

Convenient synthesis of tripodal-pyrrole receptor and anion binding properties

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Abstract Pyrrole-based tripodal receptors have been synthesized and characterized. The synthesis utilized an unusual direct nucleophilic substitution of tris-(bromo-methyl)-2,4,6-trimethylbenzene with pyrrole. The anion binding studies indicate that the acetate anion binds preferentially with synthesized receptors over other anions.

Keywords Anion recognition · Tripodal receptor · Pyrrole · Tri-substituted benzene

The development of selective recognition for anions has received considerable interests in supramolecular chemistry due to increasing importance of anions in expanding areas such as the environment and biology [1–4]. A useful way of recognition of anions is to exploit the non-covalent interaction between host and guest. In general, most of the anion receptors commonly possess amide, urea, amidinium or pyrrole, which are capable of binding anion *via* hydrogen bonding [5]. Recently, we also have reported several model systems based on the calix[4]pyrroles. The system, so called ‘strapped-calix[4]pyrroles’ have shown significant enhancement in affinity and even in selectivity toward various anionic species [6–11]. Since pyrrole-based anion receptors developed by us and others [12–15] possess high affinity with various anions, we are interested in incorporation of pyrrole moiety to the tripodal arm as recognition elements. The tripodal receptor systems have been

demonstrated the potential utilities as recognition motif for various guest molecules [16]. Most of the reported systems utilize stilbazolium [17], oxazoline [18], trifluoroacetophenone [19] and imidazole [20, 21]. However, there are limited reported examples of tripodal anion receptors utilizing pyrroles as hydrogen bond donors [22–24]. Accordingly, we are currently examining to develop new pyrrole-based receptor tripodal systems, which potentially bind with multi-oxo anions possibly with high selectivity.

With these regards, we report herein a convenient synthesis of new tripodal receptor bearing three pyrroles on the side of 1,3,5-trisubstituted-2,4,6-trimethylbenzene scaffold. The receptor is based on pyrrole as hydrogen bonding donor and benzene as cavitand scaffold. Direct nucleophilic substitution of alkyl halide with pyrrole is rare. Although the C-alkylation of pyrrole on C2 position using reactive alkyl halides such as allyl and benzyl has been reported [25, 26], there is only few report for the regioselective one-pot pyrrole alkylation from simple alkyl halides and pyrrole [27].

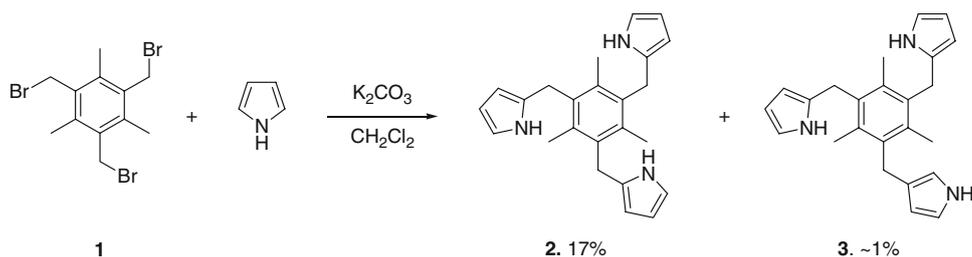
Experimental

Proton NMR spectra (400 MHz) were recorded using TMS as the internal standard. High and Low resolution FAB mass spectra were obtained on an AUTO SPEC M-363 high-resolution mass spectrometer. Column chromatography was performed over silica gel (Merck, 230–400 mesh). All other reagents were obtained from Aldrich and used as received unless noted otherwise.

Synthesis of compound 2 and 3

To the solution of compound 1 (1.00 g, 2.51 mmol) and K_2CO_3 (1.04 g, 7.53 mmol) in CH_2Cl_2 (5 mL) was added

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Scheme 1 Synthesis of receptor **1**

pyrrole (17.4 mL, 251 mmol). The whole mixture was allowed to stir for 4 h at room temperature. The reaction was combined with water (50 mL), then the mixture was extracted with CH_2Cl_2 (30 mL \times 3). The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica (hexanes/EtOAc = 4/1) to afford compound **2** (0.15 g, 17%) and **3** (3 mg, 1%) as white solid. Spectroscopic data for **2**: ^1H NMR (400 MHz, CDCl_3) δ 2.27 (s, 9H), 4.06 (s, 6H), 5.80 (s, 3H), 6.11–6.13 (m, 3H), 6.61–6.63 (m, 3H), 7.72 (brs, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.47, 29.12, 105.55, 108.53, 116.19, 129.87, 134.06, 134.56; EI MS Calcd. for $\text{C}_{24}\text{H}_{27}\text{N}_3$ 357.22, Found 357.00; for **3**: ^1H NMR (400 MHz, CDCl_3) δ 2.24 (s, 3H), 2.29 (s, 6H), 3.92 (s, 2H), 4.06 (s, 4H), 5.82 (s, 2H), 6.02–6.03 (m, 1H), 6.11–6.13 (m, 2H), 6.29 (s, 1H), 6.59–6.61 (m, 2H), 6.69–6.71 (m, 1H), 7.26 (brs, 2H) 7.96 (brs, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.38, 16.46, 28.41, 29.08, 105.39, 108.48, 108.59, 115.39, 116.01, 117.73, 122.27, 130.18, 133.57, 133.64, 134.25, 137.08; EI MS calcd. for $\text{C}_{24}\text{H}_{27}\text{N}_3$ 357.22, Found 357.00.

Results and discussion

As shown in Scheme 1, direct nucleophilic substitution reaction of 1,3,5-trisubstituted benzene [28] **1** with pyrrole in the presence of K_2CO_3 afforded desired products **2** in 17% yield and small amount of compound **3** was also identified. The identity of the synthesized receptors **2** and **3** was fully confirmed by proton NMR spectroscopy and high resolution mass spectrometry.

The ^1H NMR spectrum of receptor **2** showed one set of pyrrolic NH protons at 7.72 ppm along with three sets of pyrrolic protons. The single Ar- CH_3 proton appeared at 2.27 ppm and single benzylic protons shown at 4.06 ppm clearly reveal that compound **2** is C_3 symmetry. In the case of compound **3**, two different signals of pyrrole N–H protons were observed at 7.26 and 7.96 ppm with 2/1 integration ratio, which clearly indicate that one of the three appended pyrroles on the rim of benzene has different connection.

The study of the anion binding properties of receptor **2** was carried out in CDCl_3 using proton NMR spectroscopy

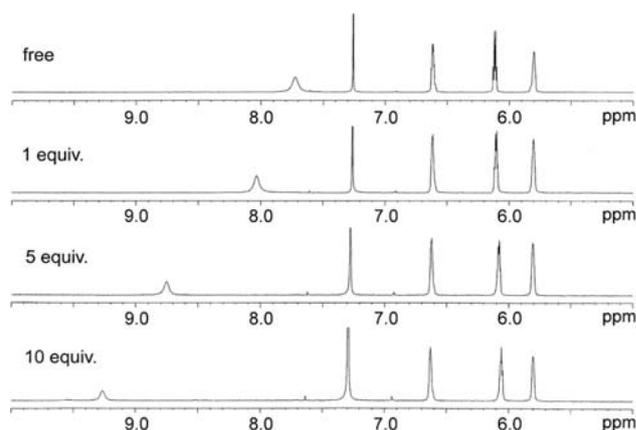


Fig. 1 ^1H NMR spectral change of receptor **2** (8.96 mM) upon titration with AcO^- (as its tetrabutylammonium salt) in CDCl_3 at 25 $^\circ\text{C}$

(Fig. 1). Anion concentration-dependent shifts of signals were observed upon titration with anions (F^- , Cl^- , Br^- , AcO^- and H_2PO_4^- , as their tetrabutylammonium salts, at 25 $^\circ\text{C}$). Typical spectral changes upon titration with anion were shown in Fig. 1.

Upon addition of tetrabutylammonium acetate to a solution of **2** (8.96 mM) in CDCl_3 , significant complexation-induced downfield shift of the pyrrolic NHs and slight upfield shifts of β -pyrrole protons were observed. The pyrrole N–H protons originally observed at 7.72 ppm were shifted to 9.26 ppm in the presence of 10 equivalents of acetate anion.

As shown in Fig. 2, addition of the tetrabutylammonium acetate induced the largest chemical shifts changes compared with other anions. In the case of the fluoride anion, the NH signal was broadened after ~ 5 equivalents of anion were added. Based on the corresponding binding isotherm, association constant (K_a) was then calculated using a nonlinear curve fitting with a 1:1 association model [29, 30]. Unfortunately, the poor interaction abilities were observed with low stability constants of $\sim 10 \text{ M}^{-1}$. The affinity constants for fluoride, chloride, bromide, and dihydrogenphosphate were lower than $\sim 5 \text{ M}^{-1}$. However, the system displayed somewhat selective toward acetate anion and fluoride anion over other anions. Quantitative data were not obtained due to the small differences in binding affinity.

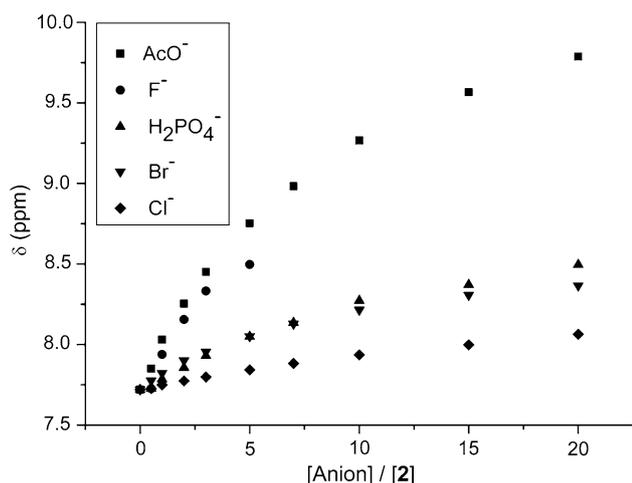


Fig. 2 ^1H NMR titration profiles of receptor **2** (8.96 mM) with various anions in CDCl_3 . The chemical shift change of the pyrrole N–H was plotted against anion concentration. In the case of the fluoride anion, the NH signal was broadened after ~ 5 equivalents of anion were added

In conclusion, pyrrole-based tripodal for anion receptor attached on the upper rim of benzene scaffold was synthesized. Although the poor interaction abilities were observed, the receptor **2** showed higher affinity toward acetate anion over other anions. We are currently focused on the functionalization of appended pyrroles for enhanced anion selectivity and sensitivity.

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