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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 125–128

Homochiral tripodal imidazolium receptors: structural and anion-receptor studies

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Received 11 November 2005; revised 17 October 2006; accepted 26 October 2006
Available online 20 November 2006

In memory of Dr. Joshua Howarth

Abstract—Two homochiral tripodal receptors were characterised by X-ray crystallography, the first examples for this class of imidazolium receptor. These receptors were also screened for anion recognition. Both receptors demonstrated selectivity towards chloride and bromide with binding constants as high as 16,000.

Recently, the ability of 1,3-disubstituted imidazolium cations to enter into hydrogen bonds with halide ions has led to the design of new receptor systems based on the imidazolium entity.[1–6] It has been demonstrated that acyclic tripodal imidazolium receptors (Fig. 1) connected through a 1,3,5-trimethylphenyl spacer selectively bind halide anions via hydrogen bonding. The binding constants for these receptors were extremely high ranging from 46,000 for bromide to 75,000 $dm^3\ mol^{-1}$ for chloride.[7,8]

We earlier published a report on the preparation and evaluation of four new homochiral tripodal receptors designed for anionic enantioselective recognition, one of which demonstrated moderate selectivity for (*R*)-2-aminopropionate over (*S*)-2-aminopropionate.[9]

Here, we report an X-ray crystal structure for this tripodal receptor. We have also evaluated receptors **1a** and **1b** as potential anion receptors.

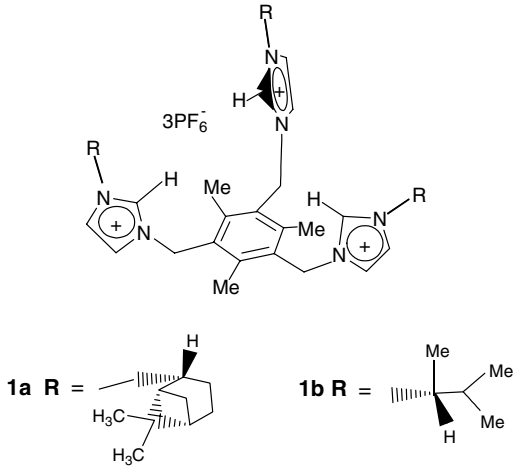

Figure 1.

The syntheses of compounds **1a**,**b** have been previously described[9] and the structures completely characterised.[10] Crystals of **1a** and **1b** suitable for X-ray crystallography were grown from an ethanol–acetonitrile solution.

Figure 2 shows a perspective view of the molecule and Figure 3 shows a perspective view of the crystal packing.

Keywords: Tripodal imidazolium receptors; Homochiral; Anion recognition; X-ray; *Candida albicans*.
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doi:10.1016/j.tetlet.2006.10.143

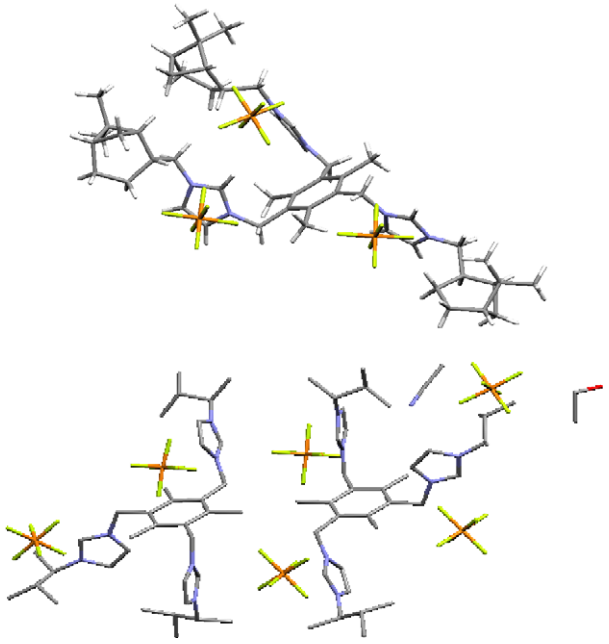

Figure 2. Side view of the crystal structures of **1a** (above) and **1b** (below) (hydrogens are not shown for clarity).

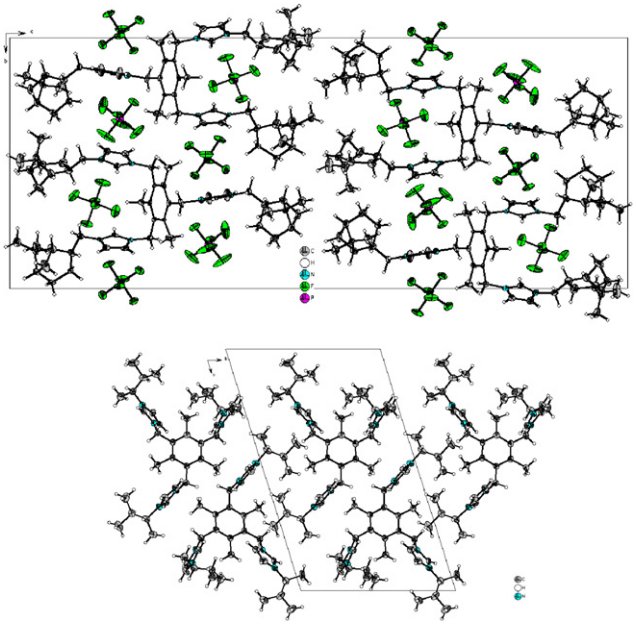

Figure 3. Crystal packing of **1a** (above) and **1b** (below).

In the solid state, **1a** does not possess a preformed receptor cavity, which is typical of most receptor systems. Only two of the imidazolium groups lie above the plane of the trimethylphenyl with each 2-hydrogen of the imidazolium groups pointing inwards and spaced 4.96 Å from each other. Similar results have been found for a benzene based tripodal imidazolium receptor containing *n*-butyl substituents.[11] Thus the cavity is only partially formed in the solid state. Compound **1b** shows a very similar structure to **1a** again with two of the imidazolium groups lying above the plane of the trimethylphenyl ring and again spaced 4.96 Å from each other. It is also evident from Figure 3, that the PF_6^- counter anion is positioned near the H-2 protons of the imidazolium rings in both **1a** and **1b** suggesting hydrogen bonding.

Receptors **1a**,**b** possess far larger steric bulk than previously reported tripodal imidazolium systems and we were interested in determining the effect this would have on receptor selectivity and binding constants.

Shown in Figure 4 is the ^{1}H NMR spectrum of **1a** in the absence and presence of chloride anions. There is a large chemical shift change observed for the H-2 proton of the imidazolium substituents indicating a hydrogen bonding interaction involving all three imidazolium groups of the receptor. Both receptors showed the same strong hydro-

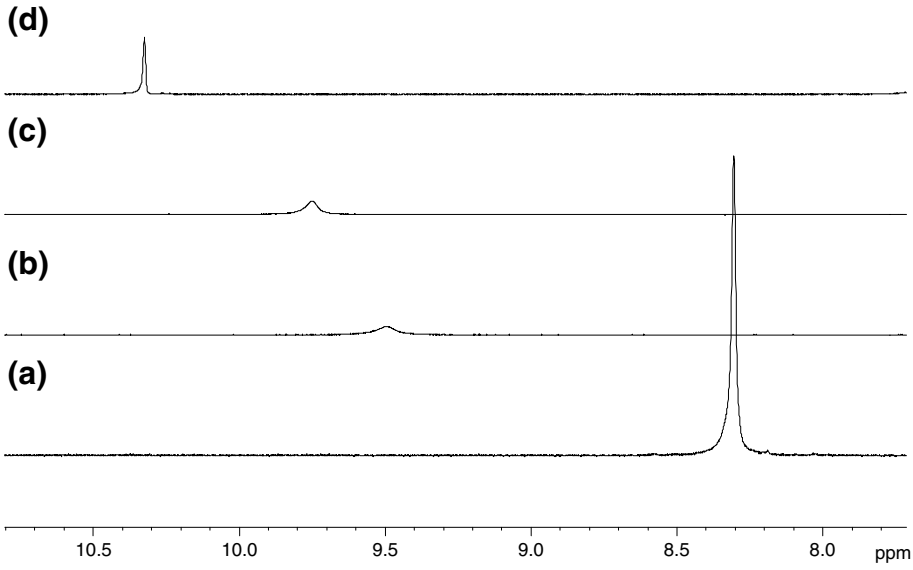

Figure 4. The ^{1}H NMR spectrum (CD_3CN, 400 MHz) of receptor **1a** with (a) no chloride anion, (b) 1:0.4 **1a**:chloride, (c) with 1:0.6 **1a**:chloride and (d) 1:1 **1a**:chloride.

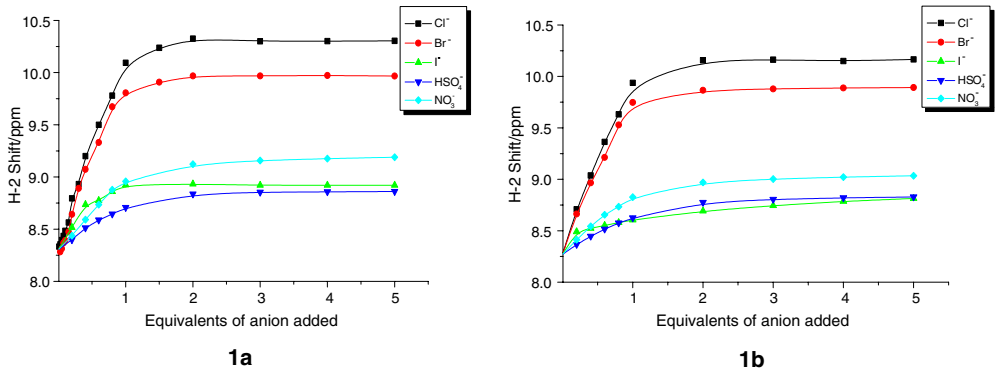

Figure 5. ^{1}H NMR titration curve of tripodal imidazolium salts **1a** and **1b** with various anions added as their tetrabutyl or ethylammonium salts in CD_3CN.

gen bonding interaction in the presence of anions. The relative magnitudes of chemical shift changes were in the order $Cl^- > Br^- > I^- > HSO_4^- > NO_3^-$.

^{1}H NMR titration studies were carried out with compounds **1a**,**b** (Fig. 5). The H-2 protons of the imidazolium handles were monitored with respect to change in chemical shift of the 1,3-dialkylimidazolium salts.[12–15] Binding constants were obtained using a nonlinear curve-fit to the function of the chemical shift dependence versus the equivalent of anion in Excel and are shown in Table 1.[16–19] In both cases the receptors bind in a 1:1 stoichiometry with guest anions. From the values in Table 1 it can be seen that both receptors were able to bind strongly with anions such as Cl^- and Br^-. Receptor **1b** showed a selectivity towards Cl^- and Br^- over, NO_3^- and HSO_4^-, (a binding constant could not be calculated for I^-) whereas receptor **1a** also showed a selectivity towards Cl^- and Br^- over NO_3^- and HSO_4^- (I^- was not included because it was not possible to fit the data properly).

Recently, it has been found that the size of alkyl substituents on the imidazolium moieties does not seem to be detrimental for anion binding.[8] Our results indicate that the incorporation of large substituents does lower the binding constants, however, selectivity for the halides is still observed.

Receptors **1a** and **1b** were also screened for antibiotic and antifungal activities. Receptor **1a** showed a modest antibiotic activity against *P. aeruginosa* showing a 50% reduction in growth at 75 μg/ml, unfortunately, this activity is too low for any useful therapeutic use. Compound **1b** did not show any significant activity. Receptor **1a** also showed insignificant activity against *C. albicans*.

Table 1. Calculated binding constants for receptors **1a**,**b**

Anions	**1a**	**1b**
Cl^-	16,000>	10,000>
Br^-	16,000>	10,000>
I^-	—	—
NO_3^-	1473	2647
HSO_4^-	2780	1163

CCDC numbers 619141 and 619142 contain the supplementary crystallographic data for compounds **1a** and **1b**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.143.

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