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2,7-Functionalized Indoles as Receptors for Anions

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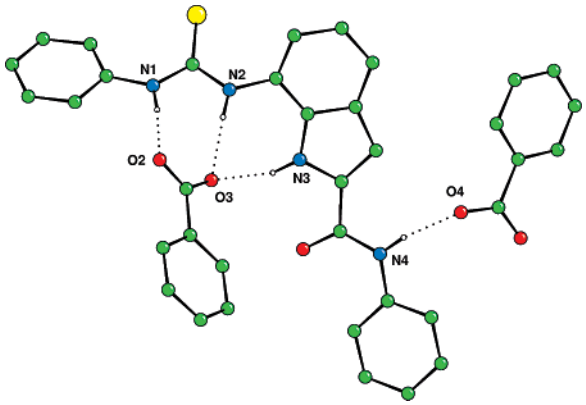

A series of 2,7-functionalized indoles have been synthesized with appended amide and/or urea or thiourea groups. Anion complexation studies show a marked difference in the mode of interaction of carboxylates with indole−ureas vs indole−amides.

Introduction

The design and synthesis of a wide variety of different anion receptors has been the focus of intense research over recent years.[1] Despite the great variety of hydrogen-bond donor systems studied in this context, indole (or biindole) has been neglected as an anion receptor moiety. However, recently, in a series of elegant papers, Jeong and co-workers,[2] Sessler and co-workers,[3] and others[4] have shown that indole- or biindole-containing receptors exhibit high affinities and selectivities for anions. The lack of effort directed toward the study of the anion-binding properties of indole derivatives is somewhat surprising as Nature employs this group (as tryptophan) in the sulfate binding protein as a hydrogen bond donor to stabilize sulfate bound within this protein[5] and in the enzymatic active site of haloalkane dehalogenase to complex a choride anion.[6]

Previously, the Southampton group has studied a wide variety of 2,5-dicarboxamidopyrroles as putative anion receptor systems,[7] while the Aachen group have employed functionalized quinolines as anion receptor systems.[8] We decided to combine both these approaches to anion receptor design and explore the anion receptor ability of indoles functionalized with amides or

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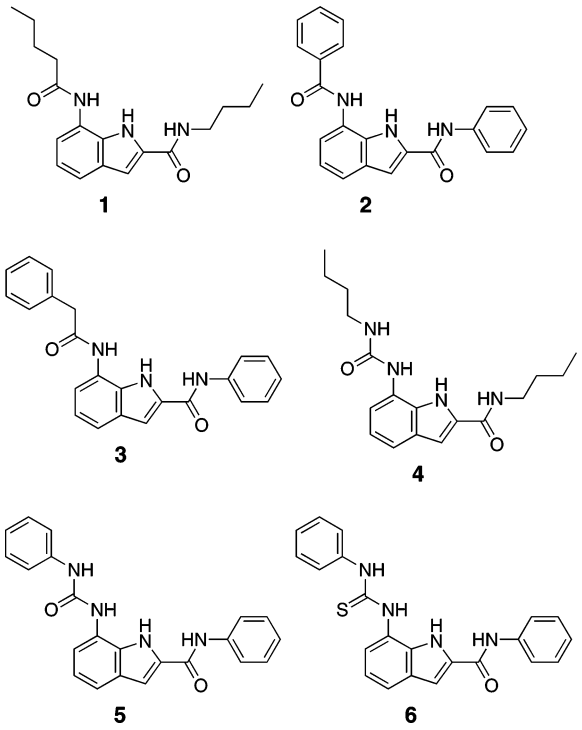
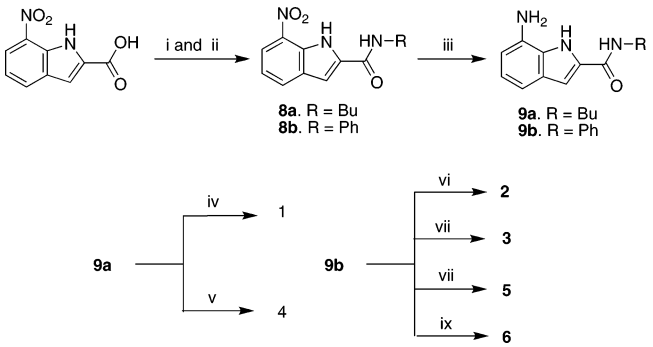
ureas[9] in the 2- and 7-positions. We consequently synthesized receptors **1**−**6** and studied their anion complexation properties. These studies revealed a selectivity for acetate[10] in wet DMSO solution.



Results and Discussion

Compounds **1**−**6** were prepared by a simple three-step synthesis (Scheme 1). Commercially available 7-nitroindole-2-carboxylic acid (**7**) was converted to the acid chloride by reaction with excess thionyl chloride at reflux. The acid chloride was trapped with either butylamine or aniline to afford compound **8a** and **8b** in 78% and 89% yields respectively. Compounds **8a** and **8b** where then reduced with hydrazine monohydrate/10% Pd/C. The resulting amine **9a** was immediately used in subsequent reactions with valeroyl chloride and butylisocyanate to afford compounds **1** and **4** in 43% and 45% respective yields. Reaction of compound **9b** with benzoyl chloride, phenylacetyl chloride, phenyl isocyanate, and phenyl isothiocyanate afforded derivatives **2** (83%), **3** (83%), **5** (45%), and **6** (48%).

SCHEME 1. Synthesis of Compounds 1−6[a]



[a] Key: (i) $SOCl_2$; (ii) R-NH_2, Et_3N, DMAP, and DCM; (iii) $NH_2NH_2 \cdot H_2O$, 10% Pd/C, EtOH; (iv) *N*-BuCOCl, Et_3N, DMAP, and DCM; (v) *n*-BuNCO, DCM, (vi) C_6H_5COCl, Et_3N, DMAP, and DCM; (vii) $C_6H_5CH_2COCl$, Et_3N, DMAP, and DCM; (viii) C_6H_5NCO, DCM; (ix) C_6H_5NCS, DCM.

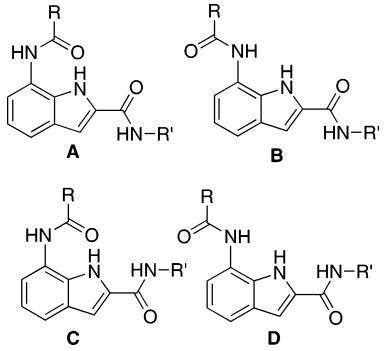


FIGURE 1. Possible conformations of the amide/urea units in compounds **1**−**6**.

Compounds **1**−**6** can adopt a variety of different conformations **A**−**D** at the amide or urea units as shown in Figure 1. The indole NH unit is located in the center of the cleft, which is formed by the 2,7-disubstituted indole. Each of the substituents can adopt two "planar" conformations. In one of these, the carbonyl oxygen atoms are pointing to the front of the molecule, while the NH units are orientated to the "outside". As an alternative, the NH is directed toward the concave face of the molecule and the oxygens are directed outward. For effective binding of anions, an orientation as shown in D appears to be most appropriate. However, in the absence of guest species, this conformation should be disfavored due to the repulsion between the NH protons.

To give us a first insight into the conformational properties of these compounds, we performed crystallization studies. X-ray quality crystals of compound **2** were obtained by slow evaporation of a dimethylsulfoxide solution. The structure of **2** was elucidated and shows that a solvent molecule is bound to the receptor by two hydrogen bonds from the indole NH and the 7-position amide NH groups with N···O distances of 2.875(2) Å and 2.928(2) Å, respectively (Figure 2). Interestingly, the amide group in the 2-position is orientated away from the "cleft" and is bound to an adjacent 7-position amide to form a dimer in the solid phase (N···O distances of 2.907(2) Å). Thus,

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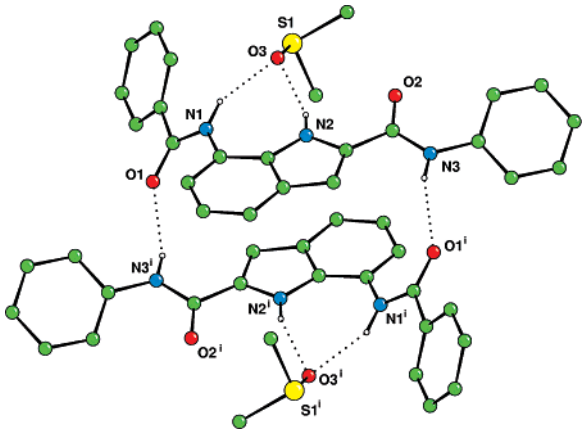

FIGURE 2. X-ray crystal structure of the DMSO solvate of compound **2**. Nonacidic hydrogen atoms have been omitted for clarity.

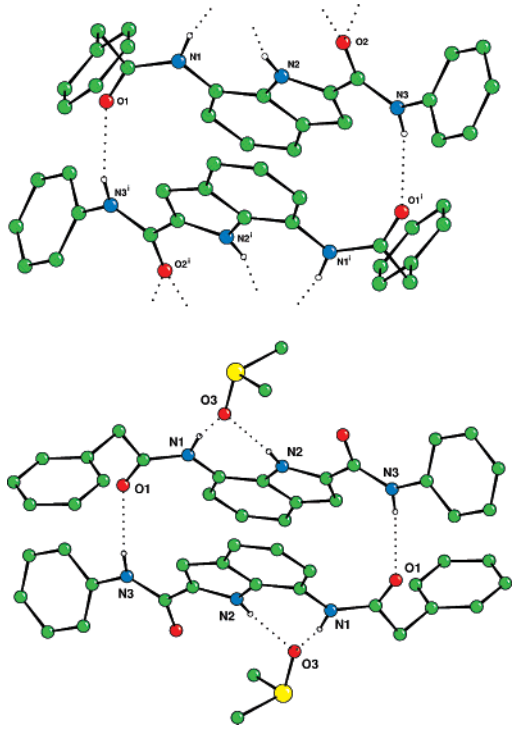

FIGURE 3. X-ray crystal structure of compound **3** (top) and the DMSO solvate of compound **3** (bottom). Nonacidic hydrogen atoms have been omitted for clarity.

conformation B (Figure 2) is observed in the crystal structure of the DMSO adduct of **2**.

X-ray quality crystals of compound **3** were obtained by slow evaporation of separate solutions of the receptor in acetonitrile and DMSO (Figure 3). The structure resulting from crystals of **3** obtained from dimethyl sulfoxide resulted in a similar structure **B** to that of **2** in that a dimethyl sulfoxide molecule was bound to the indole NH and the 7-position amide NH groups with N···O distances of 2.856(2) Å and 2.907(2) Å, respectively, and a dimer was formed by the interaction of the 2-position amide NH and the 7-position carbonyl group (N···O distance of 2.859-(2) Å). The crystal structure of **3** obtained from acetonitrile solution reveals that the receptor forms a dimer in the solid state with the indole and 7-position amide NH groups bound to an adjacent CO group from the 2-position amide with N···O distances of 2.8812(18) Å and 2.9607(18) Å, respectively.

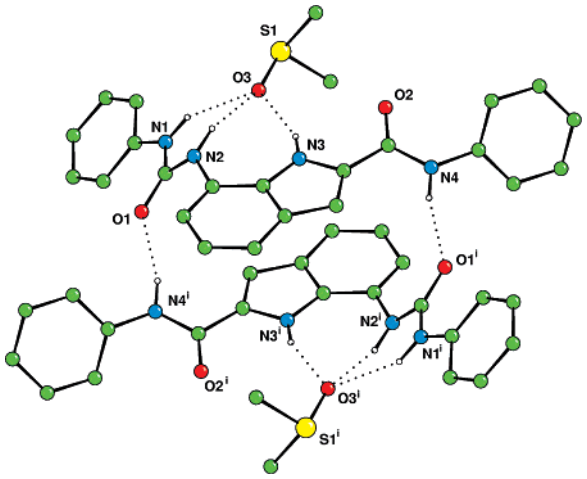

FIGURE 4. X-ray crystal structure of the DMSO solvate of compound **5**. Nonacidic hydrogen atoms have been omitted for clarity.

TABLE 1. Stability Constants of 1−3 (M-1) with Various Anionic Guests (Added as Their TBA Salts) in DMSO-d_6/0.5% Water at 298 K[a]

anion	1	2	3
$H_2PO_4^-$	390	310	350
$CH_3CO_2^-$	425	650	900
$C_6H_5CO_2^-$	115	100	140
Cl^-	<10	<10	11

[a] Errors estimated to be no more than ±10%.

A similar dimethyl sulfoxide complex of compound **5** (conformation **B**) was obtained by slow evaporation of dimethyl sulfoxide solutions of the receptor (Figure 4). The structure again shows the formation of a dimer (similar to the structures of compounds **2** and **3**) by interaction of the amide NH groups in the 2-position with the adjacent carbonyl oxygen atom of the urea group (N···O 2.877(2) Å). The solvent molecule is bound by the two urea NH groups (N···O distances of 2.830(2) Å and 3.012(2) Å) and the indole NH (N···O distance of 2.949(2) Å).

Thus in the solid state, conformer **B** (Figure 1) appears to be a favorable conformation. The amide in 2-position is directed to the outer face of the molecules and is only involved in intermolecular hydrogen bonding. However, these findings do not give us information about the conformations adopted by these compounds in solution in the presence of an anionic guest.

Proton NMR titration experiments were used to investigate the anion binding properties of the receptors **1**−**3** with the stability constants being obtained by analysis of the titration data with EQNMR.[11] Due to the limited solubility of certain receptors the titration experiments were conducted in DMSO-d_6/0.5% water. The stability constants for receptors **1**−**3** with acetate, benzoate, dihydrogen phosphate, and chloride (added as their tetrabutylammonium salts) are presented in Table 1. All the titration curves fitted a 1:1 receptor/anion binding model.

Compounds **1**−**3** were found to bind the anions according to their basicity in the order $CH_3CO_2^-$ > $H_2PO_4^-$ > $C_6H_5CO_2^-$ > Cl^-. Appreciable differences in the affinity of the receptors were only observed with the titrations involving acetate where compound **1** was found to have the lowest affinity for acetate (425 M^{-1}) and **3** the highest (900 M^{-1}).

Examination of the NMR titration curves upon addition of acetate (Figure 5) show that all three of the NH groups shift

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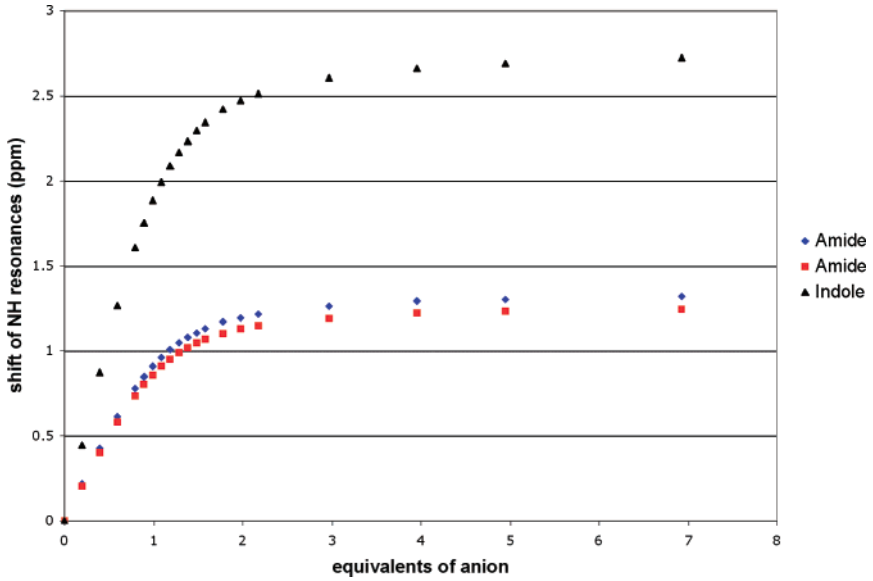

FIGURE 5. Proton NMR titration curves for NH protons in compound **2** upon addition of acetate.

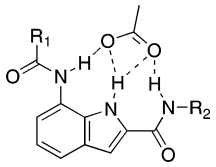

FIGURE 6. Proposed binding mode of acetate to compounds **1**−**3**.

downfield by an appreciable amount (>1 ppm) upon addition of this anion. This suggests that all three of the NH groups are involved in complexing this anion in solution (Figure 6). Thus, in contrast to the results from the X-ray analyses of the amide derivatives, conformation **D** seems to be most appropriate for the interaction of the bisamide receptor with acetate as anion in solution.

Stability constants were determined for receptors **4**−**6** by ^{1}H NMR titration experiments under identical condition as used to determine the stability constants for compounds **1**−**3**.

Receptors **4**−**6** were found to bind the anions in the same trend as for **1**−**3** ($CH_3CO_2^-$ > $H_2PO_4^-$ > $C_6H_5CO_2^-$ > Cl^-) however much higher affinities for anions were observed with receptors **4**−**6**. The urea functionalized receptor **4** was found to bind acetate approximately 5 times more strongly than its amide analogue **1** (2060 vs 425 M^{-1}, respectively). In the case of **5**, acetate was found to bind by over an order of magnitude greater than with the amide analogue **3** (10000 vs 900 M^{-1}, respectively). Interestingly, when the urea group in **5** was replaced with a more acidic thiourea group (**6**), a significant decrease in the association constants was observed. This observation may be due to steric interactions between the large sulfur atom and CH groups of the receptor in the "syn−syn"-like conformation of the molecule leading to destabilization of this conformation of the receptor and hence loss of the convergent hydrogen bonding array.[12]

Comparison of the NMR data upon addition of acetate (excess) to the receptors gives some hint as to the preferred receptor conformations and its dynamics. Addition of the anion

SCHEME 2. Acetate Is Bound to the Urea/Thiourea Moiety and the Indole NH Group with a Weaker Interaction to the Pendant Amide NH

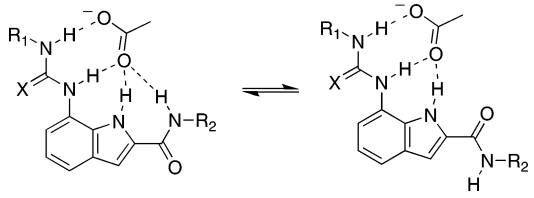

TABLE 2. Apparent Stability Constants of 4−6 (M^{-1}) with Various Anionic Guests (Added as Their TBA Salts) in DMSO-d_6/0.5% Water at 298 K[a]

anion	4	5	6
$H_2PO_4^-$	940	4950[b]	1600
$CH_3CO_2^-$	2060	10000	*c*
$C_6H_5CO_2^-$	680	4460	780
Cl^-	20	38	16

[a] Errors estimated to be no more than ±10%. [b] Errors estimated to be no more than ±12%. [c] Not determined due to peak coalescence and broadening upon the addition on TBA acetate.

results in a downfield shift of the pendant amide group by less than 0.5 ppm. Examination of the titration curves of the NH proton resonance shifts of compound **5** with acetate (Figure 7) shows that while the indole and urea NH groups reach a plateau upon addition of 1 equiv of added anionic guest, the amide NH group continues to shift downfield and does not reach a plateau. We believe this may be due to the possibility that this NH group does not interact strongly with acetate (which is bound predominantly by the other NH groups present in the receptor) leading to the preferred conformation **B**. Here the hydrogen atom may point out of the binding site (Scheme 2) as observed in the crystal structures of the free receptors above. This allows this amide NH group to interact weakly with further additions of acetate resulting in the continuous downfield shift. Thus as the binding process is not a simple 1:1 binding process the data in Table 2 should be regarded as being apparent stability constants only.

X-ray quality crystals of the tetrabutylammonium chloride complex of compound **5** were grown by slow evaporation of a

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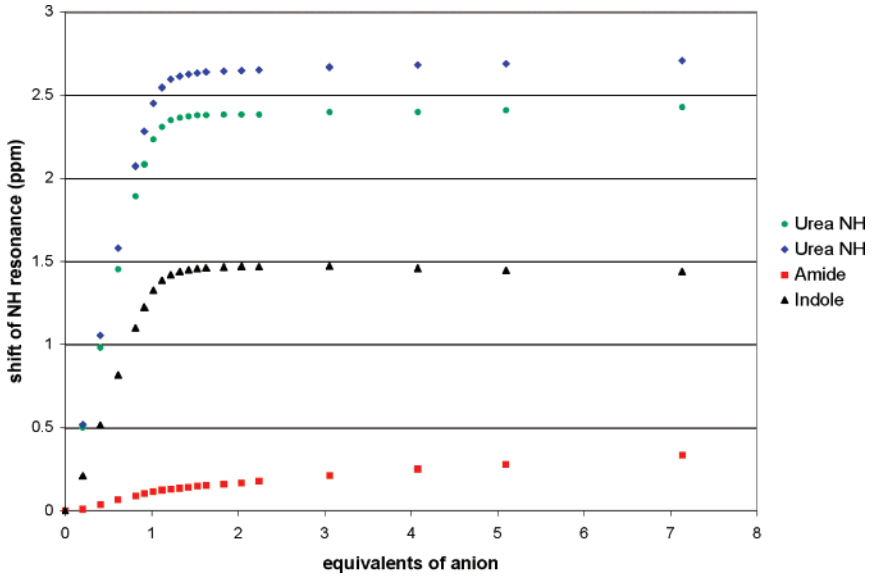

FIGURE 7. Proton NMR titration curves for NH protons in compound **5** upon addition of acetate.

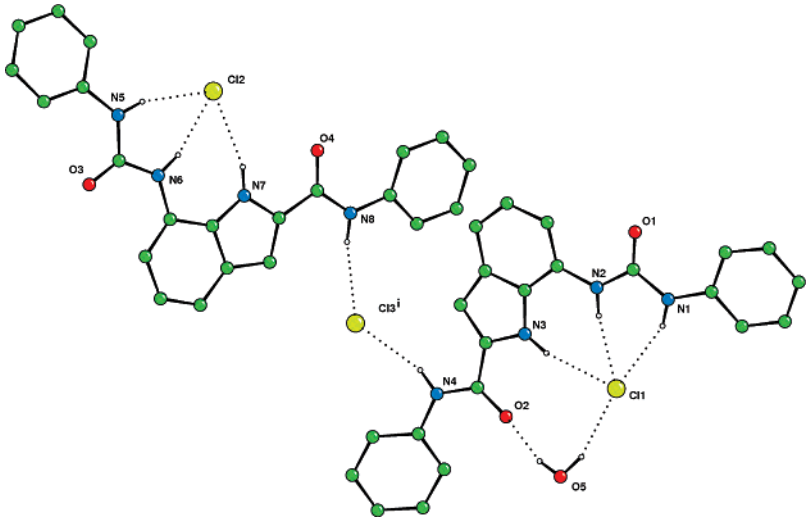

FIGURE 8. Chloride complex of compound **5**. Nonacidic hydrogen atoms and countercations have been omitted for clarity.

DMSO solution of the receptor in the presence of excess chloride salt. The structure reveals two crystallographically distinct receptors in the unit cell bridged by a chloride anion bound to the amide NH groups in the 2-position of each receptor (N···Cl distances of 3.272(4) Å and 3.350(4) Å (Figure 8). A chloride is bound to each receptor via three hydrogen bonds from the urea and indole NH groups with N···Cl distances in the range 3.144(4)−3.357(4) Å. In addition, a molecule of water is observed in the crystal that connects by hydrogen bonding the amide oxygen atom and the chloride. In this way, the water reduces the repulsion between the electron pairs at oxygen and the negative charge at chloride.

X-ray quality crystals of the benzoate complex of **6** were obtained by slow evaporation of a dimethyl ulfoxide solution of compound **6** in the presence of excess tetrabutylammonium benzoate. The structure shows the formation of a 2:1 anion/receptor complex in the solid state (Figure 9). One benzoate anion is bound by a single hydrogen bond provided by the 2-position amide NH group with a distance of 2.869(3) Å. The second benzoate anion is bound by three hydrogen bonds with a single benzoate oxygen atom bound to the outer thiourea NH (N···O distances of 2.865(3) Å), and the second interacting with both the inner thiourea NH groups and the indole NH (N···O distances of 2.719(3) and 2.2.767(3) Å, respectively).

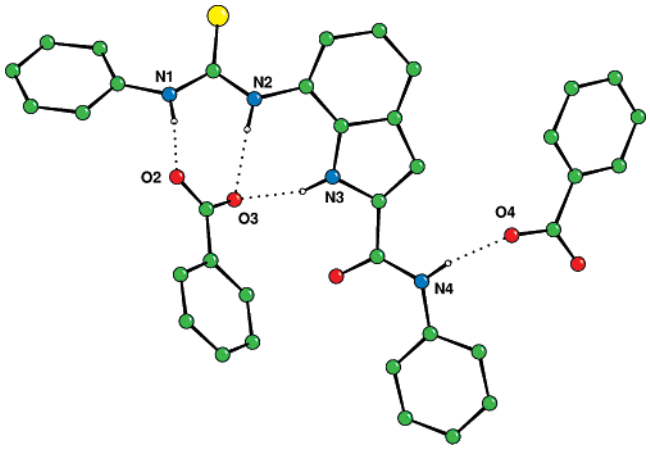

FIGURE 9. Benzoate complex of compound **6**. Nonacidic hydrogen atoms and countercations have been omitted for clarity.

In conclusion, we have shown that the indole skeleton can be used as a scaffold upon which numerous hydrogen-bonding groups can be attached to generate receptors capable of anion recognition. The urea or thiourea containing receptors appear to bind carboxylates predominantly via the urea/thiourea NH groups and the indole NH while the bis-amide receptors **1**−**3** utilize all the available NH groups to bind carboxylates in solution. This suggests that three hydrogen-bonding interactions are most appropriate for the binding of this kind of anion. We are continuing our investigation into the anion binding and spectroscopic properties of indole containing receptors, the results of these studies will be reported in due course.

Experimental Section

7-Nitro-1*H*-indole-2-carboxylic Acid Butylamide, 8a. 7-Nitroindole-2-carboxylic acid, **7** (2.00 g, 10 mmol), was heated at reflux in thionyl chloride (30 mL) for 2 h. The thionyl chloride was then evaporated, and the resultant solid was dissolved in DCM (50 mL) and added dropwise to a stirring solution of butylamine (0.75 g, 11 mmol), triethylamine (5 mL), and a catalytic amount of DMAP in DCM (50 mL) after which the reaction mixture was stirred for 24 h. The reaction mixture was then concentrated and purified via column chromatography (SiO_2, DCM/3%methanol). The pure product was isolated as a yellow solid: yield 78%, 2.03 g; mp 124−126 °C; IR ν cm^{-1} 3257, 3094, 2958, 2927, 1595, 1329, 1303; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, ^3J = 7.3 Hz, 3H), 1.38−1.50 (m, 2H), 1.59−1.69 (m, coincident with H_2O, 2H), 3.51 (m, 2H), 6.19 (s, 1H), 6.94 (d, ^4J = 1.9 Hz, 1H), 7.26 (m, coincident with $CDCl_3$, 1H), 7.99 (d, ^3J = 7.9 Hz, 1H), 8.25 (d, ^3J = 7.9 Hz, 1H), 10.51 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.1, 20.5, 32.2, 40.0, 102.9, 120.4, 121.8, 129.6, 130.3, 131.7, 134.0, 160.7; HRMS (positive ESI) *m*/*e* calcd for $C_{13}H_{16}N_3O_3^+$ (M + H$^+$) 261.1186, found 262.1186.

7-Nitro-1*H*-indole-2-carboxylic Acid Phenylamide, 8b. 7-Nitroindole-2-carboxylic acid, **7** (2.00 g, 10 mmol), was heated at reflux in thionyl chloride (30 mL) for 2 h. The thionyl chloride was then evaporated, and the resultant solid was dissolved in DCM (50 mL) and added dropwise to a stirring solution of aniline (1.00 g, 10.7 mmol), triethylamine (5 mL), and a catalytic amount of DMAP in DCM (50 mL). After addition, the reaction was stirred for 24 h. Water (250 mL) was then added, and the organic layer was separated and washed with water. The organic layer was dried with sodium sulfate, filtered, and concentrated in vacuo. The pure product was obtained by recrystallization from acetonitrile. The product was isolated as a brown solid: yield 89%, 2.51 g; mp 209−211 °C; IR ν cm^{-1} 3849, 3743, 3673, 3455, 2361, 1651, 1544, 1316; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.15 (t, ^3J = 7.4 Hz, 1H), 7.35−7.43 (m, 3H), 7.62 (s, 1H), 7.80 (d, ^3J = 7.5 Hz, 2H), 8.25−8.29 (m, 2H), 10.66 (s, 1H), 11.44 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 107.5, 120.0, 121.1, 121.7, 124.7, 129.1, 129.9, 130.6, 131.7, 133.7, 134.9, 138.6, 158.9; HRMS (EI) calcd for $C_{15}H_{11}N_3O_3$ [M]$^+$ 281.0800, found 281.0800.

7-Pentanoylamino-1*H*-indole-2-carboxylic Acid Butylamide, 1. 7-Nitro-1*H*-indole-2-carboxylic acid butylamide, **8a** (1.00 g, 3.8 mmol), Pd/C (0.20 g, 10 wt %), and hydrazine monohydrate (2 mL) were dissolved in ethanol (100 mL) and heated at reflux for 1 h. The reaction mixture was then filtered hot through Celite and washed with ethanol (50 mL). The filtrate was concentrated in vacuo, and the resulting white solid was used directly in the next reaction where it was dissolved in DCM (50 mL) with triethylamine (5 mL) and DMAP (catalytic amount). To this solution was added dropwise a solution of valeroyl chloride (0.39 g, 3.8 mmol), and the reaction was stirred overnight. Water (250 mL) was then added, and the organic layer was separated and washed with water. The organic layer was dried with sodium sulfate, filtered, and concentrated in vacuo. The pure product was then obtained by recrystallization from acetonitrile. The product was isolated as a white solid: yield 43%, 0.52 g; mp 126−129 °C; IR ν cm^{-1} 3278, 2957, 2929, 2871, 1615, 1569, 1540, 1275; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90−0.95 (m, 6H), 1.30−1.42 (m, 4H), 1.50−1.57 (m, 2H) 1.60−1.67 (m, 2H), 2.43 (t, ^3J = 7.4 Hz, 2H), 3.33 (m, 2H, coincident with H_2O), 6.98 (t, J = 7.8 Hz, 1H), 7.13 (d, ^4J = 2.0 Hz, 1H), 7.32 (d, ^3J = 7.8 Hz, 1H), 7.92 (d, ^3J = 7.8 Hz, 1H), 8.50 (bt, 1H), 9.76 (s, 1H) 11.42 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 12.87, 12.93, 18.8, 21.0, 26.5, 30.5, 35.3, 37.6, 101.8, 112.4, 115.9, 119.2, 123.8, 126.2, 127.7, 130.7, 160.0, 170.6; HRMS (positive ESI) *m*/*e* calcd for $C_{18}H_{26}N_3O_2^+$ (M + H$^+$) 316.2020, found 316.2019.

7-Benzoylamino-1*H*-indole-2-carboxylic Acid Phenylamide, 2. 7-Nitro-1*H*-indole-2-carboxylic acid phenylamide, **8b** (0.50 g, 1.8 mmol), Pd/C (0.20 g, 10 wt %), and hydrazine monohydrate (2 mL) were dissolved in ethanol (100 mL) and heated at reflux for 1 h. The reaction was then filtered hot through Celite and washed with ethanol (50 mL). The filtrate was concentrated in vacuo, and the resulting white solid was used directly in the next reaction where it was dissolved in DCM (100 mL) with triethylamine (5 mL) and DMAP (catalytic amount). To this solution was added dropwise a solution of benzoyl chloride (0.25 g, 1.8 mmol), and the reaction was stirred overnight. Water (250 mL) was then added, and the organic layer was separated and washed with water. The organic layer was dried with sodium sulfate, filtered, and concentrated in vacuo. The pure product was obtained via recrystallization from acetonitrile. The product was isolated as a pale yellow solid: yield 83%, 0.53 g; mp 257−260 °C; IR ν cm^{-1} 3227, 1631, 1598, 1548, 1250; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.11 (m, 2H), 7.38 (t, ^3J = 7.7 Hz, 2H), 7.50−7.66 (br, 5H), 7.80 (d, ^3J = 7.7 Hz, 2H), 7.93 (d, ^3J = 7.7 Hz, 1H), 8.00−8.02 (m, 2H), 10.20 (s, 1H), 10.27 (s, 1H), 11.83 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 104.9, 116.6, 118.5, 120.7, 124.1, 124.8, 128.4, 128.8, 129.1, 129.2, 129.4, 131.9, 132.0, 135.7, 139.3, 160.1, 166.6; HRMS (positive ESI) *m*/*e* calcd for $C_{22}H_{18}N_3O_2^+$ (M + H$^+$) 356.1394, found 356.1390.

7-Phenylacetylamino-1*H*-indole-2-carboxylic Acid Phenylamide, 3. 7-Nitro-1*H*-indole-2-carboxylic acid phenylamide, **8b** (0.50 g, 1.8 mmol), Pd/C (0.20 g, 10 wt %), and hydrazine monohydrate (2 mL) were dissolved in ethanol (100 mL) and heated at reflux for 1 h. The reaction mixture was filtered hot through Celite and washed with ethanol (50 mL). The filtrate was then concentrated in vacuo, and the resulting white solid was used directly in the next reaction where it was dissolved in DCM (100 mL) with triethylamine (5 mL) and DMAP (catalytic amount). To this solution was added dropwise a solution of phenylacetyl chloride (0.28 g, 1.8 mmol), and the reaction was stirred overnight. Water (250 mL) was then added, and the organic layer was separated and washed with water. The organic layer was dried with sodium sulfate, filtered, and concentrated in vacuo. The pure product was obtained by recrystallization from acetonitrile. The product was isolated as a white solid: yield = 83%, 0.55 g; mp 213−215 °C; IR ν cm^{-1} 3378, 3246, 3033, 2360, 2160, 1668, 1539; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.78 (s, 2H), 7.03 (t, ^3J = 7.7 Hz, 1H), 7.13 (t, ^3J = 7.3 Hz, 1H), 7.24−7.44 (br, 8H), 7.49 (d, ^4J = 1.9 Hz, 1H), 7.82 (d, ^3J = 7.7 Hz, 2H), 7.95 (d, ^3J = 7.7 Hz, 1H), 10.08 (s, 1H), 10.29 (s, 1H), 11.66 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 42.6, 103.7, 113.3, 116.7, 117.3, 119.6, 123.0, 123.9, 125.9, 127.7, 127.8, 128.1, 128.5, 130.5, 135.3, 138.2, 159.0, 168.62; HRMS (positive ESI) *m*/*e* calcd for $C_{23}H_{20}N_3O_2^+$ (M + H$^+$) 370.1550, found 370.1550.

7-(3-Butylureido)-1*H*-indole-2-carboxylic Acid Butylamide, 4. 7-Nitro-1*H*-indole-2-carboxylic acid butylamide, **8a** (1.00 g, 3.8 mmol), Pd/C (0.20 g, 10 wt %), and hydrazine monohydrate (2 mL) were dissolved in ethanol (100 mL) and heated at reflux for 1 h. The reaction was then filtered hot through Celite and washed with ethanol (50 mL). The filtrate was then concentrated in vacuo, and the resulting white solid was used directly in the next reaction where it was dissolved in DCM (100 mL). To this solution was added butyl isocyanate (0.38 g, 3.8 mmol) dropwise, and the

reaction was stirred overnight. Water (250 mL) was then added, and the organic layer was separated and washed with water. The organic layer was dried with sodium sulfate, filtered, and concentrated in vacuo. The pure product was obtained by recrystallization from acetonitrile. The product was isolated as a white solid: yield 45%, 0.57 g; mp 116−118 °C; IR ν cm^{-1} 3288, 2957, 2359, 2160, 1615s, 1558s; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (t, 6H, ^3J = 7.2 Hz, CH_3), 1.28−1.57 (m, 8H), 3.14 (m, 2H), 3.33 (m, 2H, coincident with H_2O), 6.03 (bt, 1H), 6.93 (t, ^3J = 7.9 Hz, 1H), 7.10 (d, ^4J = 1.9 Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 8.47 (bt, 1H), 8.61 (s, 1H), 11.06 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 14.2, 20.0, 20.1, 31.8, 32.3, 38.9, 103.1, 112.2, 115.3, 120.7, 126.4, 127.5, 129.0, 131.7, 155.8, 161.3; HRMS (positive ESI) *m*/*e* calcd for $C_{18}H_{26}N_4O_2^+$ (M + H$^+$) 331.2129, found 331.2128.

7-(3-Phenylureido)-1*H*-indole-2-carboxylic Acid Phenylamide, 5. 7-Nitro-1*H*-indole-2-carboxylic acid phenylamide, **8b** (1.00 g, 3.6 mmol), Pd/C (0.20 g, 10 wt %), and hydrazine monohydrate (2 mL) were dissolved in ethanol (100 mL) and heated at reflux for 1 h. The reaction was then filtered hot through Celite and washed with ethanol (50 mL). The filtrate was then concentrated in vacuo, and the resulting white solid was used directly in the next reaction where it was dissolved in DCM (100 mL). To this solution was added phenyl isocyanate (0.43 g, 3.6 mmol) dropwise, and the reaction was stirred overnight. Water (250 mL) was then added, and the organic layer was separated and washed with water. The organic layer was dried with sodium sulfate, filtered, and concentrated in vacuo. The pure product was obtained via recrystallization from acetonitrile. The product was isolated as a pale yellow solid: yield = 48%, 0.64 g; mp 210−213 °C; IR ν cm^{-1} 3320, 3242, 3033, 1599, 1560, 1497, 1439; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.97−7.14 (m, 3H), 7.28−7.41 (m, 5H), 7.48−7.56 (m, 4H), 7.82 (d, ^3J = 8.0 Hz, 2H), 8.63 (s, 1H), 8.91 (s, 1H), 10.28 (s, 1H), 11.36 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 104.9, 114.2, 116.6, 118.9, 120.7, 121.0, 122.4, 124.1, 125.4, 128.8, 129.0, 129.2, 129.2, 131.6, 139.3, 140.2, 153.3, 160.0; HRMS (EI) calcd for $C_{22}H_{18}N_4O_2$ [M]$^+$ 370.1430, found 370.1430.

7-(3-Phenylthioureido)-1*H*-indole-2-carboxylic Acid Phenylamide, 6. 7-Nitro-1*H*-indole-2-carboxylic acid phenylamide, **8b** (1.00 g, 3.6 mmol), Pd/C (0.20 g, 10 wt %), and hydrazine monohydrate (2 mL) were dissolved in ethanol (100 mL) and heated at reflux for 1 h. The reaction was then filtered hot through Celite and washed with ethanol (50 mL). The filtrate was then concentrated in vacuo, and the resulting white solid was used directly in the next reaction where it was dissolved in DCM (100 mL). To this solution was added phenyl isothiocyanate (0.49 g, 3.6 mmol) dropwise, and the reaction was stirred overnight. Water (250 mL) was then added, and the organic layer was separated and washed with water. The organic layer was dried with sodium sulfate, filtered, and concentrated in vacuo. The pure product was obtained via recrystallization from acetonitrile. The product was isolated as a pale yellow solid: yield = 52%, 0.72 g; mp 185−187 °C; IR ν cm^{-1} 3415, 3244, 3058, 2916, 1647, 1632, 1539, 1344, 1316; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.06−7.15 (br, 3H), 7.32−7.41 (m, 4H), 7.46−7.59 (m, 5H), 7.81 (d, ^3J = 7.7 Hz, 2H), 9.63 (s, 1H), 9.93 (s, 1H), 10.28 (s, 1H), 11.52 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 103.9, 117.9, 119.1, 119.2, 122.4, 122.7, 123.3, 123.6, 127.4, 127.8, 130.4, 130.7, 137.9, 138.7, 158.5, 179.1; HRMS (positive ESI) *m*/*e* calcd for $C_{22}H_{19}N_4OS^+$ (M + H$^+$) 387.1274, found 387.1274.

All data were collected on a Bruker Nonius KappaCCD mounted at the window of a Mo rotating anode. Crystal data for the DMSO solvate of compound **2** (CCDC 655122): $C_{24}H_{23}N_3O_3S$, M_r = 433.51, T = 120(2) K, triclinic, space group P-1, a = 7.6003(2) Å, b = 12.0848(4) Å, c = 12.5665(4) Å, α =83.469(2)°, β = 78.876(2)°, γ = 71.766(2)°, V = 1073.89(6) Å^3, ρ_{calc} = 1.341 g cm^{-3}, μ = 0.182 mm^{-1}, Z = 2, reflections collected: 16956, independent reflections: 4853 (R_{int} = 0.0369), final R indices [$I > 2\sigma I$]: R1 = 0.0585, wR2 = 0.1195, R indices (all data): R1 = 0.0782, wR2 = 0.1322.

Crystal data for compound **3** (CCDC 655121): $C_{23}H_{19}N_3O_2$, M_r = 369.41, T = 120(2) K, monoclinic, space group $C2/c$, a = 23.6704(5) Å, b = 9.3018(2) Å, c = 16.9937(3) Å, β = 98.9440-(10)°, V =3696.13(13) Å^3, ρ_{calc} = 1.328 g cm^{-3}, μ = 0.087 mm^{-1}, Z = 8, reflections collected: 26892, independent reflections: 4231 (R_{int} = 0.0731), final R indices [$I > 2\sigma I$]: R1 = 0.0507, wR2 = 0.1134, R indices (all data): R1 = 0.0832, wR2 = 0.1290.

Crystal data for the DMSO solvate of compound **3** (CCDC 655120): $C_{25}H_{25}N_3O_3S$, M_r = 447.54, T = 120(2) K, triclinic, space group P-1, a = 9.8982(5) Å, b = 10.0741(4) Å, c = 11.5990(6) Å, α =76.080(3), β = 88.484(2)°, γ = 87.099(2)°, V =1121.07(9) Å^3, ρ_{calc} = 1.326 g cm^{-3}, μ = 0.177 mm^{-1}, Z = 2, reflections collected: 21219, independent reflections: 5119 (R_{int} = 0.0752), final R indices [$I > 2\sigma I$]: R1 = 0.0500, wR2 = 0.0976, R indices (all data): R1 = 0.1174, wR2 = 0.1167.

Crystal data for the DMSO solvate of compound **5** (CCDC655123): $C_{24}H_{24}N_4O_3S$, M_r = 448.53, T = 120(2) K, triclinic, space group P-1, a = 8.3464(3) Å, b = 10.5112(3) Å, c = 13.0482(4) Å, α =76.453(2), β = 85.668(2)°, γ = 84.522(2)°, V = 1106.12(6) Å^3, ρ_{calc} = 1.347 g cm^{-3}, μ = 0.181 mm^{-1}, Z = 2, reflections collected: 22815, independent reflections: 5063 (R_{int} = 0.0612), final R indices [$I > 2\sigma I$]: R1 = 0.0476, wR2 = 0.1082, R indices (all data): R1 = 0.0728, wR2 = 0.1215.

Crystal data for the chloride complex of compound **5** (CCDC 656115): $C_{92}H_{146}N_{11}O_5Cl_3$, M_r = 1592.55, T = 120(2) K, monoclinic, space group $P2_1/n$, a = 8.2521(2) Å, b = 26.0932(10) Å, c = 42.7518(15) Å, β = 92.152(2)°, V =9199.0(5) Å^3, ρ_{calc} = 1.150 g cm^{-3}, μ = 0.155 mm^{-1}, Z = 4, reflections collected: 4452, independent reflections: 15599 (R_{int} = 0.1138), final R indices [$I > 2\sigma I$]: R1 = 0.0836, wR2 = 0.1909, R indices (all data): R1 = 0.1833, wR2 = 0.2441.

Crystal data for the benzoate complex of compound **6** (CCDC 655303): $C_{68}H_{100}N_6O_5S$, M_r = 1113.60, T = 120(2) K, triclinic, space group $P1$, a = 8.5044(2) Å, b = 12.4661(4) Å, c = 16.0520-(5) Å, α = 91.9460(10)°, β = 99.404(2)°, γ = 109.096(2)°, V =1579.53(8) Å^3, ρ_{calc} = 1.171 g cm^{-3}, μ = 0.105 mm^{-1}, Z = 1, reflections collected: 26382, independent reflections: 12893 (R_{int} = 0.0466), final R indices [$I > 2\sigma I$]: R1 = 0.0542, wR2 = 0.1176, R indices (all data): R1 = 0.0842, wR2 = 0.1300.

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Supporting Information Available: ^{1}H and ^{13}C{^{1}H} NMR data for the compounds reported in the paper, NMR titration curves, COSY ^{1}H NMR spectra, ORTEP plots of the crystal structures, and alternative synthetic procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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