Journal of Inclusion Phenomena and Macrocyclic Chemistry (2006) 54: 129–132
DOI 10.1007/s10847-005-5478-x

Acetate-Selective Anion Receptor With Methylene-Bridged Bis-Imidazolium Rings

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(Received: 28 January 2005; in final form: 13 April 2005)

Key words: anion receptor, methylene bridged bis-imidazolium ring

Abstract

Methylene-bridged bis-imidazolium receptor **1** has been synthesized. Anion binding studies carried out using ^{1}H NMR revealed that this compound displayed good affinities for acetate, while binding spherical halide anions weakly.

Introduction

The design and synthesis of artificial receptors capable of binding anionic guests is of crucial importance due to their importance in bio-medicine, industry and the environment. [1–5]

As anions display wide range of geometries, a host-guest complementarity is required for the design of anion receptor. Therefore, hydrogen bonds are frequently used by many researchers as recognition elements due to their directionality. Correct orientation of hydrogen bonds can differentiate among anionic guests with different geometries. While most of hydrogen bonding anion receptors utilize N–H – anion hydrogen bonds, 1,3-disubstituted imidazolium group is recently introduced as new anion binding hydrogen bonding moiety by forming $(C–H)^+$ – anion hydrogen bond between the imidazolium ring and the guest anion. Depending on the spatial arrangement of 1,3-disubstituted imidazolium groups, halide [6, 7], dihydrogen phosphate [8, 9], dicarboxylate [10] selective receptors have been introduced and reported. In addition, imidazolium ring based cyclic compounds are reported, which are interacting with anions in solid and solution state [11].

While we were developing various imidazolium ring based cyclic compounds, we found that methylene bridged bis-imidazolium receptor **1** has affinity toward various anions. Here we would like to report the synthesis and binding properties of receptor **1** with various anions.

Experimental

Instrumentation

^{1}H NMR spectra were measured on a 200 MHz Bruker ASPECT 3000 spectroscopy. All titration measurements were carried out in 10 % DMSO-d_6 in CD_3CN.

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Synthesis and characterization

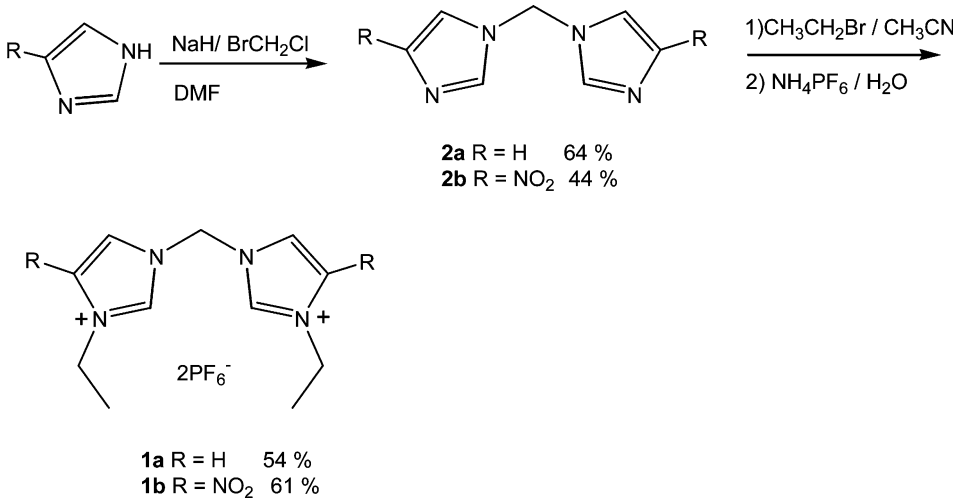
The synthesis of the receptor **1** was achieved as depicted in Scheme 1 synthesis started from the reaction between imidazole and bromochloromethane in the presence of sodium hydride. The reaction gave the product **2a** in 64% yield. Then the compound **2a** was refluxed with ethyl bromide in acetonitrile for 3 h. The precipitated solid was filtered and washed with clean acetonitrile. The solid was dissolved in distilled water and 6 equiv. of ammonium hexafluorophosphate were added to the solution. Filtration of white solid after 3 h stirring gave the product **1a** in 54% yield. The same procedure was applied for the synthesis of the receptor **1b**, which has 4-nitroimidazole ring.

Compound 2a

To a solution of 1 g imidazole in 15 ml DMF was added 105 mg (1.5 eq.) of sodium hydride and 1.4 ml (1.5 equiv.) bromochloroethane. After the reaction mixture was stirred for 3 h, the solvent was evaporated in vacuo. Recrystallization in dichloromethane gave 700 mg of compound **2a** in 64% yield. ^{1}H NMR($CDCl_3$) 7.6 (s, 2H) 7.0(s, 2H) 6.9 (s, 2H) 5.9 (s, 2H) ^{13}C NMR (CD_3CN) δ137.5, 130.1, 119.0, 56.0 HRMS (FAB) calculated for $C_7H_8N_4H^+$, 149.0827 ; found for 149.0835.

Compound 1a

To a solution of 100 mg of compound **2a** in 6 ml acetonitrile was added 0.3 ml (6 equiv) of ethyl bromide. The solution was refluxed for 3 h. The precipitated solid was filtered and washed with acetonitrile. Then the solid was dissolved in 30 ml distilled water. Addition of 500 mg ammonium hexafluorophosphate formed immediate solid precipitation. Filtration of the solid gave 390 mg of compound **1a** in 54% yield. ^{1}H NMR(CD_3CN) 8.7 (s, 2H) 7.5 (t, 2H, J = 1.8) 7.5



2a R = H 64 %
2b R = NO_2 44 %

1a R = H 54 %
1b R = NO_2 61 %

Scheme 1. The synthetic procedure for the anion receptors **1**.

(d, 2H, J = 1.8) 6.3 (s, 2H) 4.2 (q, 4H, J = 7.3) 1.4 (t, 6H, J = 7.3) ^{13}C NMR(CD_3CN) δ 136.21, 123.21 122.06 58.47 45.40 13.82 HRMS (FAB) M-PF_6 calculated for $C_{11}H_{18}F_6N_4P$, 351.1173 ; found for 351.1170.

Compound 2b

To a solution of 300 mg 4-nitro imidazole in 10 ml DMF was added 153 mg (1.2 equiv) of sodium hydride and 0.17 ml (1 equiv) bromochloroethane. After the reaction mixture was stirred for 12 h, the solvent was evaporated in vacuo. Silicagel chromatography in 10% methanol in dichloromethane gave 140 mg of compound **2b** in 44% yield. ^{1}H NMR(CD_3CN) 8.1 (d, 2H, J = 1.5) 7.8 (d, 2H, J = 1.5) 6.1 (s, 2H) ^{13}C NMR (DMSO-d_6) δ147.4, 137.4, 121.1, 56.4 HRMS (FAB) calculated for $C_7H_6N_6O_4H^+$, 239.0529 ; found for 239.0547.

Compound 1b

To a solution of 100 mg of compound **1b** in 7 ml acetonitrile was added 0.6 ml (12 equiv) of diethyl sulfate. The solution was refluxed for 18 h. The precipitated solid was filtered and washed with acetonitrile. Then the solid was dissolved in 30 ml distilled water. Addition of 100 mg ammonium hexafluorophosphate formed immediate solid precipitation. Filtration of the solid gave 33 mg of compound **1b** in 61% yield.. ^{1}H NMR(CD_3CN) 8.9 (s, 2H) 8.5 (d, 2H, J = 1.6) 6.5 (s, 2H) 4.6 (q, 4H, J = 7.2) 1.6 (t, 6H, J = 7.2) ^{13}C NMR(CD_3CN) δ 138.93 124.36 122.35 60.25 47.66 13.38 HRMS (FAB) M-PF_6 calculated for $C_{11}H_{16}F_6N_6O_4P$, 441.0875 ; found for 441.0874.

NMR study

The NMR titration of receptor **1** and tetrabutylammonium anion salts : To a 0.5 ml, 4 mM solution (CD_3CN : CD_3SOCD_3 = 9:1) of receptor **1** was added 10 μl of various concentration of tetrabutyl ammonium anion salts. The chemical shift of C(2) proton of imdazolium moieties was measured.

Results and discussion

The complexation abilities of compounds **1a** and **1b** were measured by standard ^{1}H NMR titration experiments in 10% DMSO-d_6 in CD_3CN using a constant host concentration(4 mM) and increasing concentrations of anions(0.1–10 equiv) [12]. The chemical shift data were analyzed by EQNMR [13]. The addition of tetrabutylammonium anion salts to the solution of **1a** in 10% DMSO-d_6 in CD_3CN resulted in downfield shifts in C(2) proton of imdazolium moieties. In case of acetate ions, C(2) protons of **1a** moved from 9.28 to 11.29 ppm with 5 equiv of acetate ions, which clearly suggest **1a**-acetate complexation by $(C–H)^+$ – acetate hydrogen bonds. Job plot experiments showed 1:1 binding stoichiometry (Figure 1). The association constants calculated from NMR titration gave 1.6×10^3. In the receptor **1b**, nitro group was introduced to the C(4) position of imidazole ring to increase the positive charge in the imidazolium ring. For **1b**, C(2) protons moved downfield about 0.1 ppm for 1 equiv acetate ion and no more shift was observed, which also indicates 1:1 binding between **1b** and acetate. The association constant between **1b** and acetate was calculated as 2.6×10^4. The large difference of chemical shift change between **1a** and **1b** with acetate is not clearly understood.

The possible binding mode and energy minimized structure of receptor **1a** and acetate were shown in Figure 2. Modeling(Cache 3.2 MOPAC calculation) showed the distance between hydrogen in the C(2)–H and oxygen in the acetate fell in the range of 1.98–2.10 Å.

We also investigated the associations of receptor **1** and other anions. Job plot experiments showed 1:1 binding stoichiometry for all kinds of anions

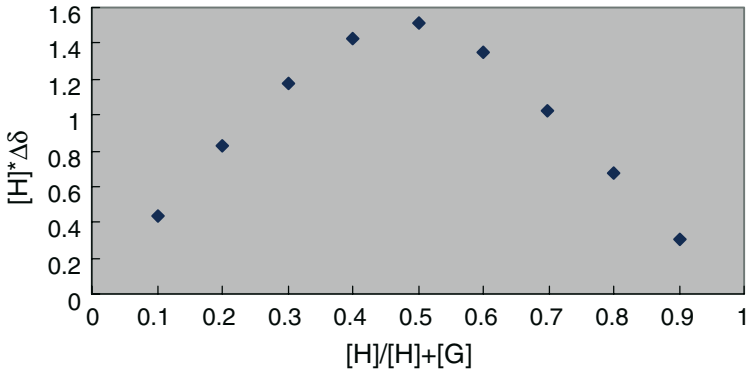


Figure 1. The Job plot of **1a** with tetrabutylammonium acetate.

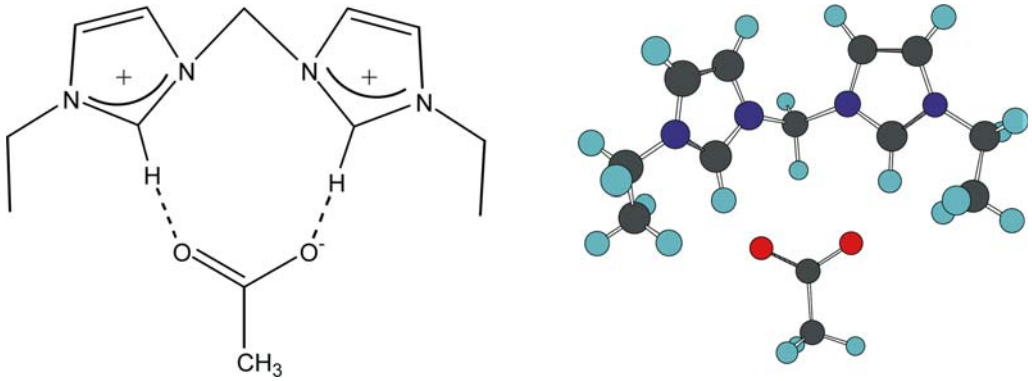


Figure 2. The possible binding mode of receptor **1** and acetate and energy minimized structure of 1:1 complex between receptor **1** and acetate (Cache 3.2 MOPAC calculation).

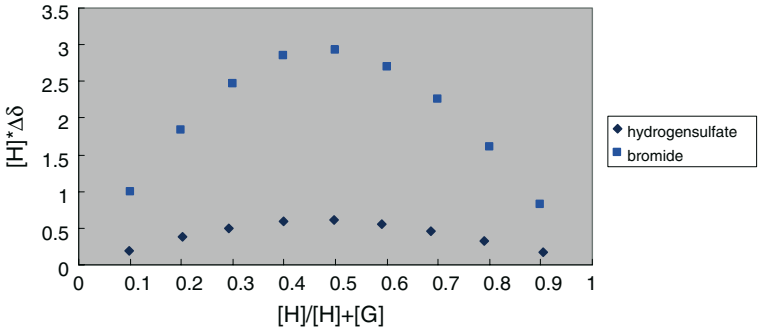


Figure 3. The Job plot of **1a** with tetrabutyammonium bromide(■) and hydrogen sulfate(♦).

investigated irrespective of anion shapes (Figure 3). The results are summarized in Table 1.

For receptor **1b**, the association constants were calculated as 1.7×10^3 for hydrogen sulfate and 5.4×10^2 for chloride, which are much smaller values than acetate. The association constant for acetate is about 15–50 times higher than those of hydrogen sulfate or chloride. Perchlorate or cyanide did not show any chemical shift change for the receptor **1a** and **1b**. Probably the binding site of receptor **1a** and **1b** is fitting well only to the Y shaped anion such as acetate ion. However, the association constants still reflect basicity of these anions [14] as acetate showed higher association constant than nitrate. As expected, receptor **1a** showed smaller association constants than **1b** for the acetate, nitrate and hydrogen sulfate. However, for halide ions, there were almost no differences in association constants among the receptors **1a** and **1b**. The effect of $(C–H)^+$ acidity does not seem to play much role for the anions which does not fit to the binding site of receptor.

Conclusion

We have developed new anion receptor **1**, which has methylene-bridged bis-imidazolium receptor. The receptor **1** displays good affinities for Y-shaped carboxylate anions over other anions in the Table 1.

Table 1. Association Constants (M^{-1}) of **1** with tetrabutylammonium anions in 10% DMSO-d_6 in CD_3CN from ^1H NMR titration

Anion	**1a**	**1b**
$CH_3CO_2^-$	$1.6 \times 10^{3\dagger}$	$2.6 \times 10^{4\dagger}$
NO_3^-	$3.0 \times 10^{2\dagger}$	$1.1 \times 10^{3\dagger}$
HSO_4^-	$8.1 \times 10^{2\dagger}$	$1.7 \times 10^{3\dagger}$
Cl^-	$5.1 \times 10^{2\dagger}$	$5.4 \times 10^{2\dagger}$
Br^-	$4.3 \times 10^{2\dagger}$	$4.4 \times 10^{2\dagger}$
I^-	$1.6 \times 10^{2\dagger}$	$1.4 \times 10^{2\dagger}$

†Errors in K_a are estimated to be less than 10%.

Acknowledgement

This study was supported by a grant from the Korea Association of Small Businesses Innovation Research 2004.

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