SYNTHESIS AND ANION BINDING PROPERTIES OF STEROID-BASED IMIDAZOLIUM RECEPTORS

By

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Department of Chemistry

Submitted

in fulfillment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

to the

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Dedicated to my parents

CERTIFICATE

This is to certify that the thesis entitled, **"Synthesis and anion binding properties of steroid-based imidazolium receptors"**, being submitted by Miss Mamta Chahar, to the Indian Institute of Technology, Delhi, for the award of the degree of 'Doctor of Philosophy in Chemistry', is a record of bonafide research work carried out by her. Miss Mamta Chahar has worked under my guidance and supervision and has fulfilled all the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard. The results embodied in this thesis have not been submitted, in part or in full to any other University or Institute for the award of any degree or diploma.

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Thesis Supervisor

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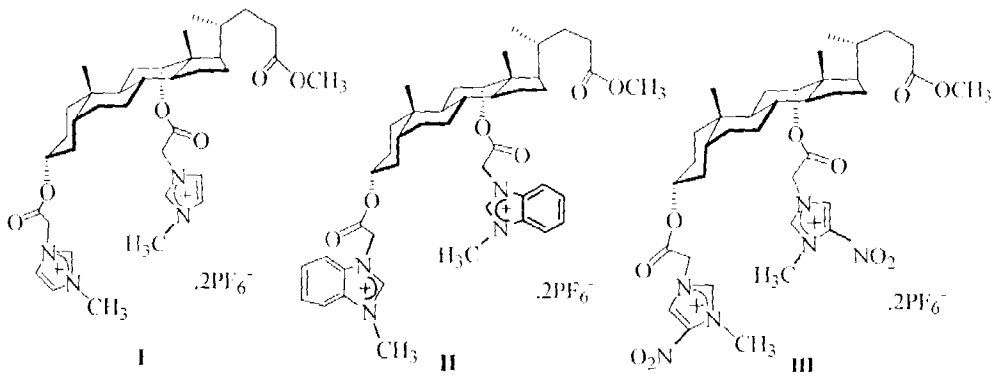
And finally, God who continues to look after me despite my flaws....

Mamta Chahar

Mamta Chahar

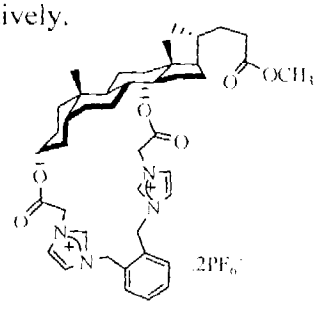
ABSTRACT

The design and synthesis of efficient receptors capable of binding anionic guests is an emerging field in supramolecular chemistry. Anion recognition has attracted considerable interest in recent years due to the biological, medical and environmental significance of anions. Present thesis deals with the design, synthesis and study of bile acid-based acyclic and cyclic receptors for recognition of anionic species. The thesis has been divided into four chapters. **Chapter 1** describes a brief literature survey on the recent developments in design of positively charged and neutral receptors containing 1,3-disubstituted imidazolium, ammonium, pyridinium, amide, urea and pyrrole groups for recognition of anions. **Chapter 2** deals with the synthesis and study of deoxycholic acid-based acyclic and cyclic receptors containing imidazolium and benzimidazolium groups and cholic acid-based cyclic receptors containing imidazolium group for anion recognition. 1,3-Disubstituted imidazolium groups have been introduced to bind anions by forming $(C\text{-}H)^{+}\cdots X^{-}$ polar hydrogen bonds between C(2)-H of imidazolium rings and the anion. First, deoxycholic acid-based acyclic receptors **I, II** and **III** were synthesized and anion binding properties of these receptors have been studied by ^{1}H NMR titration experiment.



The addition of tetrabutylammoniun salts of anions (F^-, Cl^-, Br^-, I^-, CH_3COO^-) to the receptors resulted in large downfield chemical shifts of C-2 protons of imidazolium/benzimidazolium/nitroimidazolium moieties attributed to $(C\text{-}H)^+\text{---}X^-$ hydrogen bonding interaction with anions. In addition to the downfield shifts for the C-2 protons of imidazolium/benzimidazolium/nitroimidazolium groups, significant changes and downfield shift in the methylene protons were also observed. The involvement of -CH_2- hydrogens as an important motif was established on the basis of the ^1H NMR and single crystal X-ray studies. Receptor **I** showed high selectivity and binding for chloride ion with an association constant 2500 M^{-1} whereas receptors **II** and **III** displayed preference for the acetate and chloride ions, respectively, with the association constants 285 and 220 M^{-1}, respectively.

We were particularly interested in fluoride ion recognition because of its significant role in dental care and treatment of osteoporosis. This prompted us to target tuning the cavity size of the receptor by varying the spacer group to get the better fluoride-selective geometry. Thus we synthesized cyclic deoxycholic acid-based imidazolium and benzimidazolium receptors **IV-VII,** with o-xylelene and naphthyl groups. The receptors **IV** and **V** with *o*-xylelene group displayed selectivity for chloride ion with the association constants 1040 and 2300 M^{-1}, respectively while receptors **VI** and **VII** with naphthyl group showed high selectivity for fluoride ion with the association constants 1800 and 3200 M^{-1}, respectively.



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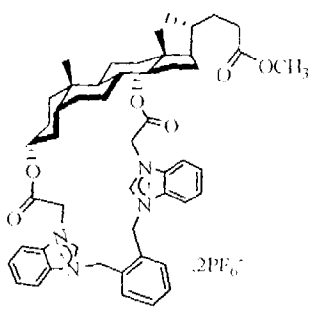

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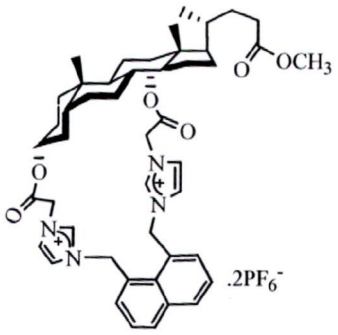

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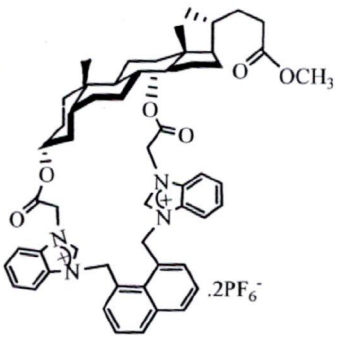
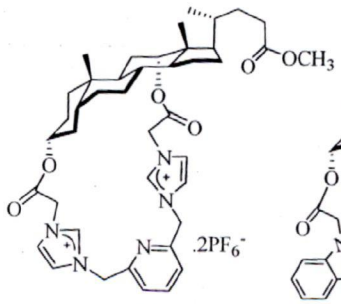
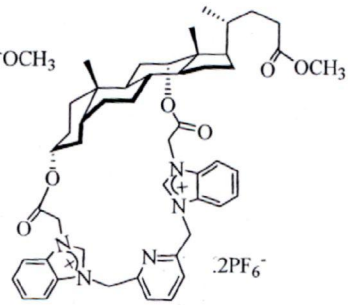


VII

To see the effect of pyridyl spacer on the binding affinity of anions, we also synthesized receptors **VIII** and **IX**. These receptors displayed very weak binding properties towards anions indicating the negative effect of the pyridyl moiety on binding of anions. However, they showed high selectivity for chloride ion with binding constants 250 and 1400 M^{-1}, respectively. The presence of pyridyl unit as spacer drastically reduces their binding affinity for anions, may be due to the presence of the lone pair of electrons on nitrogen atom of the pyridyl group which prevents the anions to bind properly in the cavity of these receptors.

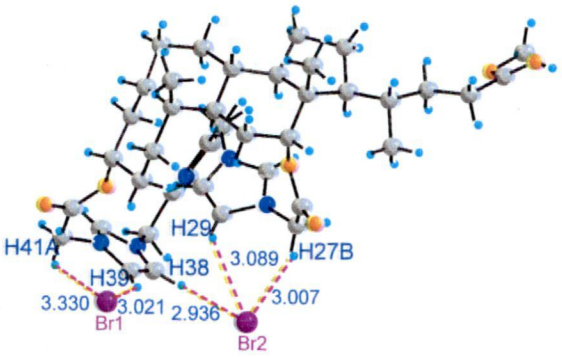


VIII

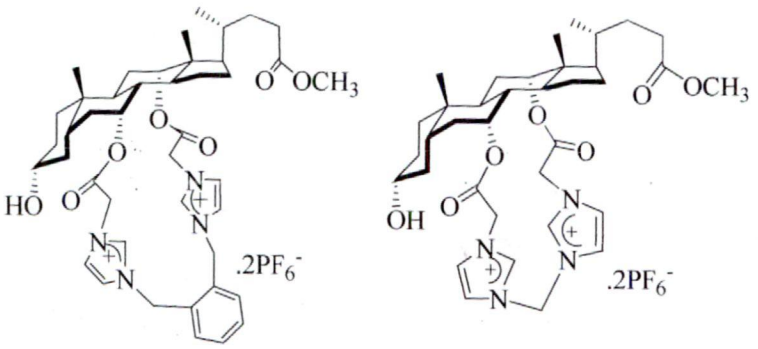


IX

The single crystal X-ray structure of compound **VIII(Br)$_2$** also showed the binding of bromide ion outside the cavity of the receptor.



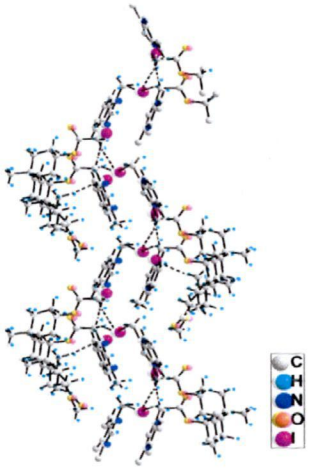
For comparative studies, cholic acid-based cyclic receptors **X** and **X1** containing imidazolium group bridged with o-xylelene and methylene groups at 7α- and 12α-positions of methyl cholate were also synthesized from methyl cholate. The binding constants for receptors **X** and **X1** with fluoride ion were found to be 860 and 720 M^{-1}, respectively.

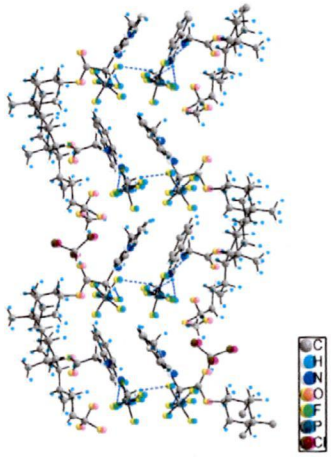


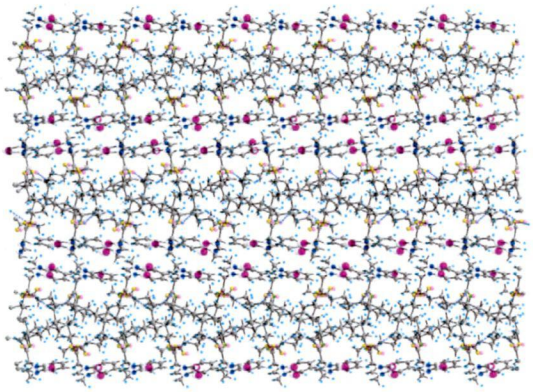
X **XI**

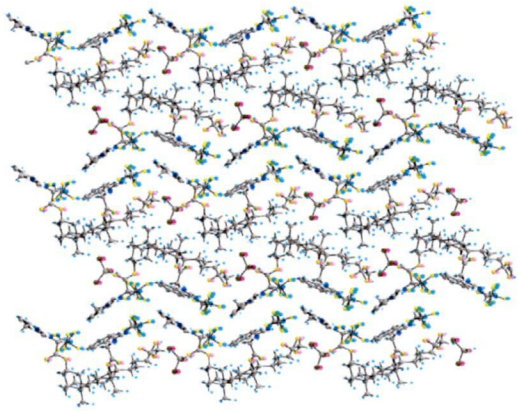
Chapter 3 describes the crystallographic studies of the synthesized steroidal receptors **II(I)$_2$, II(PF$_6$)$_2$** and **VIII(Br)$_2$** described in Chapter 2. The crystal structures showed the role of anions and solvent molecules like chloroform, water etc. in crystal packing. The involvement of methylene protons was confirmed by the single-crystal X-ray structures of receptors **II(I)$_2$, II(PF$_6$)$_2$** and **VIII(Br)$_2$.** The crystal packing is mainly dominated by CH…I⁻/CH…F⁻, CH…π interactions as shown in following Figures. These

intermolecular interactions lead to the formation of 2D-supramolecular sheets consisting of layers of molecules running in a zigzag manner throughout the crystal lattice.





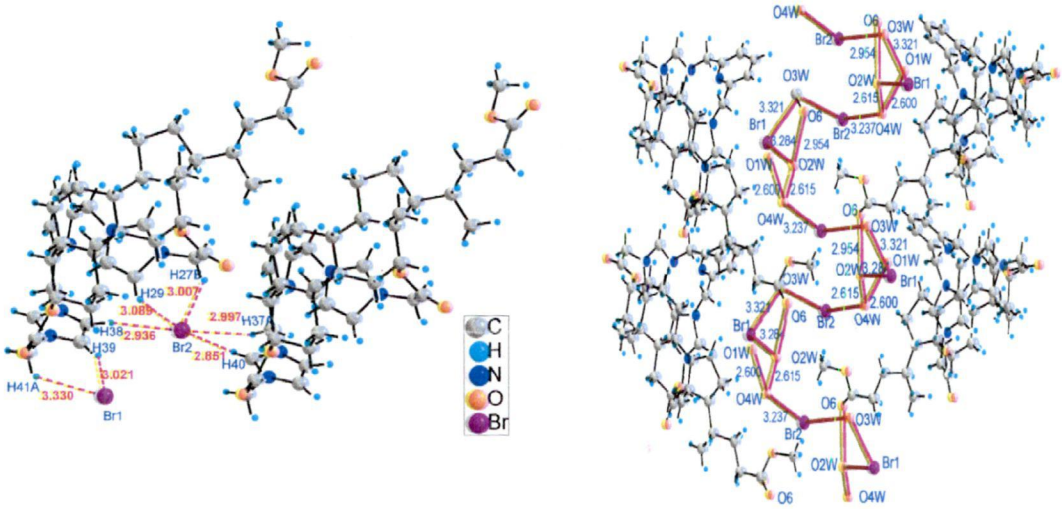




II(I)$_2$ **II(PF$_6$)$_2$**

The packing diagram of **VIII(Br)$_2$** showed that the bromide ion (Br2) is positioned outside the cavity and acts as a bridging ion to assemble the molecules into a 1D supramolecular chain. The Br1 connects these supramolecular chains into 2D supramolecular sheets. Importantly, the crystal contains four water molecules (O1w, O2w, O3w and O4w). Three water molecules O1w, O2w and O4w interact among

themselves in such a way that they form an acyclic trimer, which further interacts with the bromide ions (Br1 and Br2) through O2w and O4w, respectively. This supramolecular assembly is interconnected to form a 1D zigzag chain through O3w. These chains are found in the interchannel regions connecting the steroidal moieties in the crystal packing.



VIII(Br)$_2$

Chapter 4 describes the experimental procedures for the synthesis of compounds used in this study and presents their physical and spectroscopic characterization data.

CONTENTS

CHAPTER II. Bile acid-based acyclic and cyclic imidazolium receptors for anion recognition

CHAPTER III. X-ray crystallographic studies of steroidal receptors

CHAPTER IV: Experimental Section