A Cyclic Hexapeptide Comprising Alternating α-Aminoxy and α-Amino Acids is a Selective Chloride Ion Receptor

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Abstract: In nonpolar solvents, the cyclic hexapeptide **2**, which comprises alternating D-α-amino and D-α-aminoxy acids, adopts a C_3-symmetric conformation with alternating eight (N–O turns)- and seven (γ turns)-membered-ring hydrogen bonds. A series of anion-binding studies has suggested that **2** can function as an effective anion receptor that not only displays a high selectivity for chloride ions, but also the capability to extract chloride ions from aqueous solutions into organic phases.

Keywords: amino acids · anion receptors · chloride ions · hydrogen bonds · peptides

Introduction

Simulation of the recognition, binding, and transport processes of physiologically important anions is the driving force behind the development of artificial anion receptors.[1] Chloride ions are ubiquitous in the biosphere and are critical for a large number of biological processes.[2] In nature, the transport of chloride ions across cell membranes is regulated by neutral anion binding proteins (chloride channels). The dysfunction of chloride channels has been implicated in several human diseases, including cystic fibrosis, Bartter's syndrome, and Dent's disease,[2b] and, consequently, chloride channels have become significant targets for drug development. The high specificity of chloride channels toward chloride ions is due to a recognition site in which the anion is completely desolvated and bound exclusively through hydrogen bonds.[3] Unfortunately, there are few electroneutral artificial anion receptors that can bind to chloride ions with high selectivity through hydrogen bonds alone.[4] Receptors with a high net positive charge,[5] and those containing Lewis acid moieties,[6] can bind chloride ions selectively; however, because of their insolubility in nonpolar solvents and potential heavy metal toxicity, respectively, they are considered to be unsuitable for application in biological membrane systems.[7] In response to this problem, we have developed a new class of anion receptors that have a special preference for chloride ions.

Previously, we demonstrated that α-aminoxy acids have a strong tendency to induce an eight-membered-ring intramolecular hydrogen bond (the N–O turn) when incorporated into peptides.[8] Aminoxy amide NH units have high acidities relative to regular amide NH groups, and are, therefore, the better hydrogen-bond donors when binding anions. Our group has developed a cyclic hexapeptide **1**, comprising D,L-α-aminoxy acids, that binds selectively to chloride ions (association constant $K_a = 11880\,M^{-1}$).[9] Herein, we report that cyclic hexapeptide **2**, comprising alternating D-α-amino and D-α-aminoxy acids, functions as a more effective anion receptor, displaying a high selectivity for chloride ions and a good ability to extract chloride ions from aqueous solutions into organic phases.

Results and Discussion

Synthesis and characterization of linear hexapeptide 3 and cyclic hexapeptide 2: Linear hexapeptide **3**, of alternating D-α-amino and D-α-aminoxy acids, was prepared according to our previously developed, convergent synthetic scheme.[10] The ^1H NMR spectroscopy study in $CDCl_3$ showed that the chemical shifts of all regular amide NH groups of **3** were

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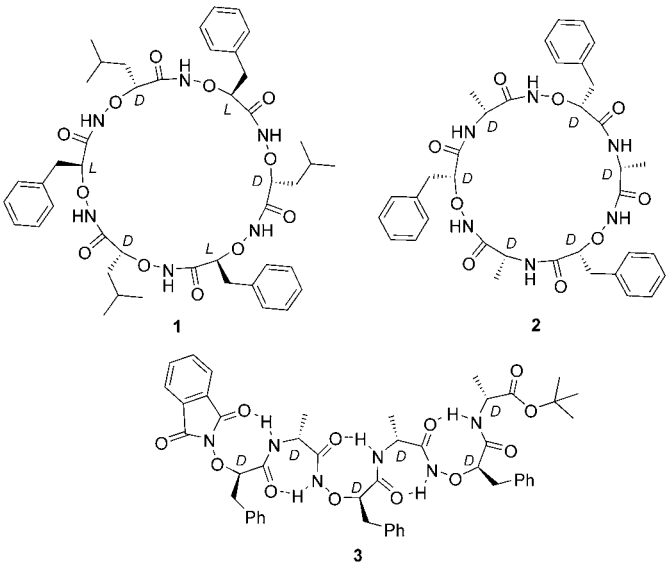

rather downfield (7.3–7.9 ppm) and independent of concentration.[10] This indicates that they form strong, intramolecular hydrogen bonds, most likely the N–O turns. The unchanged downfield chemical shifts of aminoxy amide protons (9.6–10.0 ppm) during ^{1}H NMR dilution tests implied the formation of seven-membered-ring intramolecular hydrogen bonds (γ turns) between aminoxy amide O–NH_i and C–O_{i-2}, as we had previously reported.[11]

Hexapeptide **3** was then deprotected at both ends and treated with diphenylphosphoryl azide (DPPA) to give cyclic hexapeptide **2** in 30% overall yield for three steps. In the ^{1}H NMR spectrum of **2** recorded in CD_2Cl_2,[8c,10] we observed only two sets of sharp peaks that originate from the α-amino and α-aminoxy acid residues, respectively. The signals of both the regular (8.3 ppm) and aminoxy (9.6 ppm) amide NH units of **2** appear quite downfield at very low concentration (4 mM); their appearance is independent of concentration,[10] indicating that they form intramolecular hydrogen bonds. Furthermore, we found that in nonpolar solvents, the NOE pattern[10] of the aminoxy acid residues of **2** was in accordance with the second-lowest-energy N–O turn conformation that we determined previously by theoretical calculations.[12] As Figure 1a indicates, the NOE observed between the O–NH_i and O–$C_\alpha H_i$ protons was of a similar intensity to that observed between the NH_{i+1} and O–$C_\alpha H_i$ protons. For each α-D-alanine residue of **2**, the NOE intensity observed between the NH_i and $C_\alpha H_i$ protons is similar to that observed between the O–NH_{i+1} and $C_\alpha H_i$ protons. This agrees with our previously reported inverse γ turn conformation,[11] in which the α proton resides in an axial position. Therefore, we believe that all of the subunits of **2** adopt cyclic conformations possessing alternating N–O and γ turns. This supposition is supported by the results of a conformational search[13] that suggested **2a** as the global minimum (Figure 3). In this structure, the backbone of **2** folds into alternating N–O and γ turns, and adopts a C_3-symmetric conformation.

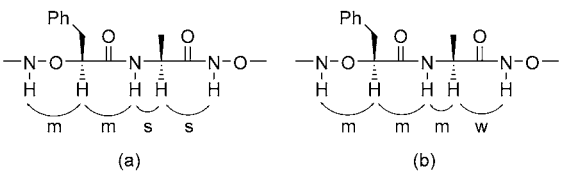

Figure 1. Summary of the NOEs observed for (a) free **2** and (b) a 1:2.5 mixture of **2** and Ph_4PCl (4 mM in CD_2Cl_2 at 298 K; s, strong NOE; m, medium NOE; w, weak NOE).

Anion binding studies: We examined the anion binding ability of cyclic hexapeptide **2**. Initially we screened the following anions in a chloroform solution of **2** by using the electrospray ionization mass spectrometry (ESI-MS) technique (negative-ion mode): F^-, Cl^-, Br^-, I^-, NO_3^-, NO_2^-, N_3^-, HCO_3^-, CO_3^{2-}, HSO_4^-, SO_4^{2-}, $H_2PO_4^-$, HPO_4^{2-}, and PO_4^{3-}. We observed peaks in the spectra corresponding only to free $[\mathbf{2}-H]^+$ (*m*/*z* 701.3) and the complexes $[\mathbf{2}+Cl]^-$ (*m*/*z* 737.1), $[\mathbf{2}+Br]^-$ (*m*/*z* 783.1), and $[\mathbf{2}+NO_3]^-$ (*m*/*z* 764.1).[10]

We studied the anion binding properties of **2** in a solution of CD_2Cl_2 by using the ^{1}H NMR spectroscopic titration technique.[14] The ^{1}H NMR spectra of **2** display dramatic changes in the values of chemical shifts of both the aminoxy and regular amide protons upon addition of the anions (Figure 2); the signals of the aminoxy amide protons moved downfield,

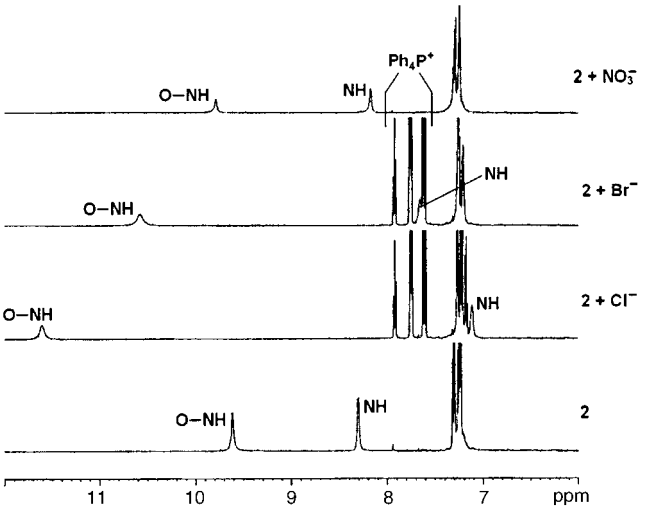

Figure 2. The amide NH region of overlaid ^{1}H NMR spectra of free **2** and 1:1 mixtures of **2** with Ph_4PCl, Ph_4PBr, or Bu_4NNO_3 (4 mM in CD_2Cl_2 at 298 K).

whereas those of the regular amide protons shifted upfield. Quantitative assessments of the anion binding affinities of **2** in CD_2Cl_2 (a nonpolar solvent) reveal that **2** is not only effective in forming a 1:1 complex with anions, but is also selective for chloride ions (Table 1). Comparison with our previously reported cyclic hexapeptide **1**, comprising D,L-α-aminoxy acids, reveals that the cyclic hexapeptide **2**, which has fewer aminoxy amide NH units, displays enhanced binding

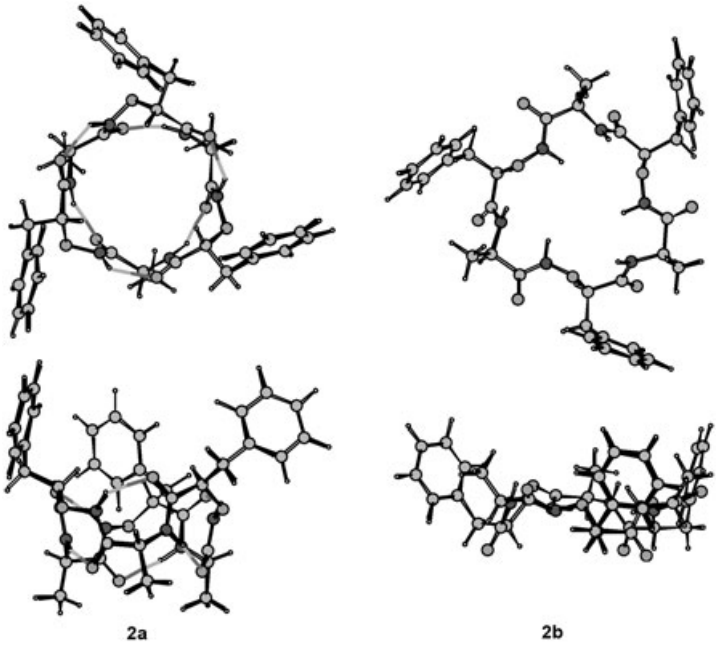

Figure 3. Calculated structures of conformations **2a** and **2b** of cyclic hexapeptide **2**.

Table 1. Association constants for the binding of **2** with anions[a] in CD_2Cl_2 at 298 K.

Anion	K_a [M^{-1}][b]	$\Delta\delta_{max}$(O–NH)[c]	$\Delta\delta_{max}$(NH)[c]
Cl^-	15000±1500	2.39	−1.39
Br^-	910±43	1.70	−1.07
I^-	51±3	–[d]	–[d]
NO_3^-	440±42	1.43	−0.55

[a] Anions were added as concentrated CD_2Cl_2 solutions of Ph_4PCl, Ph_4PBr, Bu_4NI, or Bu_4NNO_3. To account for dilution effects, these anion solutions also contained receptor **2** at its initial concentration (2–4 mM). [b] Determined by following the changes that occurred to the resonances of the aminoxy amide NH protons. [c] Estimated maximum change in chemical shift (ppm). [d] Cannot be estimated from the titration curve.

toward anions, whilst maintaining good selectivity toward the chloride ion. To account for the stronger anion binding that **2** displays relative to **1**, we note that the N–O turn is more stable than the γ turn.[12] The backbone of **2**, comprising alternating N–O and γ turns, should be more flexible than that of cyclic hexapeptide **1**, whose D,L-α-aminoxy acid residues adopt consecutive N–O turns. Consequently, it is easier for **2** to adjust its conformation upon binding to an anion than it is for **1**.

Notably, the aminoxy amide NH group is not only a better hydrogen-bond donor than the regular amide NH unit, it is also involved in a relatively weak intramolecular hydrogen bond (the γ turn). Upon binding to the chloride ion, the three acidic aminoxy amide NH units may form hydrogen bonds with the anion by breaking the original γ turns adopted by the α-D-alanine residues of **2**, resulting in the downfield shift of the signal of the aminoxy amide protons. This hypothesis is supported by the two-dimensional NOESY spectrum of **2** complexed with a chloride ion;[10] this spectrum exhibits a different NOE pattern for the α-D-alanine residues (medium-intensity NOEs between the NH_i and $C_\alpha H_i$ protons, and weak NOEs between the $O{-}NH_{i+1}$ and $C_\alpha H_i$ protons) to that of free **2** under the same conditions (Figure 1). Such a conformational change in the α-D-alanine residues would also disturb the original N–O turns to such an extent that the signals of the regular amide protons become shifted upfield.

Extraction studies: As a preliminary step toward ion transport, we also studied the extraction capabilities of cyclic hexapeptide **2** toward chloride and nitrate ions by using the single extraction method.[15] As expected, **2** proved capable of extracting anions from aqueous solution into chloroform. ^1H NMR spectroscopic analysis of the extracts revealed that the extraction efficiency[16] of chloride ions (77%) was clearly higher than that of nitrate ions (35%). This is in agreement with the relative association constants of **2** toward these anions, even though nitrate ions are more lipophilic than chloride ions. Control experiments established that no significant extraction of anions took place in the absence of receptor **2**.

Theoretical calculations: The conformational search of **2** was first performed by using the MACROMODEL program[17] and AMBER94 force field.[18] A total of four structures with a pseudo C_3-symmetry were found. These structures and anion-bound structures were subjected to full geometrical optimization by the B3LYP method[19] using a hybrid basis set: C, H, N: 6–31G*; O, Cl, Br: 6–31+G*; the six amide hydrogens: 6–311++G**. Each structure was confirmed to be minimum by harmonic vibration frequency calculation, from which the thermal property of the structure was evaluated. Solvent effect was also estimated by using the IEFPCM solvent model with UAKS radii.[20] The free energy of each structure in solution was derived from the calculated free energy in the gas phase corrected by the solvent effect on the electronic energy. All quantum mechanics calculations were performed by using the Gaussian 03 program.[21]

In the case of anion-free cyclic peptide **2**, we found two significant conformations, **2a** and **2b** (Figure 3). Structure **2a** is the global minimum. It is in a fully hydrogen-bonded geometry with alternating seven- and eight-membered-ring hydrogen bonds. In structure **2b**, all six hydrogen bonds are broken and all six N–H bonds point inward; therefore, it can be regarded as the conformation for anion binding. Structure **2b** was found to be less stable than **2a** by around 10.0 kcal mol^{-1}.

Structure **2b** was used to bind Cl^- or Br^- ions. The optimized structures of the **2**-Cl^- and **2**-Br^- complexes are represented in Figure 4. Upon binding with the Cl^- ion, all six of the hydrogen bonds initially present in **2** become disrupted. The backbone of **2** rearranges into a rather flat conformation with all of the amide NH hydrogen atoms pointing inward. The Cl^- ion sits above the plane of the peptide

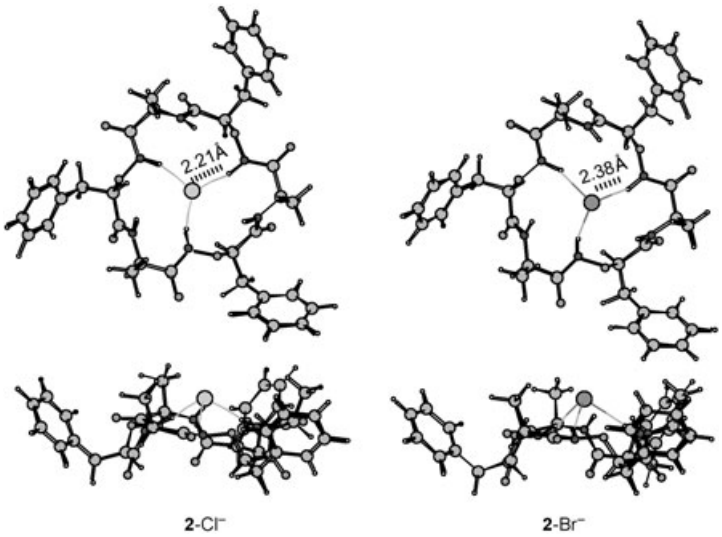

Figure 4. Calculated structures of complexes **2**-Cl^- and **2**-Br^-.

backbone and forms strong hydrogen bonds with the three O–NH hydrogen atoms, as indicated by Cl···H distances of 2.21 Å. The three regular amide NH groups do not undergo strong binding with the Cl^- ion (Cl···H distance is 3.00 Å), but these hydrogen atoms are positioned close to the backbone oxygen atom (O···H distance is 2.13 Å). This structure is consistent with the experimental observation that the signal of the aminoxy amide protons in the ^{1}H NMR spectrum shifts significantly downfield upon binding of the chloride ion, whereas that of the regular amide protons shifts upfield (Table 1). The calculated interatomic H···H distances between the α protons and their adjacent amide protons (O–C_αH/O–NH, 2.88 Å; O–C_αH/NH, 3.19 Å; C_αH/O–NH, 3.55 Å; C_αH/NH, 2.96 Å) in both the aminoxy and amino acid residues correspond well with the NOE patterns observed for the **2**-Cl^- complex (Figure 1b).

Conclusion

Cyclic hexapeptide **2**, which consists of alternating D-α-amino and D-α-aminoxy acids, adopts a highly C_3-symmetrical conformation featuring alternating N–O and γ turns. Its anion binding properties demonstrates that, as a electroneutral receptor, it has great potential to be an effective anion receptor. In particular, it not only has a high selectivity for chloride ions, but it can also extract chloride ions from aqueous solutions into organic phases. This discovery may afford new opportunities for studies of chloride ion transport. In view of aminoxy amide protons being excellent hydrogen-bond donors, we believe that aminoxy acids will be useful building blocks for various anion receptors with practical applications.

Experimental Section

General methods: All reagents and solvents were of analytical grade and were dried and distilled as necessary. ^{1}H and ^{13}C NMR spectra were recorded at 600 MHz for protons and at 75.5 or 100.0 MHz for carbons by using Bruker Avance DPX 300, 400, or 600 Fourier Transform Spectrometers. Infrared spectra were obtained by using a Bio-Rad FTS 165 FTIR spectrometer. Melting points were determined by using an Axiolab ZEISS microscope and were uncorrected. Optical rotations were measured by using a Perkin–Elmer 343 polarmeter. Both low and high resolution mass spectra were recorded by using a Finnigan MAT 95 mass spectrometer.

Characterization data for compound 1: Colorless oil; $[\alpha]_D^{20} = +114.0°$ (c = 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.98 (s, 1H), 9.59 (s, 1H), 7.91 (d, J = 6.7 Hz, 1H), 7.79–7.76 (m, 5H), 7.35–7.02 (m, 16H), 4.68 (t, J = 5.1 Hz, 1H), 4.54 (dd, J = 8.3, 3.0 Hz, 1H), 4.50–4.42 (m, 1H), 4.31–4.26 (m, 2H), 4.17–4.16 (br, 1H), 3.48 (dd, J = 14.4, 4.9 Hz, 1H), 3.27 (dd, J = 14.4, 5.5 Hz, 1H), 3.18–3.12 (m, 2H), 3.01–2.97 (m, 1H), 2.93–2.87 (m, 1H), 1.42 (s, 9H), 1.29–1.23 (m, 6H), 1.05 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.46, 170.53, 170.27, 170.13, 169.97, 169.27, 163.66, 136.54, 136.12, 135.12, 134.52, 129.85, 129.46, 129.38, 128.35, 128.30, 128.05, 127.24, 126.83, 126.50, 124.08, 88.48, 87.92, 86.26, 81.36, 48.58, 47.65, 46.47, 37.90, 37.82, 27.90, 17.14, 16.42 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3311 (br), 1735, 1677 cm^{-1}; LRMS (fast atom bombardment, FAB): m/z: 907 $[M+1]^+$; HRMS (FAB): m/z calcd for $C_{48}H_{55}N_6O_{12}$ $[M+1]^+$: 907.3800; found: 907.3896.

Characterization data for compound 2: Colorless oil; $[\alpha]_D^{20} = +99.5°$ (c = 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 9.61 (s, 1H), 8.30 (d, J = 5.9 Hz, 1H), 7.32–7.23 (m, 5H), 4.32 (dd, J = 5.1, 3.6 Hz, 1H), 4.12–4.09 (m, 1H), 3.25 (dd, J = 14.5, 3.7 Hz, 1H), 2.92 (dd, J = 14.4, 2.6 Hz, 1H), 1.24 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 170.87, 170.32, 136.35, 129.46, 129.28, 128.34, 126.83, 87.93, 46.58, 37.83, 15.84 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3280 (br), 1673 cm^{-1}; LRMS (FAB): m/z: 703 $[M+1]^+$; HRMS (FAB): m/z calcd for $C_{36}H_{43}N_6O_9$ $[M+1]^+$: 703.3013; found: 703.3101.

^{1}H NMR titration: The CD_2Cl_2 solution of **2** (2–4 mM) was titrated by addition of the concentrated CD_2Cl_2 solution of the anions (in the form of their tetrabutylammonium salts for nitrate and iodide, and their tetraphenylphosphonium salts for chloride and bromide). To account for dilution effects, these anion solutions also contained receptor **2** at its initial concentration. The data were fitted to a 1:1 binding profile, according to the method of Wilcox,[22] by using changes in both the aminoxy and regular amide NH resonances in their respective ^{1}H NMR spectra.

Extraction experiment: An aqueous solution of Ph_4PCl (or Ph_4PNO_3) (1 mL, 5 mM) was added to a solution of **2** in $CHCl_3$ (0.6 mL, 5 mM). The resulting biphasic solution was shaken vigorously in a closed glass tube for 2 h and then left to settle for 10 min. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure at temperatures < 35 °C. The residue was dissolved in $CDCl_3$ (0.6 mL) and the ^{1}H NMR spectrum was recorded.

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