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Carbamate triserine lactone receptors for anion recognition

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ABSTRACT

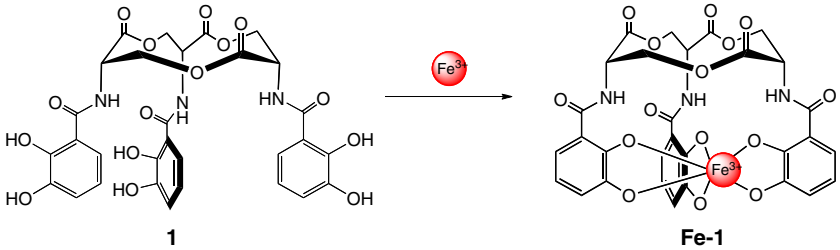
We have taken advantage of the ability of the cyclic triester of L-serine to organize ligand units appended to the three α-amine functionalities, as in enterobactin, a siderophore produced by enteric bacteria that binds ferric ion exceptionally well ($K_f = 10^{49}$). As an extension of the preorganization concept, this work describes the preparation and characterization of carbamate triserine lactone receptors **1–6** and their ability to act as molecular receptors for anions. These receptors bind halides ($F^- \gg Cl^- > Br^- > I^-$) with binding constants K in the range 21–7350 L mol^{-1}.

The important roles that anions play in medicine, biology, catalysis, and the environment have resulted in considerable interest in studying anion recognition phenomena.[1–3] Early study of anion recognition by positively charged receptors relied heavily on electrostatic interactions.[3] A recent focus has been the development of electroneutral receptors that bind via weaker hydrogen bonds.[1,2] To strengthen anion binding and selectivity, receptors have been designed to utilize rigid tripodal backbones that preorganize acidic hydrogen bond donors in well-defined binding pockets, including the hexasubstituted arene rings reported by Ansyln[4] and by Steed,[5] the cholapods by Davis,[6] tris(aminoethyl)amine analogs by Reinhoudt[7] and by Schneider,[8] and the *cis*-1,3,5-tris(aminomethyl)cyclohexane derivatives reported by Morán.[9,10]

Because of their biochemical need for iron and its environmental insolubility, microorganisms produce iron chelators (siderophores) that solubilize ferric ion and make it bioavailable.[11] Enterobactin (Scheme 1), a cyclic triester of *N*-(2,3-dihydroxybenzoyl)-L-serine that is produced by *Escherichia coli* and other enteric bacteria,[12–14] binds ferric ion with an enormous formation constant[15] ($K_f = 10^{49}$) and exclusively in a Δ-cis configuration.[16] Although many synthetic analogs have been prepared, none exhibits a greater ferric ion complex stability than enterobactin including those that use the tris(aminoethyl)amine[17] (TRENCAM $K_f = 10^{43.6}$), 2,4,6-triethylmesityl[18] (Et_3MECAM $K_f = 10^{47}$), and *cis*-1,3,5-tris(aminomethyl)-cyclohexane[19] (sat-MECAM $K_f = 10^{43}$) backbones. It has been recently shown that enterobactin's ability to sequester iron so effectively is due in good measure to the conformation of the trilactone that predisposes the catecholate groups for metal ion binding.[20]

Our ability to produce the triserine lactone platform of enterobactin[21,22] in gram scale has propelled us to investigate other applications of the preorganization concept. We describe here the preparation of carbamate triserine lactone receptors **1–6**, their conformational analysis by ^{1}H NMR, and their ability to bind halides.

Preparation of receptors **1–6** (Scheme 2) began with the trimerization of *N*-trityl-L-serine methyl ester **7** to tris-*N*-trityl trilactone **8**, followed by removing the trityl groups with anhydrous HCl to



Scheme 1. Enterobactin and Fe-enterobactin.

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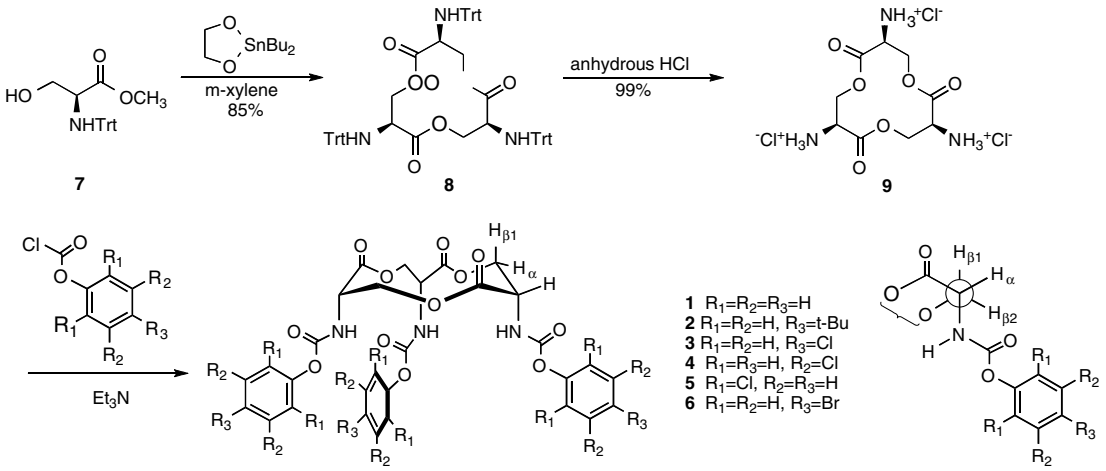

Scheme 2. Synthesis for carbamate triserine lactone receptors **1–6**.

produce tris-ammonium salt **9**.[21,22] A series of chloroformates, either commercially available or synthesized[23,24] by treating the phenol with a dilute solution of phosgene, were then reacted with backbone **9** producing carbamate ligands **1–6** in excellent yield (90–95%).

At room temperature, ^{1}H and ^{13}C NMR spectra for **1–6** reveal that they all exhibit pseudo C_3 symmetry in $CDCl_3$. The receptors display well-resolved ^{1}H NMR spectra and allow for conformational analysis using the spin–spin coupling of alpha-methine (H_α) and beta-methylene protons ($H_{\beta1}$ and $H_{\beta2}$) on each seryl unit (Scheme 2). The data are consistent with a pseudoaxial conformation for receptors **1–6**: $H_{\beta1}$ and $H_{\beta2}$ have a large geminal coupling constant (≈11 Hz), but the coupling values of both $H_{\beta1}$ and $H_{\beta2}$ to H_α are small (≈3.2 Hz) since both methylene protons are gauche to it. Consequently, results of conformational analysis in $CDCl_3$ reveal receptors **1–6** to be preorganized.

The energy minimized conformation of receptor **1** has been computed using SpartanPro at the DFT-B3LYP-6-31G* level and also confirms the pseudoaxial conformation with the carbamate N–H bonds pointing toward the interior of the receptor, while the carbonyl of the carbamate points outwards. The three NH bonds form a hydrogen bonding core defined by the trilactone ring.

Proton NMR titration experiments were used to investigate the anion binding properties of receptors **1–6**.[25] The addition of halides as either tetraethyl or tetrabutyl ammonium salts to the receptors in $CDCl_3$ caused changes in chemical shift in the receptor's ^{1}H NMR. The largest change in chemical shift was observed for the carbamate NH protons and is indicative of their role in the anion recognition event via hydrogen bonding. Anion binding constants were calculated from the titration data using a nonlinear least-squares curve-fitting program, and all titration curves fitted a 1:1 receptor/anion binding model. Compared to Davis' cholapods,[6] receptors **1–6** show moderate affinity and selectivity for fluoride ion with association constants K_a in the range of 1190–7350 L mol^{-1} (Table 1). Placement of electron-withdrawing substituents onto the aryl groups of receptors **3** and **4** show the largest binding constants for fluoride ion (K_a = 4200 L mol^{-1} and K_a = 7350 L mol^{-1}, respectively), and is consistent with enhanced acidity of the carbamate N–H leading to augmentation of its hydrogen bond donor ability. Our attempts to further increase the N–H acidity by preparing the tris-(2,4,6-trichlorophenyl) carbamate receptor has failed.

Since stronger bases form stronger hydrogen bonds to acidic protons, basicity plays an important role in anion binding.[6,8,26] The observed order of binding to our receptors parallels the order of increasing basicity, $I^- < Br^- < Cl^- < F^-$. However, the observed selectivity for fluoride ion (1.36 Å) also seems to parallel the cavity size that is generated by appending the carbamate residues onto the triserine lactone core. The larger halides Cl^- (1.81 Å), Br^- (1.95 Å), and I^- (2.16 Å) bind weakly (see Table 1).[3] For receptors **1–6**, the average distance between the hydrogen atoms on each carbamate NH is approximately 3.3 Å. Therefore, the binding core is very small and limits the binding of large anions.

Table 1
Association constants[a] of receptors **1–6** with $Bu_4N^+F^-$,[b] $Et_4N^+Cl^-$, $Et_4N^+Br^-$ and $Bu_4N^+I^-$[b] in $CDCl_3$ by ^{1}H NMR titration method at 298 K

Receptor	K_a (L mol^{-1}) with $Bu_4N^+F^-$	K_a (L mol^{-1}) with $Et_4N^+Cl^-$	K_a (L mol^{-1}) with $Et_4N^+Br^-$	K_a (L mol^{-1}) with $Bu_4N^+I^-$
1	3827[d]	140[d]	75[d]	21[c]
2	1189[d]	190[d]	161[d]	23[c]
3	4200[d]	213[d]	146[d]	75[c]
4	7350[d]	1114[d]	329[c]	109[c]
5	[e]	212[c]	175[d]	115[c]
6	3550[d]	191[d]	106[d]	81[c]

[a] Errors estimated as ⩽10% for K_a.
[b] $Bu_4N^+F^-$ and $Bu_4N^+I^-$ were used due to limited solubility of $Et_4N^+F^-$ and $Et_4N^+I^-$ in $CDCl_3$, respectively.
[c] Changes of NH chemical shift were used to calculate K_a.
[d] NH peaks were broadened so changes of seryl methylene proton chemical shifts were used to calculate K_a.
[e] Not determined due to peak broadening of NH and seryl protons.

Interestingly, dichlorophenyl carbamate receptors **4** (*meta* substituted) and **5** (*ortho* substituted) reveal large differences in their ability to bind chloride ion. Receptor **4** (K_a = 1114 L mol^{-1}) binds chloride five times stronger than receptor **5** (K_a = 212 L mol^{-1}): *ortho* substitution may decrease the binding event perhaps due to steric effects.

In conclusion, receptors **1–6** show selective binding affinity toward fluoride over other halides. Since this is the first report of anion recognition utilizing the enterobactin triserine lactone platform, we are currently examining aryl amide triserine lactone receptors for anion recognition as well as for exploring the ability of receptors **1–6** to bind other anions including nitrate and phosphate.

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Supplementary data

General procedure and spectral data (^{1}H and ^{13}C NMR) for all new compounds prepared are provided. Tables and graphs for ^{1}H NMR titrations are also provided for reference. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.081.

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