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Enantioselective recognition of sodium carboxylates by an 1,8-diaminoanthracene based ion pair receptor containing amino acid units

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ABSTRACT

An anthracene based ion pair receptor containing two amino acid units supported by cation and anion binding domains has been synthesized and shown to exhibit enhanced anion binding affinities in the presence of sodium cations. The receptor's ability to recognize enantiomers was studied using chiral carboxylates derived from 2-phenylbutyric acid, mandelic acid, and three Boc-protected amino acids. Sodium cation coordination does not influence chiral recognition but does affect the strength of anion binding. The greatest enhancement of anion binding in the presence of sodium cations was found for halides, and the highest enantiodiscrimination was found for Boc-*N*-tryptophan. Comparative anion and salt binding studies revealed that the simultaneous action of multiple binding domains in the structure of receptor **1** is responsible for its stronger salt association and better enantioselectivity than in the case of mono-supported receptor **2**.

Introduction

1,8-Diaminoanthracene is a convenient platform for constructing molecular receptors that are able to recognize anions. It is simple to synthesize, starting from commercially available 1,8-dinitroanthraquinone and reacts further with modules consisting of anion binding motifs to produce molecular receptors.[1] The two amino functional groups attached to the rigid platform make it possible to introduce two hydrogen bond donors through acylation,[2] or four hydrogen bond donors by reacting with various iso(thio)cyanates.[3] On the other hand, (thio)urea based anion binding sites can be obtained by transforming an amino functional group of 1,8-diaminoanthracene into the corresponding iso(thio)cyanate using (thio)phosgene and subsequent reaction with amines.[4] Via these routes, numerous cyclic[5] and open chain anion receptors[6] have been synthesized and found to effectively bind anions. More recently, the 1,8-diaminoanthracene scaffold has proved to be a useful platform for the construction of molecular receptors that are able to recognize chiral anions.[7] Incorporation of chiral units such as amino acids or sugars into the rigid platform resulted in chiral anion receptors that are able to recognize enantiomers. It has been shown that the proper size of the anion binding pocket in 1,8-diaminoanthracene based anion receptors is important in the chiral recognition event. To the best of our knowledge, all of the reported chiral receptors consist of anion binding domains and are devoted to the chiral recognition of anions associated with non-coordinated cations. However, in Nature ion pairs are usually formed between hard anions and hard metal cations, strongly interacting with each other. In view of the fact that hard cations can strongly influence anion binding, we decided to synthesize and characterize molecular receptors that are able to recognize chiral anions in the presence of hard, sodium cations. Recently, we found that amino acid based molecular receptors comprising of both anion and cation binding sites are able to bind sodium salts more effectively than the corresponding anions (tetrabutylammonium salts).[8] Thus, we envisioned that combining chiral amino acid based salt receptors with a rigid anthracene scaffold may lead to molecular receptors able to recognize chiral carboxylates as their sodium salts.

Results and discussion

In this regard, we designed an amino acid based ion pair receptor containing thiourea groups to bind anions with crown ether units responsible for interaction with sodium cations attached to the anthracene scaffold (see Fig. 1). Diisothiocyanate **5** was synthesized from commercially available 1,8-diaminoanthraquinone

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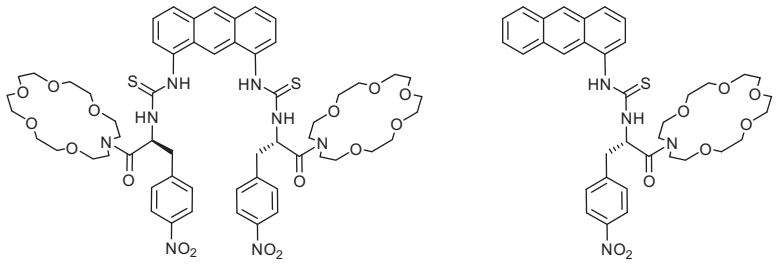


Figure 1. Structures of receptors **1** and **2**.

following a literature procedure.[4] We found that thiophosgene could be replaced with the 1,1′-thiocarbonyldi-2(1*H*)-pyridone reagent, producing **5** from 1,8-diaminoanthracene in a better yield (58% vs 20% reported).[9] The chiral units containing the amino functional group were synthesized from Boc-4-nitro-L-phenylalanine. The acylated 1-aza-18-crown ether was recently found to effectively bind sodium cations, prompting us to choose this means of incorporating a cation binding domain into the amino acid scaffold. After acylation of the amino acid with 1-aza-18-crown ether and subsequent trifluoroacetic acid mediated deprotection of the amino functional group, the resulting amine was reacted with diisothiocyanate **5** yielding receptor **1** (Scheme 1).

The binding properties of receptor **1** were monitored spectrophotometrically in an acetonitrile solution. As the thiourea and urea groups are known for their tendencies to form intermolecular hydrogen bonds, dilution studies were carried out in the investigation range which showed no evidence of self-association. The 1:1 binding stoichiometry was verified by a Job plot analysis. Then, receptor **1** was tested toward selected achiral anions (as TBA salts) and their sodium salts (in the presence of two equiv of $NaClO_4$) and was found to bind anions in the order of $Br^- < NO_2^- < Cl^- < PhCOO^- < CH_3COO^-$ (see Table 1). In all anions tested, no additional absorption band was observed at a longer wavelength, which would indicate anion-induced deprotonation of one of the NH hydrogen atoms of the thiourea binding domain.[10] As expected, receptor **1** is able to form strong complexes with Y-shaped carboxylate anions while nitrite and spherical halogen anions were weakly bound. Interestingly, weakly associated anions were bound to receptor **1** more strongly in the presence of two equivalents of sodium cations. The highest enhancement in anion binding in the presence of sodium cations was observed for bromide and chloride anions. On the other hand, carboxylate anions

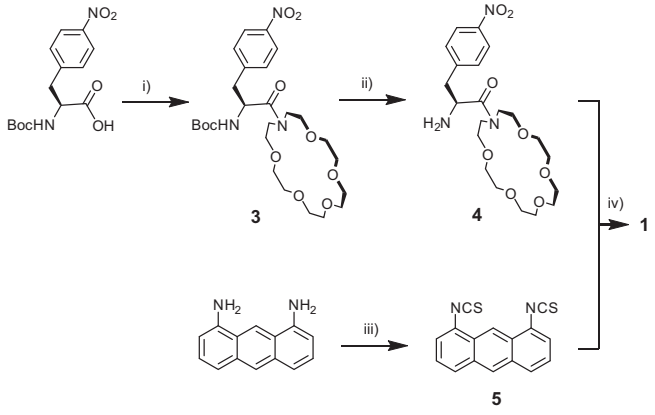
Table 1
Association constants (K_a) for interactions between receptor **1** and selected achiral anions in the absence or presence of two equivalents of $NaClO_4$[a]

	1	**1** + Na^+	K_{Na}/K_{TBA}
Br^-	110	565	5.14
NO_2^-	200	295	1.48
Cl^-	1510	7070	4.68
$PhCOO^-$	89100	28800	0.32
CH_3COO^-	144500	—[b]	—

[a] UV–Vis, CH_3CN, 293 K, [**1**] = 7.81×10^{-5} M, anions added as TBA salts [TBAX] ~3 mM, M^{-1}, sodium added as $NaClO_4$, Error <10%.
[b] CH_3COONa precipitation.

were found to associate more weakly to receptor **1** when titration experiments were conducted in the presence of sodium cations. However, unlike nitrite and bromide anions, upon addition of 1, 3, and 4.6 equiv of acetate, benzoate, and chloride anions to receptor **1** pretreated with two equivalents of sodium cations, the formation of sodium salts out of the receptor was observed.

Additional support for understanding the binding event of receptor **1** comes from ^1H NMR measurements. Specifically, ^1H NMR titration of receptor **1** with bromide anions in the absence and presence of one equivalent of sodium cations allowed the changes in the individual protons involved in anion association to be tracked. We found that upon addition of TBABr, considerable downfield shifts in both NH protons belonging to the thiourea binding site were observed, indicating the formation of strong hydrogen bonds between the anions and receptor **1**. These anion-induced shifts were higher for NH protons connected to the anthracene unit and lower for NH protons attached to the amino acid scaffold, showing the differing participation of thiourea protons in H-bond formation (Fig. 2). Moreover, less pronounced changes



Scheme 1. Synthesis of receptor **1**. Reagents and conditions: (i) DCC, 1-aza-18-crown-6, CH_2Cl_2, 0 °C to rt, 71%; (ii) (a) TFA–CH_2Cl_2 (1:1), rt, (b) $NaHCO_3$; (iii) 1,1′-thiocarbonyldi-2(1*H*)-pyridone, CH_2Cl_2, rt, 58%; (iv) *N*,*N*-diisopropylethylamine, THF, rt, 86%.

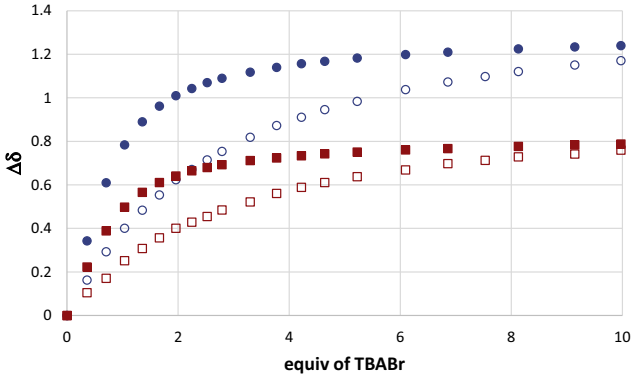


Figure 2. ^1H NMR titrations of receptor **1** with TBABr in the presence of 1 equiv of $NaClO_4$. Profiles based on the chemical shift ($\Delta\delta$) of the thiourea protons. Open symbols refer to titration in the absence of sodium cations; full symbols refer to titration in the presence of sodium cations.