) and a slightly stronger {H7 α }-H6 NOE of 2.5% allude to the predominance of C7-C7 α conformer, where H6 and H7 α are spatially closer than H1 and H7 α . The addition of chloride and bromide anions results in decrease of NOEs between H2 β and H3 as well as between H7 α and H6 (Table 2). Moreover, the increase of H1-H2 β and H1-H7 α NOEs is

consistent with conformational changes in **3** upon addition of chloride and bromide anions. In the case of the $\mathbf{3}\cdot\text{NO}_3^-$ complex, small NOE changes were observed (Table 2). Regrettably, negative NOEs in $\mathbf{3}\cdot\text{AcO}^-$ complex thwarted a conformational study of this complex.

The conformational preorganization of **4**, where H2 β and H7 α point away from indole H1 proton, is supported by strong {H2 β }-H3 and {H7 α }-H6 NOEs as well as weak NOE enhancements between H1-H2 β and H1-H7 α . The addition of chloride or bromide anions triggers conformational changes in **4**, which were clearly indicated by decreased {H2 β }-H3 and {H7 α }-H6 NOEs and increased NOEs between indole H1 and both H2 β and H7 α protons (Table 2). Insignificant changes of key NOEs in $\mathbf{4}\cdot\text{NO}_3^-$ complex lead us to suggest that predominant conformation remained mostly unchanged upon addition of nitrate anions. The saturation of proton signals in $\mathbf{4}\cdot\text{AcO}^-$ complex yielded negative NOEs, which did not allow detailed conformational analysis.

Discussion

Acquired heteronuclear NMR data on four different anion receptors showed distinct changes as a result of their interactions with anions. Both chemical shift changes and conformational rearrangements can be attributed to structural details of receptors **1-4** as well as the anions' properties including their diverse binding affinities. Perusal of chemical shift changes showed correlation between the nature of C7 substituent and the magnitude and localization of chloride-receptor interactions. $\Delta\delta$ values in **1** suggested that interactions between H1 protons and chloride anions are the strongest as deshielding is significantly more pronounced than for H2 β or H7 α amide protons. Changing the phenylacetamido moiety in **1** to a urea group in **2** led to increased deshielding of the H7 α and H7 γ protons which suggested that the anion-receptor interactions in $\mathbf{2}\cdot\text{Cl}^-$ complex involved the indole and urea NH protons. Our observed differences in proton $\Delta\delta$ values are in agreement with the published stability constants for $\mathbf{1}\cdot\text{Cl}^-$ and $\mathbf{2}\cdot\text{Cl}^-$ complexes.²⁵ The comparison of structurally related indoles **2** and **3** showed similar chemical shifts changes for both receptors upon addition of chloride anions. The largest deshielding of H1 and H2 β protons was observed in $\mathbf{4}\cdot\text{Cl}^-$ with respect to corresponding complexes of **1-3**, which suggested the predominant involvement of H1 and H2 β donor groups in interaction with chloride anions.

Interaction of bromide anions with receptors **1-4** caused analogous albeit smaller chemical shift changes in comparison to chloride anions, in agreement with bromide's lower basicity. Considerable deshielding of the H7 α and H7 γ protons was observed upon addition of Y-shaped nitrate anions to **2** and **3** which contain urea and thiourea moieties, respectively. In contrast, only minor ^1H chemical shift changes were observed upon addition of NO_3^- anions to **1** and **4** which contain amide groups at C2 and C7. Urea and thiourea moieties were shown to be preferred for interaction with trigonal planar anions due to their suitable shape and capability to form two hydrogen bonds.²³ The largest ^1H chemical shift changes were observed upon addition of acetate

anions to **1-4**. Major deshielding of H1 protons in **1-4** is consistent with a strong interaction with acetate anions. Additionally, significant $\Delta\delta$ values of H2 β and H7 α show acetate anions are strongly interact with the other two donor groups in **1** and **4**. In conclusion, acetate and nitrate are both planar oxoanions that are predisposed for bidentate interactions with the urea and thiourea moieties in **2** and **3**. Larger chemical shift changes in **1-4** upon addition of acetate with respect to nitrate anions are consistent with the lower basicity of nitrate.

Substituents attached to the indole C2 and C7 carbons make the resultant anion receptors conformationally flexible. Four conformers with respect to the orientations across C2-C2 α and C7-N7 α bonds are expected to be preferred (Figure 6). A preliminary *ab initio* computational study of C2 and C7 functionalized indoles showed that the *anti-anti* conformer is energetically preferred in the absence of anions, whereas the *syn-syn* conformer is favored for anion-receptor complexes.

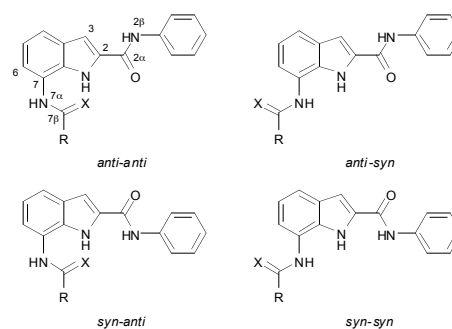


Figure 6. Four major conformational families with respect to C2 and C7 substituents in indole receptors. The first notation of individual conformer refers to the orientation along N1-C2-C2 α -N2 β , while the second refers to C6-C7-N7 α -C7 β fragment. R stands for phenyl, benzyl and phenylamine substituents, whereas X symbolizes O or S atom as shown in Figure 1.

Conformational preorganization of derivatives **1-4** has been assessed by NOE enhancements. 1D difference NOE experiments showed strong H2 β -H3 and negligible H2 β -H1 NOEs in the absence of anions which suggested the predominance of an *anti* orientation along C2-C2 α bonds in the receptors **1-4**. A relatively strong NOE between H7 α -H6 together with weak NOE between H7 α and H1 is evidence that supports the predominance of an *anti* orientation along C7-N7 α bond in the absence of anions. The prevalent *anti-anti* conformers of **1-4** where the substituents' NH groups are pointing away from indole H1 proton are in agreement with negligible H1-H2 β and H1-H7 α NOE enhancements. Arrangement of C2 α and C7 β carbonyl groups in *anti-anti* orientation is predisposed to act as intramolecular hydrogen bond acceptors for the H1 proton.

The addition of anions to receptors **1-4** resulted in significant changes of key NOE enhancements. A major decrease of H2 β -H3 as well as minor decrease of H7 α -H6 NOEs occurred upon addition of chloride, bromide and acetate anions. Simultaneous increases of NOEs among H1 and H2 β as well as H1 and H7 α furthermore suggested a conformational conversion of the receptors from *anti-anti* to *syn-syn* upon interaction with anions. Rotations along C2-C2 α

and C7–C7 α bonds are also supported by H6 chemical shift changes. As this proton is not directly involved in anion-receptor interactions its $\Delta\delta$ values are most likely result of variations of chemical environment upon conformational changes. No conformational changes were observed upon addition of nitrate anions to **1-4** as evidenced by almost unchanged NOE enhancements.

Our NMR data demonstrate that binding of chloride anions occurs primarily at H1 and H2 β or H7 α (Figure 7a) Analogous interactions were established for receptors **1-4** upon addition of bromide anions. Proton chemical shift changes upon addition of nitrate anions to **1** and **4** suggest very weak interactions. However, introduction of urea or thiourea groups significantly improves the binding properties of nitrate to **2** and **3**. Negligible NOE changes in nitrate complexes with **1-4** together with corresponding $\Delta\delta$ values indicate that interaction of NO₃⁻ anions occurs through the urea (**2**) or thiourea (**3**) group without rotation along C7–C7 α bond (Figure 7b). Figure 7c illustrates the proposed binding mode of acetate to **2**. Large chemical shift changes hint at strong interactions with indole and urea NH groups whereas interactions with H2 β proton are weaker. Rotation from *anti-anti* to *syn-syn* conformer is anticipated in the other three acetate-receptor complexes but could not be confirmed experimentally.

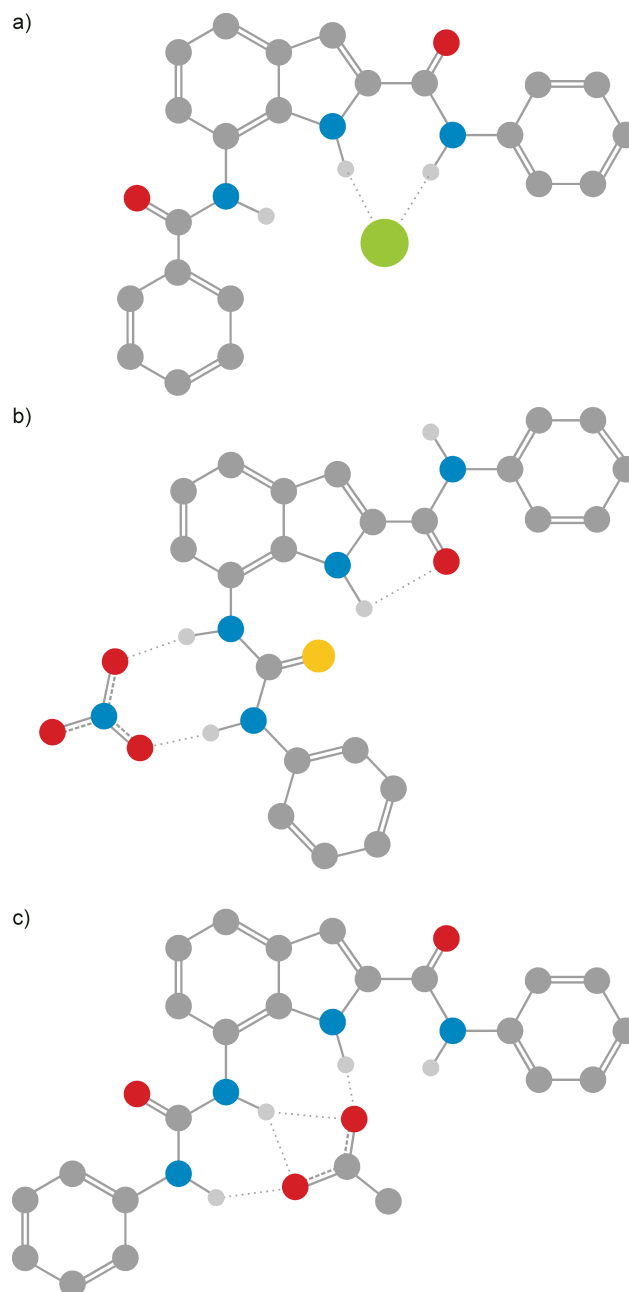


Figure 7. Conformations and positions of chloride anion in **4**·Cl⁻ (a), nitrate anion in **3**·NO₃⁻ (b) and acetate anion in **2**·AcO⁻ (c) complexes based on chemical shift changes and NOE enhancements.

Conclusions

Bis-amido and mono-amido-mono-urea 2,7-functionalised indoles **1-4** were characterized by heteronuclear NMR spectroscopy. The NOE based conformational analysis revealed that all four receptors exhibit conformational preorganization in acetone solution, where *anti-anti* conformer is predominant. Such an orientation places C2 α and C7 β carbonyl groups in the proximity of indole H1 proton which leads to stabilization by intramolecular hydrogen bonds. Anion-induced chemical shift changes demonstrate that binding of halides (chloride, bromide) takes place predominantly at H1 proton. Receptors **2** and **3** with urea and

thiourea moieties offer more donor groups and therefore the anions interact with H1, H7 α and H7 γ protons. Nitrate anions favor interaction with H7 α and H7 γ urea and thiourea protons, whereas acetate anions interact strongly with all available hydrogen bond donors. Comparison of NOE enhancements in the absence and in the presence of anions revealed conformational changes of receptors **1-4** induced by complexation of chloride, bromide and acetate anions. Anion-receptor complexes preferably adopt *syn-syn* conformation where all NH protons are spatially close and involved in interaction with anions. However, no conformational changes were observed upon addition of nitrate anions to **1-4**. Our study demonstrates that indole ring offers intriguing scaffold for design of novel anion receptors and their modification in order to tune affinities and selectivities for anions.

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Notes and references

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