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Bile Acid-Based Cyclic Bisbenzimidazolium Receptors for Anion Recognition: Highly Improved Receptors for Fluoride and Chloride Ions

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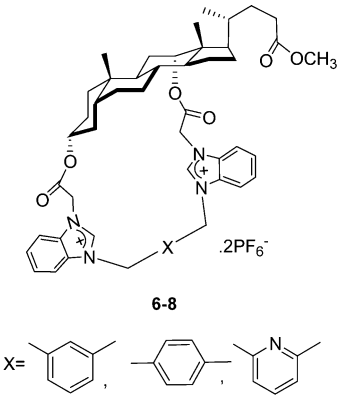

The anion binding properties of bile acid-based cyclic bisbenzimidazolium receptors **6**−**8** bridged with *m*-xylene, *p*-xylene, and 2,6-dimethylpyridine have been studied. Receptors **6** and **7** exhibit much higher binding affinity for fluoride and chloride ions, respectively, as compared to the imidazolium receptors **1** and **2**. Receptor **8**, however, shows high selectivity but very low binding affinity for anions due to the presence of pyridyl nitrogen. The single-crystal X-ray structure of imidazolium receptor **10**-$(Br)_2$ containing pyridyl spacer reveals the binding pattern.

In view of the importance of anions in various biological processes, medicine, and environment, the design of receptors for anion recognition has become an area of great interest.[1] Consequently, many receptors containing ammonium, guanidinium, pyridinium, urea, pyrrole, and amide groups have been reported.[2] These receptors selectively interact with anions of different size and geometry through formation of N−H---X^- hydrogen bonding interaction. Imidazolium salts have also been used for anion recognition, which interact with anions through formation of strong $(C-H)^+$---X^- ionic hydrogen bond.[3]

Bile acids have been well-utilized in designing receptors for anion recognition by incorporating urea, amide, and guanidinium groups in their framework.[4] We have previously reported cyclic and acyclic bisimidazolium receptors derived from deoxycholic acid for anion recognition.[5] We have found that the cyclic receptors **1** and **2** show a high degree of selectivity and affinity for fluoride and chloride ions, respectively, as compared to acyclic receptors **3** and **4** (Figure 1). This prompted us to search for better cyclic steroidal imidazolium systems which can exhibit enhanced binding affinity and selectivity for anions, and thus in the present study, we have investigated the binding properties of bisbenzimidazolium analogues of the cyclic receptors **1** and **2** toward various anions.

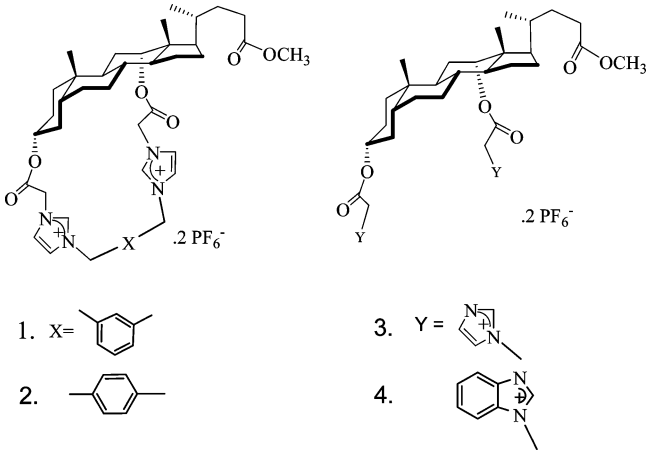

FIGURE 1. Deoxycholic acid-based imidazolium receptors.

We have also studied the binding behavior of cyclic receptors with pyridyl spacer to investigate the effect of N-atom on their

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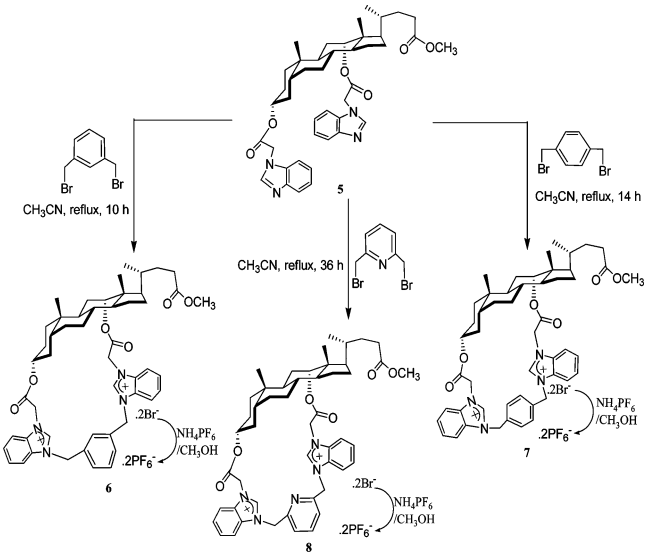
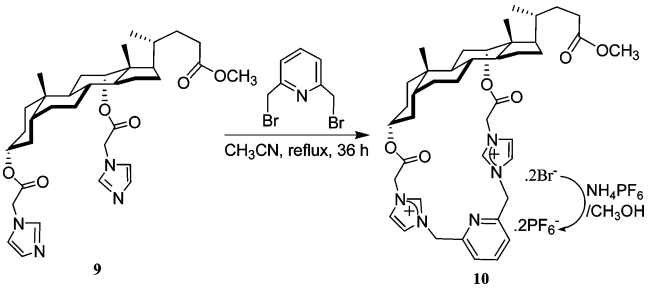
SCHEME 1. Synthesis of Benzimidazolium Receptors



SCHEME 2. Synthesis of Imidazolium Receptor



binding affinity for anions. The cyclic receptors **6**−**8** and **10** were synthesized by similar procedures as described earlier for receptors **1** and **2**.[5a]

Compound **5** was refluxed with *m*-xylelene bromide, *p*-xylelene bromide, and 2,6-bis(bromomethyl)pyridine[6] in acetonitrile for 10, 14, and 36 h to give receptors **6**, **7**, and **8**, respectively (Scheme 1). The receptor **10** was synthesized from compound **9** by refluxing **9** with 2,6-bis(bromomethyl)pyridine in acetonitrile for 36 h (Scheme 2). The hexafluorophosphate salts of these receptors were obtained by the treatment of the corresponding bromide salts with a saturated methanolic solution of ammonium hexafluorophosphate.

Anion binding properties of these receptors were studied by ^{1}H NMR titration in $CDCl_3$. Upon addition of tetrabutylammonium salts of anions, the C-2 protons of both the benzimidazolium moieties as well as the methylene protons of both the acetyl units showed significant downfield shift indicating their participation in the hydrogen bonding interaction with anions. The downfield shifts in the C-2 protons of benzimidazolium rings were monitored to calculate the association constants, K_a, by using WinEQNMR.[7] The values of association constants with different anions for 1:1 complex formation are given in Tables 1 and 2.

The results clearly show that the cyclic benzimidazolium receptors **6** and **7** are much better receptors as compared to the imidazolium receptors **1** and **2** in terms of their binding affinity toward fluoride and chloride ions, respectively. The receptor **6** shows selectivity for fluoride ion with an association constant of 3500 M^{-1} while receptor **7** exhibits the highest affinity and selectivity for chloride ion with an association constant of 20500 M^{-1}, values that are much higher than the association constants

TABLE 1. Association Constants[a] (M^{-1}) for 1:1 Complexes of Receptors 6 and 7 with Various Anions in $CDCl_3$ at 298 K

receptor	anions[b]	K_a (M^{-1})	receptor	anions[b]	K_a (M^{-1})
6	F^-	3500	**7**	F^-	2100
	Cl^-	2600		Cl^-	20,500
	Br^-	2200		Br^-	12,500
	I^-	400		I^-	850
	CH_3COO^-	800		CH_3COO^-	1500
	HSO_4^-	140		HSO_4^-	80

[a] Errors in K_a are estimated to be less than 10%. [b] Anions existed in their tetrabutylammonium salts.

TABLE 2. Association Constants[a] (M^{-1}) for 1:1 Complexes of Receptors 8 and 10 with Various Anions in $CDCl_3$ at 298 K

receptor	anions[b]	K_a (M^{-1})	receptor	anions[b]	K_a (M^{-1})
8	F^-	400	**10**	F^-	30
	Cl^-	1400		Cl^-	250
	Br^-	450		Br^-	130
	I^-	140		I^-	120
	CH_3COO^-	660		CH_3COO^-	140
	HSO_4^-	240		HSO_4^-	300

[a] Errors in K_a are estimated to be less than 10%. [b] Anions existed in their tetrabutylammonium salts.

obtained for the receptors **1** and **2** for fluoride and chloride ions, 2400 and 12000 M^{-1}, respectively.[5a] However, the selectivity order remains the same for both imidazolium and benzimidazolium analogues, as in both cases, the same spacer has been used for cyclization and hence the cavity size remains the same.

In the case of receptor **8** with pyridyl spacer, an adverse effect of pyridyl nitrogen on the binding affinity of anions is noticed, as it shows relatively much lower association constants. The highest value is 1400 M^{-1} for chloride ion, which is even lower than the association constant obtained for the acyclic imidazolium cholapod **3** (2500 M^{-1} for chloride ion).[5b] This may presumably be due to the presence of the lone pair of electrons on nitrogen, which prevents the anions from binding properly in the cavity of the receptor. However, this system shows very high selectivity for chloride ion.

To further confirm this effect, we synthesized the corresponding imidazolium analogue **10** (Scheme 2) and studied their binding properties. As expected, this receptor shows very weak binding properties toward anions as compared to other imidazolium receptors **1**, **2**, and **3** indicating the negative effect of the pyridyl moiety on the binding of anions. This also shows high selectivity for chloride ion. The single-crystal X-ray structure of compound **10(Br)$_2$** could be obtained, which also revealed the binding of bromide ion outside the cavity of the receptor (Figure 2).

Crystals of **10(Br)$_2$** were grown in acetonitrile by slow evaporation giving orthorhombic crystals. In the crystal structure, both the bromide ions are present outside the cavity. One

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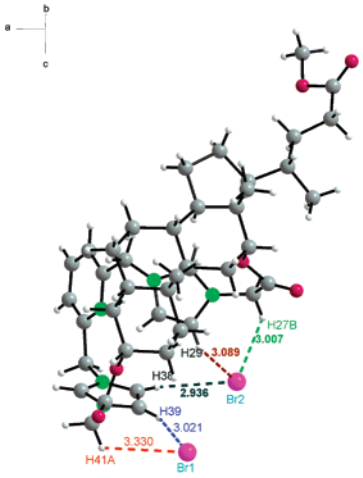

FIGURE 2. Ball-and-stick model of **10-(Br)$_2$·4H$_2$O** showing C−H---Br$^-$ hydrogen bonding. H$_2$O molecules are omitted for clarity.

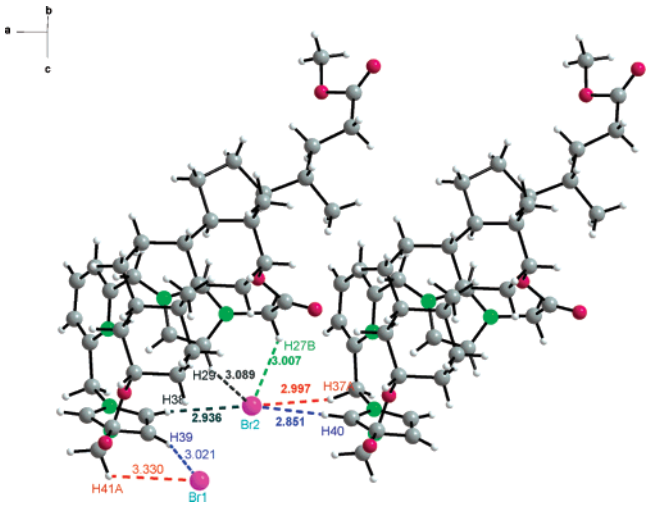

FIGURE 3. X-ray structure of **10-(Br)$_2$·4H$_2$O** showing dimer formation in the solid state via intermolecular C−H---Br$^-$ hydrogen bonding. H$_2$O molecules are omitted for clarity.

bromide (Br2) interacts with C4 and C5 protons (H29, H38) of two different imidazolium rings and a methylene proton (H27B) of an acetyl group. The H29···Br2, H38···Br2, and H27B···Br2 distances are 3.089, 2.936, and 3.007 Å, respectively, and bond angles C29−H29−Br2, C38−H38−Br2, and C27−H27B−Br2 are 109.82°, 137.67°, 136.67°, respectively. The other bromide (Br1) interacts with the C4 proton (H39) of one imidazolium ring and a methylene proton (H41A) of an acetyl group. The above distances are 3.021 and 3.330 Å and bond angles C39−H39−Br1 and C41−H41A−Br1 are 143.36° and 113.62°, respectively.

In its dimeric form, the bromine ion (Br2) also shows intermolecular interaction with the adjacent molecule through bonding with the C-2 proton (H40) of an imidazolium ring and the pyridyl-CH$_2$ proton (H37A) of the adjacent molecule. The H37A···Br2 and H40···Br2 distances are 2.851 and 2.997 Å. Hence, the bromide ion (Br2) is positioned outside the cavity and acts as a bridging ion to assemble the molecules in a particular crystal packing (Figure 3).

The binding behavior of these receptors toward HSO$_4^-$ and H$_2$PO$_4^-$ ions was also examined. All the receptors show very weak binding with HSO$_4^-$ ion (K_a = 80−300 M^{-1}, Tables 1 and 2). Receptors **8** and **10** containing a pyridyl group have been found to have better binding affinity than receptors **6** and **7**. This may be attributed to the additional hydrogen bond interaction involving pyridyl nitrogen and the proton of the anion. None of the receptors show any significant binding with H$_2$PO$_4^-$ ion as no downfield shift was observed in the C-2 protons of the receptors on addition of tetrabutylammonium dihydrogenphosphate.

In summary, the cyclic bisbenzimidazolium receptors **6** and **7** have been found to be much superior receptors for the recognition of fluoride and chloride ions, respectively, as compared to the bisimidazolium receptors **1** and **2** reported earlier. However, the presence of the pyridyl unit as spacer drastically reduces their binding affinity for anions, which may be due to charge repulsion. Interestingly in all the systems, the involvement of the methylene protons of the acetyl groups in the interaction of anions has clearly been observed showing the importance of the C−H---X$^-$ hydrogen bond interaction in the anion recognition.

Experimental Section

General Procedure for the Preparation of Cholaphanes. Benzimidazolium cholaphanes 6, 7, and 8: To a solution of 3α,-12α-bis{*O*-(*N*$_1$-benzimidazole)acetyl}deoxycholate **5** (100 mg, 0.13 mmol) in dry acetonitrile (60 mL) was added *m*-xylelene bromide/*p*-xylelene bromide/2,6-bis(bromomethyl)pyridine (36 mg, 0.13 mmol) and the reaction mixture was refluxed for 10, 14, and 36 h, respectively. After the completion of the reaction, the reaction mixture was allowed to cool at room temperature. Acetonitrile was then evaporated completely and the residue was recrystallized by using chloroform and hexane to obtain pure product as a white crystalline solid. Treatment of the bromide salts with a saturated solution of ammonium hexafluorophosphate in methanol gave PF$_6^-$ salts of **6**, **7**, and **8**.

Imidazolium cholaphane 10: To a solution of 3α,12α-bis{*O*-(*N*$_1$-imidazole)acetyl}deoxycholate **9** (100 mg, 0.16 mmol) in dry acetonitrile (60 mL) was added 2,6-bis(bromomethyl)pyridine (42 mg, 0.16 mmol) and the resulting solution was refluxed for 36 h. The workup followed by anion exchange as described above gave the PF$_6^-$ salt of **10**.

^{1}H NMR Titration Method. All NMR experiments were performed on a Bruker DPX300 (300 MHz) spectrometer at 298 K. A solution (8−12 mM) of receptor in CDCl$_3$ was titrated with small aliquots from a stock solution of the tetrabutylammonium salt (40−60 mM) in the same solvent. The changes in the chemical shift of the C-2 proton of imidazole/benzimidazole moieties in the receptor were monitored. The association constants were determined by using the WinEQNMR program. Every titration was repeated at least once. The stoichiometry of the complex was determined by using Job's method of continuous variation.

Crystal data for 10(Br)$_2$: colorless, needle shape, 0.38 × 0.12 × 0.076 mm^3, C$_{42}$H$_{57}$Br$_2$N$_5$O$_{10}$, M_r = 951.73, orthorhombic, space group $P2_12_12_1$, a = 9.133(15) Å, b = 17.51(3) Å, c = 27.99(5) Å; α = 90°, β = 90°, γ = 90°, V = 4476(13) Å^3, Z = 4, F(000)=1976, ρ_{calcd} = 1.412 g/cm^3, μ = 1.871 mm^{-1}, 4787 independent reflections, R_1 = 0.1003, wR_2 = 0.2197 [$I > 2\sigma(I)$], R_1 = 0.1771, wR_2 = 0.2197 (all data), GOF = 0.956. CCDC: 664920.

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Supporting Information Available: NMR and mass spectral data, X-ray data file (CIF), NMR and mass spectra and binding isotherms. This material is available free of charge via the Internet at http://pubs.acs.org.

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