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Journal

European Journal of Organic Chemistry, 2022(16)

ISSN

1434-193X

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Publication Date

2022-04-27

DOI

10.1002/ejoc.202101346

Peer reviewed

HHS Public Access

Author manuscript

European J Org Chem. Author manuscript; available in PMC 2023 February 10.

Published in final edited form as:

European J Org Chem. 2022 April 27; 2022(16): . doi:10.1002/ejoc.202101346.

Preorganized Homochiral Pyrrole-Based Receptors That Display Enantioselective Anion Binding

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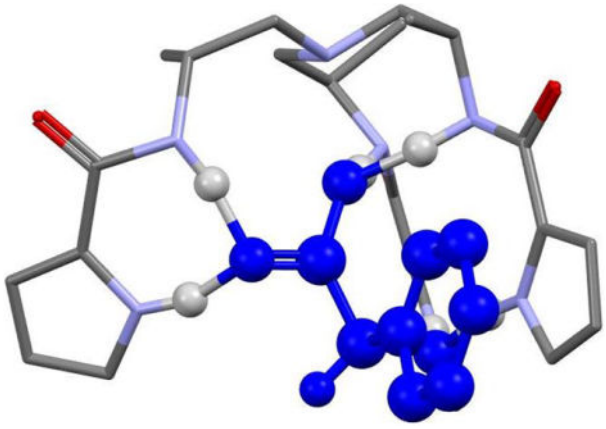
Abstract

Herein, a new scaffold for anion recognition based on a tripodal tris(pyrrolamide) motif is presented. The receptors were able to bind to a variety of anions with high affinity. Using density functional theory methods, the three-dimensional geometry of the receptor-anion complex was calculated. These calculations show that the receptors bind anions via a preorganized cavity of amide and pyrrole hydrogen bond donor groups. Based on these findings, homochiral tris(pyrrolamide) receptors were prepared, which produced as much as a 1.6-fold greater affinity for (*S*)-(+)-mandelate over (*R*)-(−)-mandelate, demonstrating the ability to differentiate between these enantiomeric anions. The interaction of (*S*)-(+)-mandelate and (*R*)-(−)-mandelate within the homochiral receptor was examined by solution NMR spectroscopy and density functional theory calculations. These findings indicate that the preorganized positioning of the pyrrole groups and subsequent sterics allows to differentiate between the stereoisomeric anions.

Graphical Abstract



Herein, a series of tris(pyrrolamide) receptors for anion recognition is presented. The receptors were able to bind to a variety of anions with good affinity, and homochiral receptors produced a

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Conflict of interest

There are no conflicts to declare.

1.6-fold greater affinity for (*S*)-(+)-mandelate over (*R*)-(−)-mandelate, demonstrating the ability to differentiate between these enantiomeric anions.

Keywords

Anions; Pyrrole; Receptors; Sensors; Supramolecular Chemistry

Introduction

Anions are an essential component of chemistry and play crucial roles in geology, biology, ecology, and various technologies. For example, nitrates and phosphates are used as agricultural fertilizers, and carbonates are found in various minerals and are typically produced via biotransformation processes. Anions are also central to the formation and integrity of enzyme-substrate/cofactor complexes, regulation of osmotic pressure, production of electrical signals, and activation of signal transduction pathways. Misregulation of anions can lead to diseases such as cystic fibrosis, Pendred syndrome, Dentś disease, osteopetrosis, and Barttes syndrome. For these reasons, the search for selective, high affinity anion receptors has received substantial attention in the chemical literature.[1]

In contrast to cation binders, the design of anionic receptors is generally more challenging. While cations are relatively small positively charged species, the corresponding isoelectronic anions are characterized by a large volume to charge ratio, resulting in more diffuse charge interactions. Anions can also possess many different geometries (i.e., spherical, linear, trigonal planar, tetrahedral, octahedral), requiring a sophisticated design of the corresponding receptors.[1–2]

A variety of different anion binding moieties, using amine, amide, urea, alcohol or electron deficient arene functional groups have been reported.[3] Among these, pyrrole and extended oligopyrrole systems have been widely investigated as anion receptors. In the 1990s, the first studies on pyrrole-based macrocycles (i.e., sapphyrin, calix[4]pyrrole, porphyrin) were reported to bind various anions.[4] Since then, considerable effort has been invested towards optimization of the structure of the calix[4]pyrrole receptor. This typically involves expanding the structural scaffold to enable secondary interactions, the binding of the anion and cation in different compartments, or the use of linkers which constrain the receptor.[5]

Enantioselective anion receptors are of value for their potential to selectively recognize and bind chiral anions (i.e., lactate, tartrate, amino acids, etc.). Some studies have used 1,1´-binaphthalene derivatives to produce chiral receptor sites.[6] Alternatively, the use of optically pure sugars,[7] peptides,[8] natural products,[9] metal complexes,[10] or chiral macrocyclic receptors[11] has been demonstrated. Upon utilizing these concepts, the enantioselective binding of mandelate has been previously reported.[12] The majority of chiral receptors display limited anion affinity and enantioselectivity, thus, there remains opportunities to develop novel chiral receptor motifs.

Herein, the synthesis of novel homochiral, tripodal tris(pyrrolamide) receptors for anion recognition is presented. The receptors bind with high affinity to anions of

varying molecular shapes. Prior studies on homochiral tris(2-aminoethyl)amine (TREN) derivatives[13] and density functional theory (DFT) calculations suggested that introduction of stereocenters into the tripodal 'backbone' could result in preorganization and a chiral bias to the receptors. A homochiral receptor was prepared that shows a 1.6-fold greater affinity for (*S*)-(+)-mandelate relative to (*R*)-(−)-mandelate.

Results and Discussion

The TREN scaffold has been used in the preparation of ligands for both cation binding and anion recognition.[14] Using density functional theory (DFT) calculations, the three-dimensional geometry of TREN was predicted (Figure S1a), and was in good agreement with crystal structure of this compound.[15] Upon incorporation of three stereogenic centers to the TREN scaffold, DFT calculations indicate that the compound has a preorganized geometry with its NH groups facing in the same direction (Figure S1b), in good agreement with a published crystal structure of this compound.[13] Notably, X-ray crystal structures of TREN in the presence of anions[16] have shown that this ligand can exhibit the same geometry as the preorganized chiral derivative.

The synthesis of the homochiral, tripodal, pyrrolamide-based anion receptors started with L-alanine, using a previously reported protocol (see Supplementary Information for details).[13] The final pyrrolamide receptors **6**-**9** (Figure 1) were generated upon addition of 2-(trichloroacetyl)pyrrole or 2-(trichloroacetyl)-5-methyl-pyrrole to either unsubstituted TREN or **5** at room temperature (Scheme S1, Figure S2–S9). The synthesis of **6** and its X-ray structure have been previously reported.[17] The alpha-carbon of pyrroles can be a reactive site on these heterocycles. Therefore, using **6** as a representative compound, we tested the stability of this compound to ensure that it was stable under conditions relevant to its use as an anion receptor. Compound **6** was studied by simple incubation in methanol or water (1% by volume of DMF) for 48 h. No change in retention time or peak height was observed by HPLC (Figure S10–S12), indicating the stability of the receptor. Calix[4]pyrrole **10** was synthesized by condensation of pyrrole with acetone[18] and used to compare the anion binding affinities to the novel pyrrolamide receptors reported here.

With the compounds in hand, their ability to bind to anions was investigated by UV-visible absorption spectroscopy. Receptors **6**-**9** were dissolved in dry 95:5 CH_2Cl_2/DMSO and fluoride, chloride, bromide, iodide, acetate, benzoate, perchlorate, and nitrate were added as the tetrabutylammonium salts. The salts were titrated into solutions of the receptor (Table S1, Figure S13), followed by a 5 min equilibration period before the absorption spectrum was recorded (Figure S14–S17). Upon anion addition, the spectrum of the sample showed a reduction in absorption intensity, indicating binding of anions to the receptor. The absorption dropped upon anion addition until a final, unchanging absorption spectrum was reached at ~1 equivalent of the anion, suggestive of a 1:1 anion-receptor complex in all cases, with the notable exception of iodide. Upon plotting the difference in absorption intensity as a function of the mole fraction of receptor/anion (Job plot) (Figure S18) a maximum of change in absorption was found at a mole fraction of ~0.5 for all anions, confirming a 1:1 anion-receptor stoichiometry. Notably, a recent study has indicated that the Job plot analysis alone can be misleading and that other binding models should be considered.[19] Based on

this report, the anion titration data was modeled using other binding stoichiometries (e.g., 1:2, 1:3, 2:1 receptor:anion). However, these models did not fit the experimentally obtained data, supporting the Job plot 1:1 anion-receptor stoichiometry.

The observed change in absorption of the receptors was used to quantitatively assess the anion binding affinity. Using the Thordarson anion binding fitting program[20] with a 1:1 receptor:anion model, the association constants (K_a) were determined. Binding affinity data are summarized in Table 1. Fluoride ($\log K_a$ = 5.02 – 5.12) produced a greater binding constant than chloride ($\log K_a$ = 4.90 – 5.01) and bromide ($\log K_a$ = 4.34 – 4.54). In comparison, calix[4]pyrrole **10** demonstrated a binding affinity of the same order of magnitude to fluoride, but weaker binding to chloride, in agreement with previous studies.[21] This trend in binding to halide anions has been reported for many other anion receptors[22] and is associated with the relatively small volume and high charge of fluoride in comparison to other anions. Due to the large volume and electronically diffuse nature of bromide ions, these anions are more challenging to bind. All of the pyrrolamide receptors reported here were found to bind to bromide ions, while the reference calix[4]pyrrole **10** did not. Among the carboxylate anions, the receptors demonstrated 1.6 – 2.5 times greater binding constants for acetate ($\log K_a$ = 4.93 – 5.00) relative to benzoate ($\log K_a$ = 4.57 – 4.75), both of which are in the same range as previously published for calix[4]pyrrole[2]carbazole derivatives.[23] Perchlorate was most weakly bound among all the anions tested ($\log K_a$ = 4.04 – 4.36). Finally, all of the receptors had a high affinity for nitrate ($\log K_a$ = 4.98 – 5.08) when compared to calix[4]pyrrole **10**. The α-methyl group on the pyrrole in receptors **7** and **9** did not significantly change their anion binding ability. However, the receptors with methyl groups on the TREN scaffold (**8**, **9**) generally showed increased receptor affinity for most anions, likely due to receptor preorganization driven by the three stereogenic centres. Overall, the homochiral receptor **8** was found to have the strongest binding (on average) for the tested anions. The binding affinity of **8** with nitrate was also evaluated at under higher dilution conditions (Figure S19), which confirmed the measured association constant ($\log K_a$ = 5.06±3.60).

Using the high association constant of nitrate for receptor **8**, the binding of nitrate was also investigated via ^{1}H NMR titration. To solutions of **8** in dry, deuterated 95:5 CD_2Cl_2/$(CD_3)_2SO$, tetrabutylammonium nitrate was titrated between 0.1 – 2 equivalents relative to **8**. Upon addition of nitrate, the solutions were allowed to equilibrate for 5 min and the corresponding ^{1}H NMR spectra were recorded. As the ratio of tetrabutylammonium nitrate to **8** increased, the resonances of the free receptor (7.43, 6.23, 5.66 ppm) diminish, while new peaks for the receptor-anion complex (7.51, 7.46, 6.53 ppm) emerged (Figure S20). Notably, during the ^{1}H NMR titration experiment no changes in the chemical shift values of the signals corresponding to the tetrabutylammonium cation was observed, suggesting formation of an anion complex and not a anion-cation pair with the receptor. To further evaluate whether these receptors were binding the anion or an anion-cation pair, receptor **8** was titrated with tetraalkylammonium nitrate and the affinity measured by UV-vis spectroscopy. The affinity for tetrahexylammonium nitrate ($\log K_a$ = 5.07 ± 3.85) and tetramethylammonium nitrate ($\log K_a$ = 5.10 ± 3.78) were within error of that for tetrabutylammonium nitrate ($\log K_a$ = 5.08 ± 3.70, Table 1), suggesting that **8** only binds

the anion. Because several of the receptors show poor solubility in organic solvents, DMSO was used as a co-solvent in anion binding studies. To investigate whether DMSO has an influence on anion binding, the binding affinity of **8** towards tetrabutylammonium nitrate in 95:5 CH_2Cl_2/DMSO, 2:1 CH_2Cl_2/DMSO, and pure DMSO was studied. Binding constants under all of these conditions were within the same range, specifically 5.08±3.70 ($\log K_a$ value) in 95:5 CH_2Cl_2/DMSO, 5.06±3.90 in 2:1 CH_2Cl_2/DMSO, and 5.01±3.95 in pure DMSO, with only a slight decrease in binding affinity observed in pure DMSO. These experiments indicate that the presence of DMSO has only minor effect on the anion binding of the receptor.

Using DFT calculations, the binding of the chloride and nitrate complexes of the unfunctionalized receptor **6** and the preorganized homochiral receptor **9** were calculated (Figure 2, Figure S21). The predicted binding poses of the spherical chloride ion show symmetric binding through the amide and pyrrole groups of the receptors by hydrogen-anion interactions. The trigonal planar nitrate ion was bound by hydrogen bonding interactions between the amide and pyrrole NH groups and nitrate oxygen atoms. This binding pose is similar to the one found upon binding of the trigonal planar acetate anion in a bicyclic cyclophane receptor.[24]

The ability of the homochiral receptor **8** to bind the chiral anions lactate and mandelate was investigated. As described above, the anion binding was monitored by UV-vis spectroscopy in dry 95:5 CH_2Cl_2/DMSO (Figure S22–S23). Receptor **8** was found to bind lactate ions ($\log K_a$ = 4.98 – 5.00) and acetate anions ($\log K_a$ = 4.97) with comparable affinity (Table 1). The receptor showed a similar association constant for both (*R*)-(−)- and (*S*)-(+)-lactate, unable to differentiate between these stereoisomers. The phenyl functionalized mandelate showed weaker binding to **8** than lactate; however, **8** displayed a 1.6-fold greater affinity for (*S*)-(+)-mandelate ($\log K_a$ = 4.93) than (*R*)-(−)-mandelate ($\log K_a$ = 4.72), showing an ability to distinguish between these chiral anions with an enantioselectivity of 1.6. The binding affinity of mandelate to **8** was also studied in dry 2:1 CH_2Cl_2/DMSO. The measured association constants were found to be in the same range for (*S*)-(+)-mandelate ($\log K_a$ = 4.86) and (*R*)-(−)-mandelate ($\log K_a$ = 4.61), indicating that the addition of DMSO did not significantly influence the binding of this anion. By contrast, the achiral receptor **6** showed no difference in K_a (Table 1).

The binding selectivity between (*S*)-(+)-mandelate and (*R*)-(−)-mandelate was compared with previously published enantioselective mandelate receptors. However, it is important to highlight that many of these experiments have been performed under different experimental conditions (i.e., solvent, concentration, etc.) and are therefore not entirely comparable with the findings reported here. As a highly investigated anion receptor system, the calix[4]pyrrole scaffold was modified to provide enantioselectivity. Aromatic extension to produce pillar[5]arene-calix[4]pyrrol receptors were found to differentiate between the stereoisomers of mandelate with a selectivity up 2.47 in DMSO[12a] and aliphatically extended calix[4]arene receptors with a selectivity up to 3.5 in DMSO[12d]. As a chiral director, substantial research efforts have ben devoted towards the incorporating the bisbinaphthyl moiety into anion receptors. Dendritic bisbinaphthyl receptors show an enantioselectivity of 2.49 in 98:2 benzene/1,2-dimethoxyethane[12b] and binaphthyl

metallocyclophanes receptors a selectivity of 2.33 in 98:2 CH_2Cl_2/1,2-dimethoxyethane solution.[12c] Complementary, other approaches use the incorporation of the naturally occurring chirality. Studies have demonstrated the use of glucosamine functionalized receptors with an enantioselectivity of 2.0 in 95:5 DMSO/H_2O[12e] and sugar-based diindolylmethane receptors with an enantioselectivity of 1.95 in 99.5:0.5 DMSO/H_2O.[12f] Notably, the enantioselectivities of these receptors are better than chiral receptor **8**; however, as stated above, the experimental conditions are not identical.

The binding pose of the receptor-mandelate complex was evaluated using DFT calculations (Figure 3). While the negatively charged oxygen atom of the carboxylic acid group is predicted to interact with the amide NH group deep in the receptor, the oxygen atom of the carbonyl group appears to associate with the receptor amide and pyrrole NH groups by hydrogen bonding. Further, the hydroxy groups on mandelate at the chiral center were found to interact with pyrrole groups of the receptor. In the complex of **8** bound to the *S*-isomer, the phenyl group is oriented parallel to a pyrrole group of the receptor. Under the assumption that the carboxylic acid and hydroxy groups of the anion would bind in a similar manner in the *R*-isomer, the phenyl group would sterically clash with a pyrrole group of the receptor, potentially explaining the difference in binding affinity between **8** and the two isomeric forms of mandelate.

Attempts to grow single crystals of these receptors with any anions were not successful. Therefore, the interactions of the (*R*)-(−)- and (*S*)-(+)-mandelate with **8** was studied using NMR. To observe the pyrrole and amide protons, the experiment was performed in a 1:2 mixture of dry CD_2Cl_2/$(CD_3)_2SO$. Due to the necessity for higher concentrations of the receptor during the NMR experiment, when compared to the UV-Vis affinity measurements, a greater amount of $(CD_3)_2SO$ was required to perform these NMR studies. The signals of the receptor-anion complex (Figure 4) were correlated to the respective protons/carbons using 2D-NMR techniques (HSQC, COSY, HMBC, Figure S24–S28). Using a selective 1D-NOESY experiment the proximity of the pyrrole nitrogen proton (11.18 ppm) with other protons was investigated (Figure 4, Figure S29–S30). As expected, the proton was found to interact with the amide proton (H_4) as well as the aromatic pyrrole proton (H_8). Importantly, the pyrrole nitrogen proton was also found in proximity of the proton at the stereocenter in mandelate (H_b) for both stereoisomers, suggesting an interaction of the receptor with the anion

The proximity of all protons in the receptor-anion complex were studied in a 2D-NOESY experiment (Figure 4, Figure S29–S30). In addition to the direct proton-proton proximity within a single molecule (COSY), the 2D-NOESY spectra showed the interactions between the receptor with the anion. The spectra of the anions with both stereo configurations showed a cross peak between the pyrrole nitrogen proton and the proton at the stereocenter in mandelate (H_7-H_b), indicating binding of anion to the receptor. The spectrum of the **8**-(*S*)-(+)-mandelate complex showed a close proximity of the aromatic protons of mandelate with the aromatic protons of the pyrrole moiety (H_8-H_b, H_8-H_d, H_8-H_e, H_9-H_f, H_{10}-H_e) of the receptor, suggesting a near parallel geometry of the two aromatic systems (Figure 4). These findings agree with the DFT-predicted geometry of the receptor-anion complex (Figure 3). In contrast, the **8**-(*R*)-(−)-mandelate complex did not exhibit these interactions,

suggesting a clear difference in orientation of the anion in the receptor cavity. In comparison to **8**-(*S*)-(+)- mandelate, **8**-(*R*)-(−)-mandelate showed a cross signal from the amide proton to the pyrrole proton (H_4-H_7), as well as between the aromatic proton of the 'backside' of the pyrrole (H_4-H_{10}), while still exhibiting an interaction between the pyrrole NH proton with the proton at the stereocenter in mandelate (H_1-H_a). These results suggest that some pyrrole moieties are interacting with the anion while others may be 'flipped' out of the receptor cavity such that the pyrrole nitrogen proton cannot interact with the anion. This finding could explain the difference in affinities and selectivity for these chiral anions by receptor **8**.

Finally, the proximity of the α-proton (H_8) on the pyrrole (6.80 ppm) to other protons was investigated in a selective 1D-NOESY experiment (Figure S29–S30). Both stereoisomers showed proximity to the pyrrole NH proton (H_7) as well as β-proton on the pyrrole (H_9). However, the spectrum of the **8**-(*S*)-(+)- mandelate complex also had signals corresponding to aromatic protons (H_d, H_e) as well as the proton at the stereocenter (H_b), confirming the receptor-anion geometry.

Conclusion

In summary, novel pyrrolamide anion receptors and their binding to various anions has been investigated. The stereochemical methyl functionalized *N,N*-bis(2-aminoethyl)-1,2-ethanediamine scaffold is able to preorganize in solution to generate a cavity of amide and pyrrole hydrogen bond donor groups. The receptors were found to bind to a wide variety of anions with different geometries. Homochiral receptor **8** showed a 1.6-fold greater affinity for (*S*)-(+)- over (*R*)-(−)-mandelate. DFT calculations and NMR experiments reveal how the receptor might differentiate between the stereoisomers of mandelate. These results suggest that pyrrolamides can serve as a novel scaffold for the development of a variety of selective receptors for anion binding and sensing.

Experimental Section

Density-functional Theory Calculations

The geometry of a compound was predicted using density-functional theory calculations with the Gaussian software package. (Gaussian, Inc., Wallingford CT, 2016). All atoms were described using the Pople double-zeta basis set with a single set of polarization functions on non-hydrogen atoms (6–31G(d)). Solvent effects were included using a polarizable continuum model (PCM). The structures of all calculated molecules correspond to ground state minima on the ground state potential energy surfaces with no imaginary frequencies present. Upon initiating the calculations from different receptor conformations, the same energetically optimized structure was obtained.

Materials and Methods

All reagents and solvents were obtained from commercial sources and used without further purification. NMR spectra were recorded at apparatus from the nuclear magnetic resonance facility located in the Department of Chemistry and Biochemistry at the University of California, San Diego. ^{1}H and ^{13}C NMR spectra were measured on a 300 MHz or 500 MHz NMR spectrometer. The spectra were analyzed by chemical shifts (δ) in parts per

million (ppm) referenced to tetramethylsilane (δ 0.00) ppm using the residual proton solvent peaks as internal standards and coupling constants (*J*) in Hertz (Hz). The multiplicity of the peaks is abbreviated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). Mass spectra were recorded at the molecular mass spectrometry facility located in the Department of Chemistry and Biochemistry at the University of California, San Diego. High resolution mass spectrometry (HR-MS) were measured with an Agilent 6230 time-of-flight mass spectrometer using a jet stream electrospray ionization source (ESI). The jet stream source was operated under positive ionization mode with the following parameters: VCap: 3500V; fragmentor voltage: 160 V; nozzle voltage: 500 V; drying gas temperature: 325 °C, sheath gas temperature: 325 °C, drying gas flow rate: 7.0 L/min; sheath gas flow rate: 10 L/min; nebulizer pressure: 40 psi.

Synthesis

Boc-L-Alanine (1).—The synthesis of this compound was previously reported.[25] L-Alanine (1.0 g, 11.2 mmol, 1.0 equiv.) was dissolved in dioxane/water (1:1, 40 mL) and the pH adjusted to the alkaline milieu with an aqueous sodium hydroxide solution (1 M, 30 mL). The mixture was cooled down with an ice-water mixture and di-*tert*-butyl dicarbonate ($(Boc)_2O$, 674 mg, 16.8 mmol, 1.5 equiv.) was slowly added. The reaction mixture was stirred at room temperature overnight. After this time, the solvent was removed under reduced pressure. The residue was dissolved in water (20 mL) and mixed with an equal amount of ethyl acetate. The solution was acidified with concentrated aqueous HCl as indicated by pH paper, the layers separated and the organic phase extracted with ethyl acetate (3×20 mL). The combined organic phase was dried over sodium sulfate and under vacuum. The product was obtained as a white solid. Yield: 1.76 g (9.3 mmol, 83%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.94 (s, 1H), 4.35–4.13 (m, 1H), 1.44 (s, 9H), 1.44 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 178.2, 155.6, 80.5, 49.2, 28.4, 18.4; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_8H_{15}NO_4Na$, 212.0893; found, 212.0895.

Boc-L-Alaninol (2).—The synthesis of this compound was previously reported.[26] Boc-L-Alanine (**1**, 1.0 g, 5.3 mmol, 1.0 equiv.) was dissolved in dry tetrahydrofuran (20 mL) under nitrogen atmosphere. The mixture was cooled in an ice-water mixture and a solution of trihydridoboron in tetrahydrofuran (BH_3, 1 M, 10.57 mL, 10.6 mmol, 2.0 equiv.) was slowly added. The reaction mixture was stirred at room temperature overnight. After this time, slowly water was added (5 mL) and then the solvent removed under reduced pressure. To the residue, equal amounts of water and ethyl acetate were added (40 mL). The layers were separated and the organic phase extracted with ethyl acetate (3×20 mL). The combined organic phase was dried over sodium sulfate and under vacuum. The product was obtained as a white solid. Yield: 658 mg (3.8 mmol, 71%). ^{1}H-NMR (500 MHz,$CDCl_3$): δ = 3.77–3.71 (m, 1H), 3.61 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.48 (dd, *J* = 11.0, 6.2 Hz, 1H), 1.43 (s, 9H), 1.12 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 156.5, 79.9, 67.4, 48.8, 28.5, 17.4; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_8H_{17}NO_3Na$, 198.1101; found, 198.1104.

Boc-L-Alaninal (3).—The synthesis of this compound was previously reported.[27] Boc-L-Alaninol (**2**, 0.5 g, 2.9 mmol, 1.0 equiv.) was dissolved in dry dichloromethane (50 mL) under nitrogen atmosphere. To the solution triethylamine (1.2 mL, 8.6 mmol, 3.0 equiv.)

and dimethyl sulfoxide (10 mL) were added and the mixture was cooled in an ice-water mixture. A solution of the sulfur trioxide pyridine complex ($PySO_3$, 1.3 g, 8.6 mmol, 3.0 equiv.) in dichloromethane (10 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. After this time, slowly water was added (5 mL) and then the solvent removed under reduced pressure. To the residue, equal amounts of water and ethyl acetate were added (40 mL). The layers were separated and the organic phase extracted with ethyl acetate (3×20 mL). The combined organic phase was dried over sodium sulfate and under vacuum. The product was obtained as a white solid. Yield: 217 mg (1.3 mmol, 44%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.55 (s, 1H), 5.18–5.07 (m, 1H), 4.25–4.17 (m, 1H), 1.44 (s, 9H), 1.30 (d, *J* = 7.4 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 200.0, 155.4, 80.0, 55.1, 28.5, 14.4; HRMS (*m*/*z*): $[M+MeOH+Na]^+$ calcd. for $C_8H_{15}NO_3Na+CH_3OH$, 228.1206; found, 228.1207.

(Boc-L-Alanine)$_3$-TREN (4).—The synthesis of this compound was previously reported.[13] Boc-L-Alaninal (**3**, 200 mg, 1.2 mmol, 3.0 equiv.) and ammonium acetate (30 mg, 0.4 mmol, 1.0 equiv.) were dissolved in dry tetrahydrofuran (25 mL) under nitrogen atmosphere. A solution of sodium triacetoxyborohydride (367 mg, 1.7 mmol, 4.5 equiv.) in tetrahydrofuran (20 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. After this time, a mixture of acetic acid/methanol (1:10, 5 mL) was added and then the solvent removed under reduced pressure. To the residue, equal amounts of water and dichloromethane were added (40 mL). The layers were separated and the organic phase extracted with dichloromethane (3×20 mL). The organic phase was washed three times with an aqueous potassium hydroxide solution (6%, 20 mL), water, and brine. The organic phase was dried over sodium sulfate and under vacuum. The product was purified by reverse phase column chromatography with a linear gradient (0%:100% - 100%:0% methanol/water). The fractions containing the product were combined and the compound dried under vacuum. The product was obtained as a white solid. Yield: 170 mg (0.4 mmol, 30%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.62–3.54 (m, 3H), 2.62–2.42 (m, 3H), 2.16–2.12 (m, 3H), 1.36 (s, 27H), 1.02 (d, *J* = 6.5 Hz, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 156.5, 78.9, 60.8, 44.1, 28.6, 19.4; MS (*m*/*z*): $[M+H]^+$ calcd. for $C_{24}H_{49}N_4O_6$, 489.7; found, 489.9.

(L-Alanine)$_3$-TREN-trihydrochloride (5).—The synthesis of this compound was previously reported.[13] (BOC-L-Alanine)$_3$-TREN (**4,** 100 mg, 0.21 mmol, 1.0 equiv.) was dissolved in dry ethyl acetate (20 mL) under nitrogen atmosphere. A solution of hydrogen chloride in diethyl ether (2 M, 10 mL) was added. The reaction mixture was stirred at room temperature for 3 h. After this time, the solvent was removed under reduced pressure. The solid was washed with diethyl ether. The product was purified by reverse phase column chromatography with a linear gradient (0%:100% - 100%:0% methanol/water). The fractions containing the product were combined and the compound dried under vacuum. The product was obtained as a white solid. Yield: 29 mg (0.16 mmol, 76%). ^{1}H-NMR (300 MHz, D_2O): δ = 3.56–3.49 (m, 3H), 2.75 (dd, *J* = 14.4, 9.6 Hz, 3H), 2.61 (dd, *J* = 14.4, 4.0 Hz, 3H), 1.26 (d, *J* = 6.7 Hz, 9H); ^{13}C-NMR (125 MHz, D_2O): δ = 58.2, 45.2, 16.1; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{21}H_{28}N_7O_3$, 189.2074; found, 189.2076.

(1*H*-pyrrole-2-carboxamide)$_3$-TREN (6).—2,2,2-Trichloro-1-(1*H*-pyrrol-2-yl)ethan-1-one (100 mg, 0.47 mmol, 3.5 equiv.) and *N*,*N*-bis(2-aminoethyl)-1,2-ethanediamine (TREN, 20 μL, 0.13 mmol, 1.0 equiv.) were dissolved in a mixture of dichloromethane/methanol (5:1, 20 mL). The reaction mixture was stirred at room temperature overnight. After this time, the solvent was removed under reduced pressure. The solid was washed three-times with dichloromethane and diethyl ether. The product was obtained as a brown solid. Yield: 52 mg (0.12 mmol, 91%). ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): δ = 11.41 (s, 3H), 7.92 (s, 3H), 6.84–6.82 (m, 3H), 6.73–6.70 (m, 3H), 6.06–6.04 (m, 3H), 3.31 (t, *J* = 7.0 Hz, 6H), 2.65 (t, *J* = 7.0 Hz, 6H); ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): δ = 160.7, 126.4, 121.2, 109.8, 108.6, 53.8, 37.0; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{21}H_{28}N_7O_3$, 426.2248; found, 426.2249; IR: ν = 3260 (brm), 1603 (m), 1560 (m), 1510 (m), 1428 (w), 1404 (w), 1363 (w), 1336 (w), 1305 (w), 1167 (w), 1124 (m), 1035 (w), 834 (w), 789 (w), 738 (s), 606 (m), 578 (m) cm^{-1}; Elemental analysis calcd. (%) for $C_{21}H_{27}N_7O_3$: C 59.28, H 6.40, N 23.04; found: C 58.90, H 6.61, N 23.07.

(1*H*-pyrrole-2-carboxamide-5-methyl)$_3$-TREN (7).—2,2,2-Trichloro-1-(5-methyl-1*H*-pyrrol-2-yl)ethan-1-one (100 mg, 0.44 mmol, 3.5 equiv.) and *N*,*N*-bis(2-aminoethyl)-1,2-ethanediamine (TREN, 19 μL, 0.13 mmol, 1.0 equiv.) were dissolved in a mixture of dichloromethane/methanol (5:1, 20 mL). The reaction mixture was stirred at room temperature overnight. After this time, the solvent was removed under reduced pressure. The product was purified by reverse phase column chromatography with a linear gradient (0%:100% - 100%:0% methanol/water). The fractions containing the product were combined and the compound dried under vacuum. The product was obtained as a brown solid. Yield: 28 mg (0.06 mmol, 46%). ^{1}H-NMR (500 MHz, CD_3OD): δ = 6.58 (d, *J* = 3.6 Hz, 3H), 5.78 (d, *J* = 3.6 Hz, 3H), 3.41 (t, *J* = 6.1 Hz, 6H), 2.72 (t, *J* = 6.1 Hz, 6H), 2.21 (s, 9H); ^{13}C-NMR (125 MHz, CD_3OD): δ = 163.9, 133.7, 125.3, 112.9, 108.8, 55.4, 38.6, 12.8; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{24}H_{34}N_7O_3$, 468.2718; found, 468.2712; IR: ν = 3265 (brm), 1610 (m), 1565 (m), 1513 (m), 1430 (w), 1402 (w), 1360 (w), 1330 (w), 1305 (w), 1170 (w), 1126 (m), 1030 (w), 835 (w), 790 (w), 738 (s), 606 (m), 578 (m) cm^{-1}; Elemental analysis calcd. (%) for $C_{24}H_{33}N_7O_3$+MeOH: C 60.10, H 7.46, N 19.62; found: C 59.84, H 7.23, N 19.86.

(*N*-L-Alanine-1*H*-pyrrole-2-carboxamide)$_3$-TREN (8).—2,2,2-Trichloro-1-(1*H*-pyrrol-2-yl)ethan-1-one (100 mg, 0.47 mmol, 3.5 equiv.) and (L-Alanine)$_3$-TREN-trihydrochloride (**5**, 25 mg, 0.14 mmol, 1.0 equiv.) were dissolved in a mixture of dichloromethane/methanol (5:1, 20 mL). Potassium carbonate (2.0 g, 14.47 mmol, 106.8 equiv.) and 4-Dimethylaminopyridine (100 mg, 0.82 mmol, 6.1 equiv.) were added and the reaction mixture stirred for 3 d at room temperature. After this time, the mixture was filtered and the solvent removed under reduced pressure. The product was purified by reverse phase column chromatography with a linear gradient (0%:100% - 100%:0% methanol/water). The fractions containing the product were combined and the compound dried under vacuum. The product was obtained as a brown solid. Yield: 27 mg (0.06 mmol, 43%). ^{1}H-NMR (500 MHz, CD_3OD): δ = 7.54–7.50 (m, 3H), 7.36–7.33 (m, 3H), 6.44–6.42 (m, 3H), 3.59–3.50 (m, 3H), 2.78 (dd, *J* = 14.4, 9.3 Hz, 3H), 2.65 (d, *J* = 14.4 Hz, 3H), 1.32 (d, *J* = 6.5 Hz, 9H); ^{13}C-NMR (125 MHz, CD_3OD): δ = 161.7, 130.6, 123.7, 112.7, 109.6, 59.4, 46.3, 17.1;

HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{24}H_{34}N_7O_3$, 468.2717; found, 468.2715; IR: ν = 3270 (brm), 1612 (m), 1568 (m), 1515 (m), 1433 (w), 1400 (w), 1365 (w), 1335 (w), 1300 (w), 1130 (m), 1025 (w), 840 (w), 795 (w), 740 (s), 605 (m), 580 (m) cm^{-1}; Elemental analysis calcd. (%) for $C_{24}H_{33}N_7O_3+H_2O$: C 59.36, H 7.27, N 20.19; found: C 59.51, H 6.92, N 19.94.

(*N*-L-Alanine-1*H*-pyrrole-2-carboxamide-5-methyl)$_3$-TREN (9).—2,2,2-Trichloro-1-(5-methyl-1*H*-pyrrol-2-yl)ethan-1-one (100 mg, 0.44 mmol, 3.5 equiv.) and (L-Alanine)$_3$-TREN-trihydrochloride (**5**, 24 mg, 0.13 mmol, 1.0 equiv.) were dissolved in a mixture of dichloromethane/methanol (5:1, 20 mL). Potassium carbonate (2.0 g, 14.47 mmol, 114.8 equiv.) and 4-Dimethylaminopyridine (100 mg, 0.82 mmol, 6.5 equiv.) were added and the reaction mixture stirred for three days at room temperature. After this time, the mixture was filtered and the solvent removed under reduced pressure. The product was purified by reverse phase column chromatography with a linear gradient (0%:100% - 100%:0% methanol/water). The fractions containing the product were combined and the compound dried under vacuum. The product was obtained as a brown solid. Yield: 17 mg (0.03 mmol, 26%). ^{1}H-NMR (500 MHz, CD_3OD): δ = 7.45 (d, *J* = 4.1 Hz, 3H), 6.24 (d, *J* = 4.1 Hz, 3H), 3.55–3.51 (m, 3H), 2.76–2.69 (m, 3H), 2.58 (dd, *J* = 14.4, 3.0 Hz, 3H), 2.38 (s, 9H), 1.31 (d, *J* = 6.6 Hz, 9H); ^{13}C-NMR (125 MHz, CD_3OD): δ = 161.6, 132.2, 124.9, 112.2, 108.6, 59.4, 46.2, 17.1, 12.9; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{27}H_{40}N_7O_3$, 510.3187; found, 510.3189; IR: ν = 3260 (brm), 1615 (m), 1560 (m), 1515 (m), 1425 (w), 1404 (w), 1363 (w), 1337 (w), 1308 (w), 1168 (w), 1123 (m), 1025 (w), 830 (w), 789 (w), 737 (s), 605 (m), 579 (m) cm^{-1}; Elemental analysis calcd. (%) for $C_{27}H_{39}N_7O_3$: C 63.63, H 7.71, N 19.24; found: C 63.76, H 7.44, N 19.01.

Calix[4]pyrrole (10).—The synthesis of this compound was previously reported.[28] Pyrrole (1.0 mL, 15.4 mmol, 4.0 equiv.) and acetone (1.14 mL, 15.4 mmol, 4.0 equiv.) were dissolved in dry dichloromethane (20 mL). Amberlyst-15 was added as a solid phase catalyst and the mixture heated at reflux overnight. After this time, the solid catalyst was removed by filtration and thoroughly washed with dichloromethane (3×20 mL). The solvent was removed under reduced pressure and the product purified by silica column chromatography with a linear gradient (0%:100% - 100%:0% dichloromethane/hexane). The fractions containing the product were combined and the compound dried under vacuum. The product was obtained as a solid. Yield: 1.20 mg (2.8 mmol, 73%). ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): δ = 9.29 (s, 4H), 5.68 (d, *J* = 2.6 Hz, 8H), 1.50 (s, 24H); ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): δ = 138.6, 101.8, 34.6, 29.1; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{28}H_{37}N_4$, 429.3013; found, 429.3012.

Anion Binding Affinity Studied by Absorption Spectroscopy

The receptor was dissolved in 1 mL of dry 95% dichloromethane and 5% dimethyl sulfoxide at a concentration of 0.1 mg/mL (**6**: 235 μM, **7**: 214 μM, **8**: 214 μM, **9**: 196 μM). Various anions (fluoride, chloride, bromide, iodide, acetate, benzoate, perchlorate, nitrate) as their tetrabutylammonium salt were added to the solution (Table S1). After each addition, the solution was mixed and equilibrated for 5 min. The absorption spectrum of the solution from 230–350 nm was measured with a Perkin Elmer UV-Vis Lambda 25 spectrometer. The

stoichiometry of the receptor was determined using a Job plot of the difference in absorption intensity at the maximum in dependence of the mole fraction of receptor/anion. The results indicated a 1:1 ratio of receptor to anion. Noteworthy, the titration of the anion without the receptor did not show any changes in the observed region of the absorption spectra. The Thordarson Fitting Program within Matlab with a 1:1 UV/VIS model was used to determine the association constants as previously described in detail (P. Thordarson, *Chem. Soc. Rev.* **2011,** *40* (3), 1305–1323). As input the absorption values at 250, 260, 270 and 280 nm during the titration were used. The convergence was performed with 1000 iterations. As an initial estimate of the association constant, the reciprocal concentration of the receptor was used (see Figure S13 and Figure S19 for representative curve fitting for the titration of receptor **8** with tetrabutylammonium nitrate).

Anion Binding Affinity Studied by NMR Spectroscopy

The receptor was dissolved in dry 95% dichloromethane and 5% dimethyl sulfoxide at a concentration of 1 mg/mL. Tetrabutylammonium nitrate was titrated into the solution. After each addition, the solution was mixed and equilibrated for 5 min. The NMR spectrum of the solution was measured with Bruker Ava 300 MHz NMR spectrometer.

Anion Binding Pose Studied by NMR Spectroscopy

The receptor and the chiral anion were dissolved in a 1:1 stoichiometry in deuterated 67% dry dichloromethane and 33% dimethyl sulfoxide at a concentration of 2 mM. ^{1}H, HSQC, COSY, HMBC, 1D-NOESY and 2D-NOESY spectra were recorded on Joel 400 MHz NMR spectrometer and ^{13}C spectrum on a Varian 500 MHz NMR spectrometer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by National Institute of Health grant R01 AI149444. This research was supported in part by W. M. Keck Foundation through computing resources at the W. M. Keck Laboratory for Integrated Biology. The authors acknowledge the support of Dr. Yongxuan Su (U.C. San Diego, Molecular Mass Spectrometry Facility) for measurement of MS samples.

Supporting information for this article is given via a link at the end of the document.

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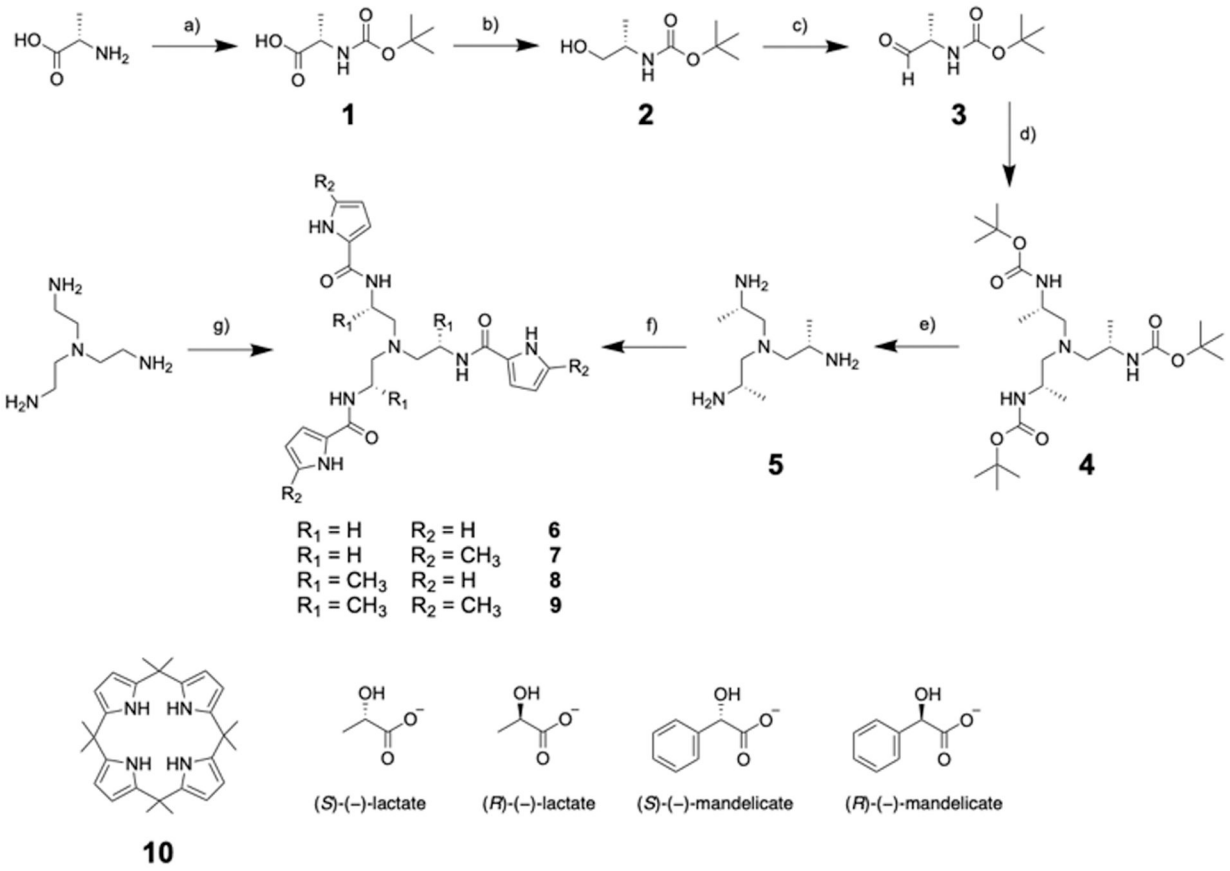

Figure 1.

Top: Synthetic scheme and structure of new pyrrolamide receptors **6**-**9** (see Scheme S1 and Supplementary Information for synthetic details). *Bottom*: Calix[4]pyrrole (**10**), and chiral anions studied here.

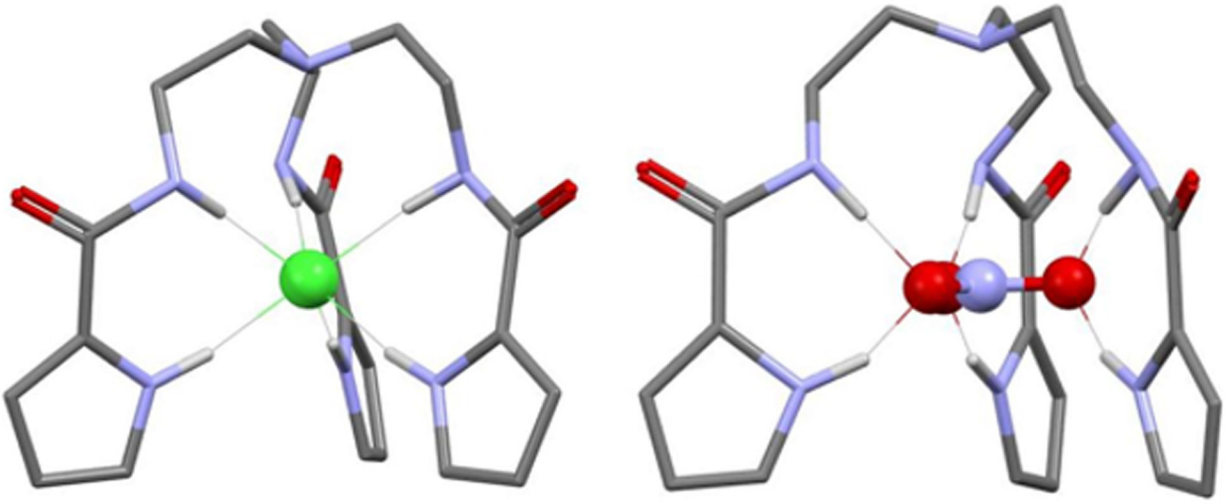

Figure 2.

DFT optimized geometries of the receptor/anion complex for **6**-chloride (*left*) and **6**-nitrate (*right*). Receptors are shown as capped sticks colored by atom, anions as ball-and-stick colored by atom, and hydrogen bonds shown in wireframe.

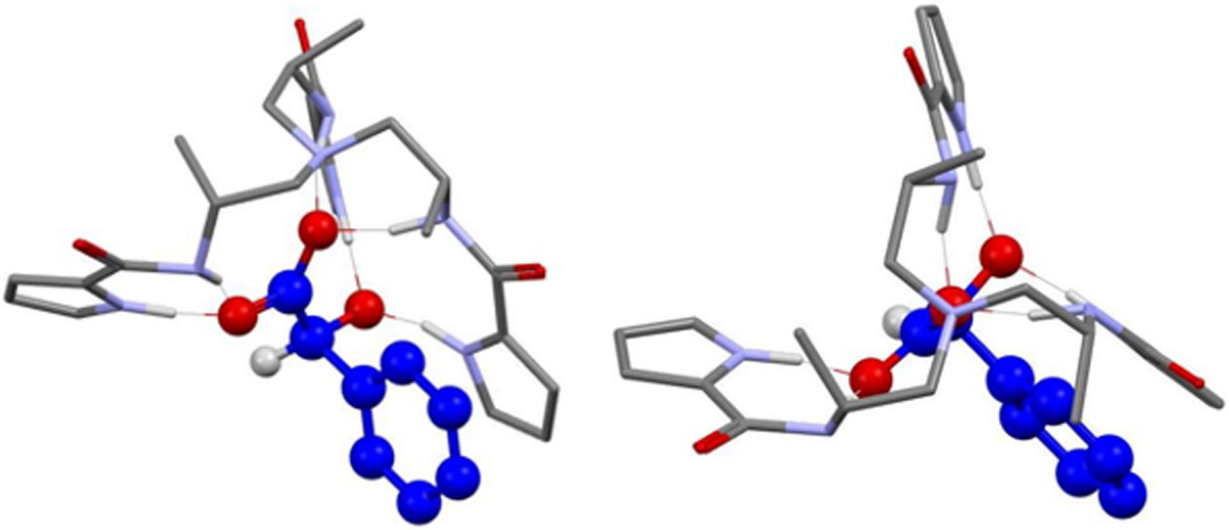

Figure 3.

Two views of the DFT optimized geometry the receptor-anion complex of **8** and (*S*)-(+)-mandelate. Receptor **8** is shown as capped sticks colored by atom, (*S*)-(+)-mandelate shown as ball-and-stick colored by atom (but with carbon atoms dark blue), and hydrogen bonds shown in wireframe.

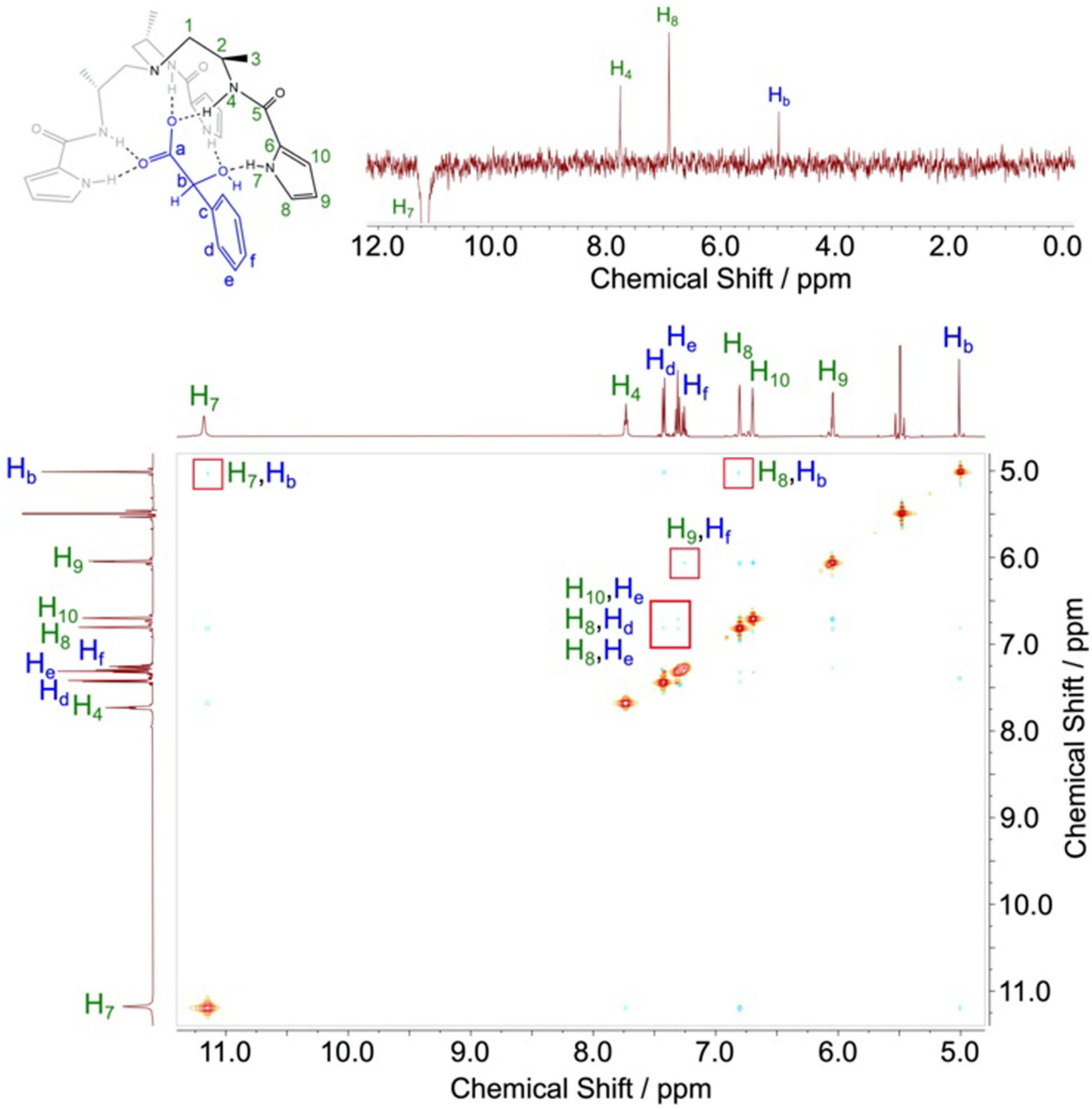

Figure 4.

Proposed structure of complex with (*S*)-(+)-mandelate with proton and carbon atom labels (*top left*). 1D-NOESY spectra upon selective excitation of the pyrrole NH (11.18 ppm) proton (*top right*). *Bottom*: 2D-NOESY spectra, the cross-signals are only marked in the left top half of the spectrum.

Table 1.

Logarithmic association constants ($\log K_a$) for receptors **6**-**10** with anions. Anions were introduced as tetrabutylammonium salts in dry 95:5 CH_2Cl_2/DMSO. Reported values were rounded to the corresponding thousands and were measured in three independent experiments. n.b. = no binding observed. n.d. = not determined.

Anion	Logarithmic association constant				
	6	**7**	**8**	**9**	**10**
Fluoride	5.02 ± 3.70	5.04 ± 3.60	5.12 ± 3.70	5.09 ± 3.60	5.15 ± 3.78
Chloride	4.90 ± 3.48	4.94 ± 3.30	4.98 ± 3.60	5.01 ± 3.60	4.72 ± 3.70
Bromide	4.52 ± 3.00	4.41 ± 3.00	4.54 ± 3.30	4.34 ± 3.00	n.b.
Iodide	n.b.	n.b.	n.b.	n.b.	n.b.
Acetate	4.93 ± 3.60	4.94 ± 3.60	4.97 ± 3.70	5.00 ± 3.60	4.79 ± 3.48
Benzoate	4.72 ± 3.48	4.64 ± 3.30	4.75 ± 3.30	4.57 ± 3.30	4.77 ± 3.60
Perchlorate	4.36 ± 3.30	4.04 ± 3.00	4.18 ± 3.00	4.20 ± 3.00	n.b.
Nitrate	4.99 ± 3.60	4.98 ± 3.70	5.08 ± 3.70	5.05 ± 3.60	4.52 ± 3.30
(*R*)-(−)-Lactate	4.91 ± 3.00	n.d.	5.00 ± 3.60	n.d.	n.d.
(S)-(+)-Lactate	4.92 ± 3.60	n.d.	4.98 ± 3.48	n.d.	n.d.
(*R*)-(−)-Mandelate	4.63 ± 3.30	n.d.	4.72 ± 3.48	n.d.	n.d.
(S)-(+)- Mandelate	4.61 ± 3.30	n.d.	4.93 ± 3.60	n.d.	n.d.