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"Unclosed Cryptands": A Point of Departure for Developing Potent Neutral Anion Receptors

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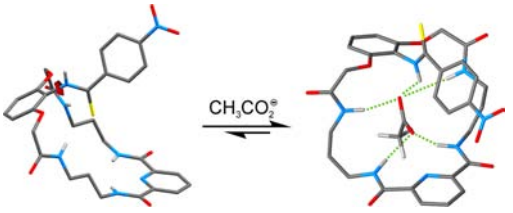
ABSTRACT



Six macrocyclic lariat-type compounds, representing a new class of anion receptors, were synthesized in a simple approach. We identified the optimal macroring size and the position of the hydrogen bond donating center in the lariat arm offering the best affinities toward chloride and carboxylate anions. The anion-binding properties of such systems were investigated by applying ^{1}H NMR titrations in DMSO/water and methanol/DMSO mixtures.

Both inorganic and organic anions take part in various biological processes and are responsible for many natural phenomena.[1,2] Consequently, investigation of anion complexation has attracted much attention in recent decades, bolstering its importance among the biosciences and leading to the discovery of its potential applications in medicine and in industrial processes.[3] For example, Gokel et al.[4] recently reported an elegant example of simple receptors based on 2,6-dipicolinic acid that facilitate the transport of large plasmids across a lipid bilayer, which may find applications in gene therapy. Reek et al.[5] developed transition metal catalysts, equipped with an anion binding pocket that functions as a selectivity controlling unit, for industrially important hydrogenation and hydroformylation reactions. Nevertheless, it remains one of the great medical challenges for anion receptor design to create an artificial anion transport system[6] that can substitute for the defective chloride channels of patients suffering from cystic fibrosis, a common genetic disease.[7] Moreover, carboxylic anions are also of interest due to the ubiquity of ionized carboxylate functions in numerous important biomolecules, ranging from simple anions, such as acetate and benzoate, up to more complex amino acids and proteins.[8] However, to date only a few neutral, efficient receptors for the above-mentioned anions operating in

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demanding solvents,[9] suitable for practical application, have been identified.[10] One successful strategy for developing such receptors is to use the chemistry of cryptands, as has recently been shown by Bowman-James et al.[11] In our laboratory we obtained compounds, structurally related to cryptands, that are in principle macrocycles with a flexible substituent–lariat arm.[12] In the study reported here, we designed, obtained, and studied the properties of this new class of putative anion receptors **1**–**4** (Figure 1), which we have called "unclosed cryptands".

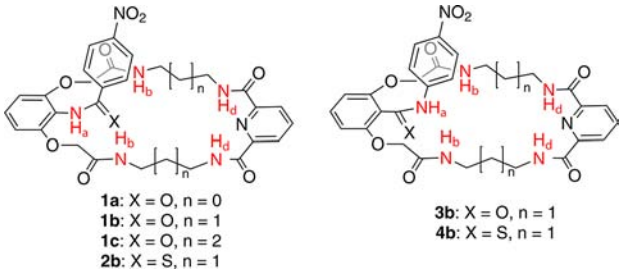
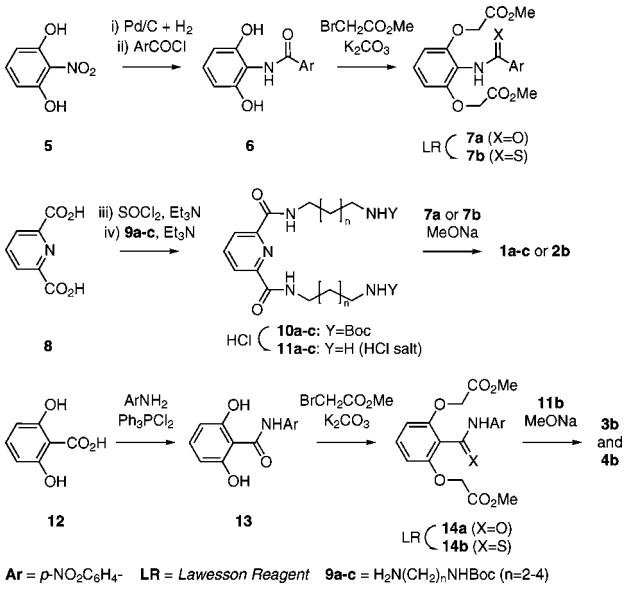


Figure 1. Structures of the receptors examined.

We presumed that these compounds' structural similarity to that of the Bowman-James cryptand-like anion receptors would provide a similar efficiency in anion binding, while on the other hand their modular synthesis would allow their selectivity to be fine-tuned toward desired anions. In this work we also examined the influence of the type and the position of the hydrogen bond donors (amide or thioamide group) in the lariat arm as well as the size of the macroring on the anion recognition process. Apart from model ligand **1a**, composed of two cooperating binding pockets and a lariat arm equipped with additional hydrogen bonding functions that, presumably, can strongly influence interaction with anions, we studied its analogues: the unclosed cryptands **1b,c** and **2**–**4b**.

Synthesis. The macrocyclic receptors **1**–**4** were obtained as shown in Scheme 1, utilizing the double amidation

Scheme 1. Synthesis of Receptors **1a**–**c** and **2**–**4b**



reaction developed in our laboratory.[13] In this reaction α,ω-diesters **7a,b** and **14a,b** react with α,ω-diamines **11a**–**c** in methanol, in the presence of sodium methoxide, affording macrocyclic receptors **1a**–**c**, **2**–**4b** in acceptable yields of 24, 56, 60, 78, 36, and 89%, respectively, without the necessity of employing high-dilution conditions. The synthesis of α,ω-diesters and α,ω-diamines, substrates for macrocyclization, is also presented in Scheme 1.

Anion Complexation Studies. The stability constants of receptors **1a**–**c** and **2b** with the examined anions were determined by a ^{1}H NMR titration technique in a mixture of DMSO-d_6 and water (ranging from 0.5 to 10% v/v) and additionally, in the case of receptor **2b**, with acetate in a mixture of MeOH-d_3 and DMSO-d_6 (20%) (Table 1). The corresponding titration curves are consistent with a 1:1 binding model[14] for all the experiments presented, except for **1a** with acetate.

Table 1. Binding Constants [M^{-1}] for the Formation of 1:1 (Host–Guest) Complexes of Ligands **1a**–**c** and **2b** with Various Anions in DMSO-d_6 + 0.5% H_2O[a]

anions	1a	1b	1c	2b
Cl^-	96	490	11	1479
$CH_3CO_2^-$	–[b]	490	191	>10000[c] 170[d]
$C_6H_5CO_2^-$	95	270	128	1202[c]

[a] Values determined by ^{1}H NMR titration experiments at T = 298 K using HypNMR 2008 software,[15] errors < 10%, TBA salts as the source of anions. [b] Complex binding interactions. [c] DMSO-d_6 + 10% water. [d] MeOH-d_3 + 20% DMSO-d_6.

Among receptors of type **1**, compound **1b** shows the best affinity toward all the anions examined, showing slight selectivity against acetate over chloride and benzoate

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anions, a finding that is in accordance with our previous results.[15]

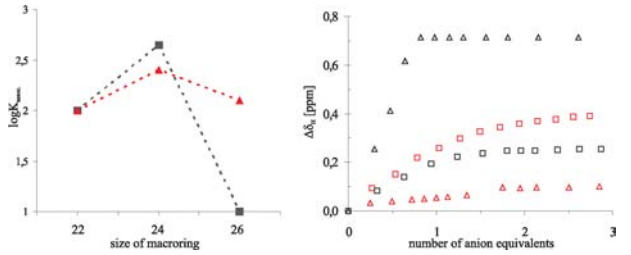

Figure 2. Plot of log(K_{assoc}) of **1a**−**c** with chloride (black squares) and benzoate (red triangles) anions vs size of the macroring (left). Typical ^{1}H NMR signal shifts of amide protons of ligand **1b** (red) and **2b** (black) with acetate (triangles) and chloride (squares) anions in DMSO-d_6 + 0.5% H_2O (right).

This rather unusual selectivity reveals the optimal geometric complementarity of receptor **1b** to the spheric chloride anion, which is bound from 4 to over 40 times more strongly than for receptors **1a** and **1c**, respectively. In the case of carboxylate anions, **1b** is about twice as efficient as the other two (Figure 2). Therefore, for further modifications we chose the 24-membered macroring (with the three-carbon linker). Moreover, replacing the amide (**1b**) with a thioamide (**2b**) group enhanced the acidity[16a] of the hydrogen NH proton; thus one can expect the disappearance of the alternatively existing intramolecular hydrogen bonds.[16b]

Fortunately, receptors **1b** and **2b** form monocrystals suitable for X-ray analysis, the results of which are presented in Figure 3.[16]

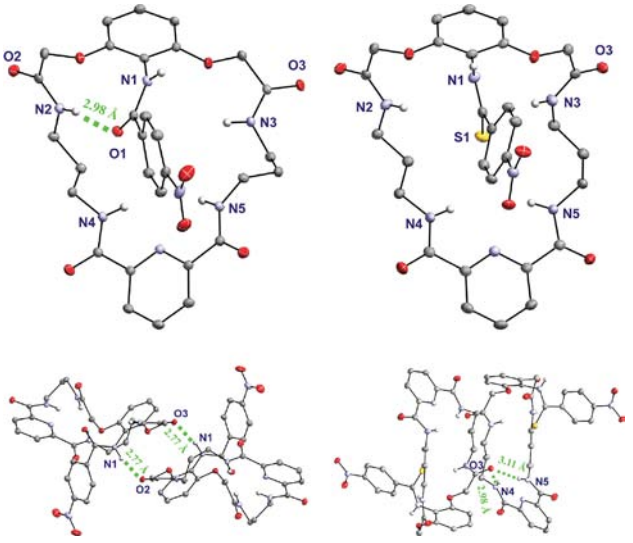

Figure 3. Structures of free ligands **1b** (top-left) and **2b** (top-right) and their respective dimeric forms (bottom). Nonacidic protons and solvent molecules were omitted for clarity.

The structures of **1b** and **2b** are similar to one another and show high levels of preorganization; all four macrocyclic amide protons are directed into the cavity; only the amide proton from the lariat group is faced outside the macrocycle. The arrangement of the latter proton is unfavorable for anion binding. Furthermore, receptor **1b** forms a dimeric structure employing two strong intermolecular H-bonds N−O (2 × 2.77 Å) between the amide N(1) proton and carbonyl oxygen atoms O(2) and O(3) from macrocyclic amide groups and one moderate N−O (2.98 Å) intramolecular H-bonding between N(2) and O(1). In the case of **2b** the amide N(1) proton does not participate in any intra- or intermolecular H-bonding, which may explain the superior binding properties of **2b** in comparison to **1b**. Moreover, in the latter case, before an anion can be bound the intramolecular H-bonding must be broken. To improve the selectivity and binding properties of our model receptor **1b** we altered the position of heteroatoms in the lariat arm, designing and obtaining compounds **3b** and **4b**, the binding properties of which are presented in Table 2.

Table 2. Binding Constants [M^{-1}] for the Formation of 1:1 (Host−Guest) Complexes of Ligands **1b** vs **3b** and **2b** vs **4b** with Various Anions in DMSO-d_6 + 0.5% H_2O[a]

anions	3b	1b	4b	2b
Cl^-	778	490	4266	1479
$CH_3CO_2^-$	642	490	–[b]	>10000[c]
				170[d]
$C_6H_5CO_2^-$	162	270	–[b]	1202[c]

[a] Values determined by ^{1}H NMR titration experiments at T = 298K, using HypNMR 2008 software,[15] errors < 10%, TBA salts as the source of anions; [b] Deprotonation of the receptor; [c] DMSO-d_6 + 10% water; [d] MeOH-d_3 + 20% DMSO-d_6.

A comparison of the binding properties of these new receptors with those of receptors **1b** and **2b** shows that this simple structural isomerism results, for example, in stability constant values almost twice as high for **3b** as for **1b**. Interestingly, the selectivity of **3b** toward anions is more perturbed than for **1b**, the chloride anion being bound more

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(17) Both crystals were obtained by slow evaporation of DMSO solution of receptors.

strongly than the acetate and benzoate ones. This unusual selectivity, against the Hofmeister bias,[19] is presumably a consequence of a perfect fit of the chloride anion to the macrocyclic cavity. This assumption is supported by DFT calculation (Figure 4).

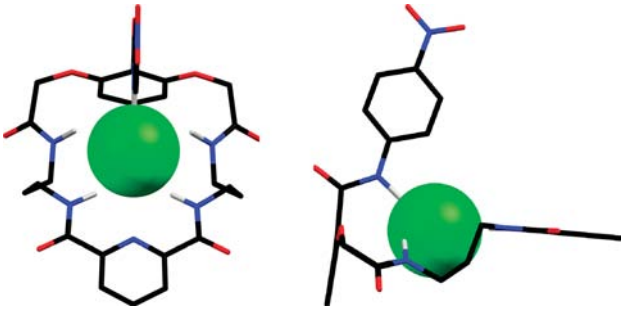

Figure 4. Top and side views of a DFT (B3LYP 6-31+G*) optimized structure of the chloride complex of receptor **3b**.

However, the situation in the case of thioamide analog **4b** is quite different; namely, the chloride anion is bound almost three times more strongly than for **3b**, while in the case of carboxylates a deprotonation process probably occurs. The latter observation, a common problem in anion complexation chemistry,[20] is supported by the titration curve profiles of aromatic protons in the lariat arm and the disappearance of the lariat NH(α) proton during titration (Figure 5). Deprotonation of **4b** is presumably enhanced by the high stabilization of both tautomeric forms: form A by two intramolecular H-bonds and form B by the *aci*- form of the nitro group. Furthermore, titration curve profiles for **4b** with carboxylate and hydroxide anions are identical and are independent of water content in DMSO-d_6 (see Supporting Information). Additionally the titration curve profiles for **4b** are different from those for **2b**, for which

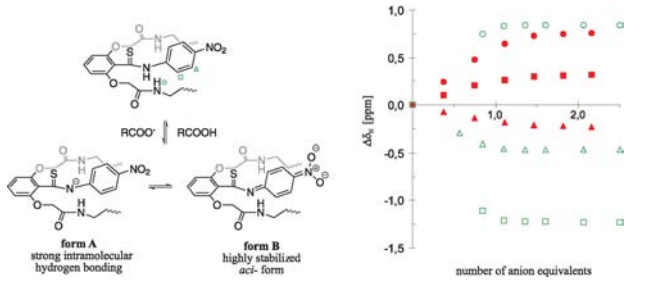

Figure 5. Proposed mechanism of deprotonation of **4b** by carboxylate anions (left). Titration curves of ligands **2b** (red color, filled symbols) vs **4b** (green color, unfilled symbols) with benzoate in DMSO-d_6 + 10% water (right).

aromatic lariat protons next to nitro groups shift upfield, and aromatic protons next to the thioamide group shift downfield (Figure 5, right).

In conclusion, we obtained a new class of receptors which present remarkable affinity and selectivity toward important anionic guests, operating in demanding media, i.e. DMSO-d_6/water and MeOH-d_3/DMSO-d_6 mixtures. Notably, the significant binding affinities of these unclosed cryptands to chloride and carboxylates are much higher than to some extent structurally similar neutral cryptands.[11] These properties, in connection with possibilities for ready structural modifications, open up prospects for constructing further receptors fulfilling the requirements for chiral recognition of carboxylates, and for potent chloride anion transporters.

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Supporting Information Available. Receptor synthesis, crystallographic data (CIFs), titration experiments, Job plots, and DFT calculated structures of the receptor complexes with anions. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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