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Novel Bile Acid-Based Cyclic Bisimidazolium Receptors for Anion Recognition

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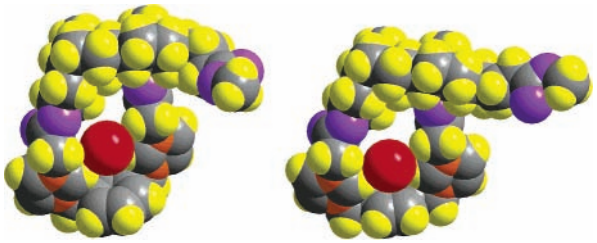
ABSTRACT



Novel deoxycholic acid-based cyclic receptors, 3 and 4, containing two imidazolium groups and *m*-xylene and *p*-xylene as spacers have been synthesized. These receptors bind anions through hydrogen bonds utilizing two imidazolium (C–H)$^+$ and inwardly directed methylene hydrogens of both acetyl groups. Receptor 3 shows a moderate selectivity for fluoride ion whereas receptor 4 shows high affinity and selectivity for chloride ion in $CDCl_3$.

In recent years, the development of receptors for recognizing anionic species has become a major area of supramolecular chemistry because of their ability to serve as models for the biological processes and their potential for the design of sensors for medical and analytical applications.[1] Most anion binding receptors utilize amide, urea, pyrrole, and guanidinium groups as binding sites to form N−H···X hydrogen bonds.[2] More recently, 1,3-disubstituted imidazolium groups have been introduced to bind anions by forming (C−H)$^+$···X$^-$ ionic hydrogen bonds between C(2)−H of imidazolium rings and the anion.[3]

Davis et al. have exploited the steroid nucleus of bile acids to design supramolecular hosts (cholapods) incorporating urea, thiourea, etc. as H-donor groups, which exhibit high affinity and selectivity toward various anionic species.[4] Certain cholapods have been shown to have the capability of transporting chloride ions across vesicle and cell membranes.[5] It has been realized that the design of receptors for fluoride and chloride ions is of special importance due to their direct applications in the treatments of dental decay

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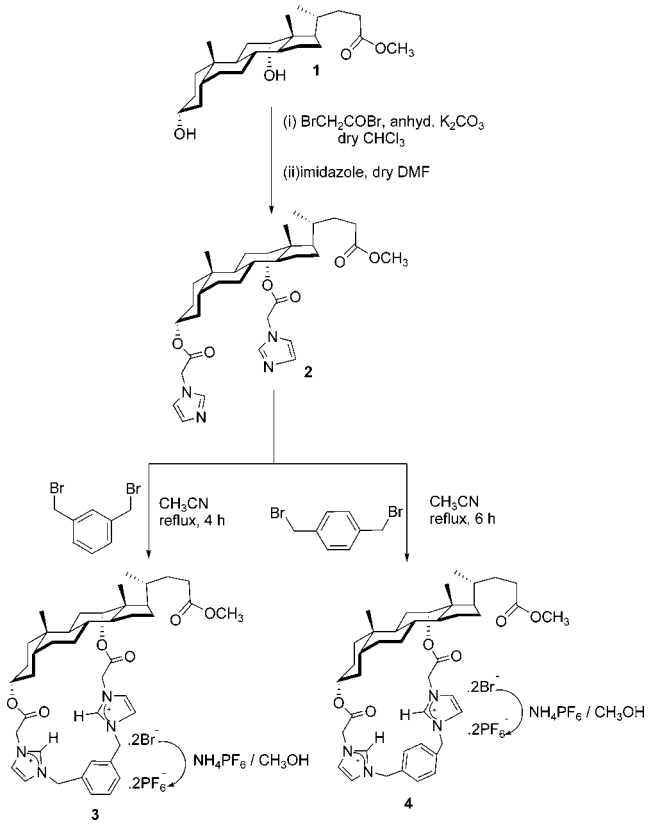
and cystic fibrosis, respectively,[6] and recently some attempts have been made to synthesize bile acid-based receptors selective for fluoride and chloride ions.[7] Although Davis et al. and others have made much effort to vary the selectivity of these receptors by modifying the H-bond donor groups, there is still considerable scope for creating new anion-specific receptors based on bile acids. To our knowledge, bile acid-based cyclic systems having imidazolium groups have not been explored for such a possibility so far. These cyclic imidazolium systems will have more well-defined positions of H-bond donor groups in their cavity and their cavity size can also be easily tuned by changing the spacers to bind anions in a more selective manner. Hence, we designed and synthesized deoxycholic acid-based cyclic bisimidazolium receptors **3** and **4** with *m*- and *p*-xylene as spacers by a remarkably simple synthetic route and studied their anion recognition properties.

Cyclic steroidal receptors **3** and **4** were prepared as shown in Scheme 1. First, methyl 3α,12α-bis{*O*-(*N*$_1$-imidazole)-acetyl}deoxycholate **2** was synthesized from methyl deoxycholate. The reaction of **2** with *m*-xylylene bromide and *p*-xylylene bromide in a 1:1 equivalent ratio in acetonitrile under reflux resulted in the bromide salts of **3** and **4**, respectively, which were subsequently anion exchanged with a saturated methanolic solution of NH_4PF_6.[8] To investigate the anion binding property of **3**-$(PF_6)_2$ and **4**-$(PF_6)_2$, we studied the ^{1}H NMR spectral changes caused by the addition of tetrabutylammonium salts of the anions to $CDCl_3$ solution containing receptors. Upon additions of Bu_4NX (X = F, Cl, Br, I, CH_3COO) to receptors, significant changes were observed in their ^{1}H NMR spectra. As expected, large downfield shifts were observed for the C(2)−H proton of each imidazolium moiety suggesting complexation of the anion by $(C-H)^+$ hydrogen bonds. But to our surprise, significant changes and downfield shift were also observed for bridging methylene protons indicating participation of methylene hydrogens upon anion recognition. The involvement of methylene hydrogens in hydrogen bonding with bromide ion was further confirmed by the HSQC {^{13}C−H} spectrum of **3**-$(Br)_2$. The methylene protons of acetyl units became nonequivalent and appeared as a pair of doublets and one doublet of each pair significantly shifted downfield due to hydrogen bonding with X^-. The earlier *m*-xylene bridged imidazolium receptors designed by Kang et al. utilize two imidazolium $(C-H)^+\cdots X^-$ ionic hydrogen bonds and one benzene hydrogen bond.[9]

Scheme 1. Synthetic Procedure for Receptors **3** and **4**



The exact mode of binding was confirmed by the single-crystal structures of **3**-$(Br)_2$ and **4**-$(Br)_2$.[10] Crystals of **3**-$(Br)_2$ and **4**-$(Br)_2$ were obtained upon slow evaporation of chlo-

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(10) Crystallographic data for 3-$(Br)_2$·2$CHCl_3$·2H_2O: T = 100 K, M_r = 1157.47, 0.39 × 0.06 × 0.02 mm^3, monoclinic, space group $P2_1$, a = 13.409(2) Å, b = 13.645(2) Å, c = 14.854(2) Å, V = 2642.9(7) Å^3, Z = 2, ρ_{calcd} = 1.454 g cm^{-3}, μ = 1.889 mm^{-1}, $F(000)$ = 1188, GoF = 0.973, $2\theta_{max}$ = 25.50, 8952 independent reflections, R1 = 0.0687 for 6579 reflections with $I > 2\sigma(I)$ and wR2 = 0.1633 for all data, 604 parameters. CCDC: 283499. Crystallographic data for 4-$(Br)_2$·1.5H_2O: T = 298 K, M_r = 1825.50, 0.24 × 0.17 × 0.08 mm^3, monoclinic, space group C2, a = 27.172(5) Å, b = 8.5342(16) Å, c = 23.688(4) Å, V = 4668.0(15) Å^3, Z = 2, ρ_{calcd} = 1.299 g cm^{-3}, μ = 1.787 mm^{-1}, $F(000)$ = 1904, GoF = 0.917, $2\theta_{max}$ = 25.5, 8707 independent reflections, R1 = 0.0609 for 4349 reflections with $I > 2\sigma(I)$ and wR2 = 0.1904 for all data, 516 parameters. CCDC: 283500.

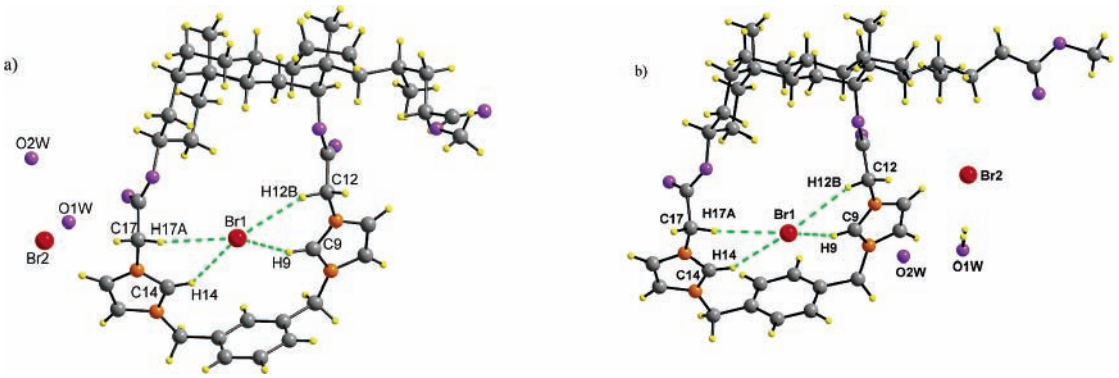

Figure 1. X-ray crystal structure of (a) 3-$(Br)_2$·$2CHCl_3$·$2H_2O$ and b) 4-$(Br)_2$·$1.5H_2O$ showing C−H···Br ionic hydrogen bonding. Br2 and water molecules (O1W and O2W) located outside the cavity are not showing any direct interaction with the imidazolium or aromatic hydrogen atoms. $CHCl_3$ molecules are omitted for clarity in part a.

roform/hexane and chloroform/methanol solutions of the dibromide salts of **3** and **4**, respectively. Single-crystal structures of **3**-$(Br)_2$·$2CHCl_3$·$2H_2O$ and **4**-$(Br)_2$·$1.5H_2O$ are shown in Figure 1. The crystal structures show bromide bound within the molecular cavity in a 4-fold array of strong hydrogen bonds to the C(2)−H atom of each imidazolium ring and inwardly directed methylene protons of both acetyl units (consistent with the observed ^{1}H NMR changes). The selected distances and bond angles are given in Table 1. In

Table 1. Selected Geometrical Parameters for 3-$(Br)_2$·$2CHCl_3$·$2H_2O$ and 4-$(Br)_2$·$1.5H_2O$[a]

crystals	H12B···Br1	H17A···Br1	H14···Br1	H9···Br1
3	2.777(3)	2.801(1)	2.676(2)	2.587(1)
4	2.945(4)	2.911(2)	2.782(2)	2.770(1)

crystals	C12−H12B−Br1	C17−H17A−Br1	C14−H14−Br1	C9−H9−Br1
3	154.66(56)	137.78(49)	145.59(56)	149.69(56)
4	144.77(55)	144.77(55)	151.07(59)	149.67(65)

[a] Distances in Å and angles in deg.

3-$(Br)_2$·$2CHCl_3$·$2H_2O$, the distances between the bromide and the C(2)−H protons of the imidazolium rings are 2.587 and 2.676 Å, which are significantly shorter than the sum of the van der Waals radius of H-atom and the ionic radius of a bromide anion (3.15 Å), suggesting the formation of C−H···Br^- ionic hydrogen bonds. Similarly in **4**, the above said distances are 2.770 and 2.782 Å. These results are unequivocal evidence for the attractive C−H···X^- interaction between the dicationic imidazolium macrocycles and the anion.

The crystal structure of **3**-$(Br)_2$·$2CHCl_3$·$2H_2O$ also reveals that there is no intramolecular C−H···Br^- hydrogen bonding with benzene hydrogens, but bromide ion, which is inside the cavity, forms an intermolecular hydrogen bond with one benzene hydrogen of the adjacent molecule. It also forms an intermolecular hydrogen bond with one methylene proton of the benzylic unit (Figure 2a). The H7···Br1 and H8B···Br1 distances are 2.832(1) and 2.927(1) Å, respectively, and C7−H7−Br1 and C8−H8B−Br1 bond angles are 159.69(51)° and 163.09(56)°, respectively. In **4**-$(Br)_2$·$1.5H_2O$ too, one benzene hydrogen is involved in intermolecular hydrogen bonding with bromide ion (Figure 2b). The H6···Br1 distance is 3.092(1) Å and the C6−H6−Br1 bond angle is 135.22(38)°.

The analysis of ^{1}H NMR saturation data with WinEQNMR software[11] suggested 1:1 stoichiometry in each case. A Job Plot analysis also showed formation of 1:1 complexes. The association constants were determined from their titration curves by monitoring chemical shift changes of the C(2)−H proton of imidazolium units and are collected in Table 2. Receptor **3** showed the highest affinity for the fluoride anion with an association constant of 2400 M^{-1}. It also showed more selectivity for fluoride anion than for chloride, bromide, and iodide, with the selectivity trend $F^- > Cl^- > Br^- > I^-$. It should be noted that the binding constant for the F^- ion was determined in the presence of a trace amount of water, as trihydrate salt was used. Receptor **3** also exhibits affinity for the acetate anion. The imidazolium moieties could rotate slightly to form an ionic hydrogen bond with the V-shape acetate anion.

The association constant for $H_2PO_4^-$ ion could not be calculated because of the disappearance of the C(2) proton

Table 2. Association Constant (K_a) for 1:1 Complexes of Hosts with Anions in $CDCl_3$ at 298 K

host	anions[b]	K_a (M^{-1})	host	anions[b]	K_a (M^{-1})
3	F^-	2400	**4**	F^-	930
	Cl^-	1980		Cl^-	12000
	Br^-	1470		Br^-	7600
	I^-	150		I^-	300
	CH_3COO^-	470		CH_3COO^-	900

[a] Estmated error <10%. [b] Anions used in this assay were in the form of their tetrabutylammonium salts.

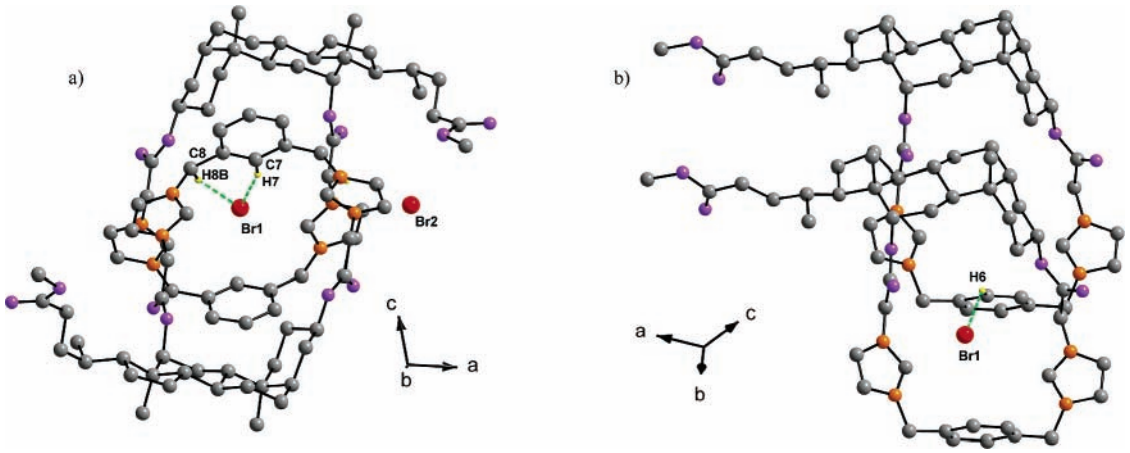

Figure 2. Intermolecular C−H···Br1 hydrogen bonding between two adjacent molecules of (a) **3**-$(Br)_2$·$2CHCl_3$·$2H_2O$ and (b) **4**-$(Br)_2$·$1.5H_2O$. Solvent molecules and other hydrogens are omitted for clarity.

signal upon addition of tetrabutylammonium dihydrogenphosphate. In the case of receptor **4**, because of the para-substituted benzene ring, the size of the cavity becomes bigger and, hence, receptor **4** showed different selectivity and affinity toward anions as compared to receptor **3**. The observed selectivity trend was $Cl^- > Br^- > F^- > I^-$. It showed the highest affinity for the chloride anion with a strong binding constant of 12 000 M^{-1}.

In summary, novel bile acid-based receptors for the selective recognition of fluoride and chloride ions have been synthesized by incorporating imidazolium rings as anion binding subunits. The receptor with *m*-xylene shows a moderate selectivity for fluoride ion whereas the receptor with *p*-xylene exhibits high affinity and selectivity toward the chloride ion. Due to their distinct selectivity these systems may have great potential for applications in biology and medicine.

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Supporting Information Available: Experimental details for the synthesis of **3** and **4**, CIF files, and ^1H NMR titration methodology. This material is available free of charge via the Internet at http://pubs.acs.org.

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