CHAPTER – 2

Uracil Based Molecular Receptors

The design of new chemical entities capable of inducing selective binding and transport of ionic or neutral species or mimicking biological processes are of interest due to their exploitability in emerging technological processes as well as due to the role played by them in the understanding of a variety of biological phenomena. Starting with crown ethers - the first generation synthetic receptors, followed by their second generation – cyclodextrins, the calixarenes as defined by Seiji Shinkai the “third generation of supramolecules” have provided unlimited opportunities due to modifications both at lower rim (phenolic OH) and upper rim (p-position to phenolic OH) for designing new host molecules for supramolecular interactions. Structurally, calix[n]arenes offer a pre-organized scaffold with a certain degree of flexibility and co-operativity of the appendages at either or both the lower and the upper rims. These are a category of \( m \)-cyclophanes, e.g., 1 (calix[4]arene, \( n = 1 \)), elaborating a cyclic array of aromatic phenolic rings joined at 1,3- positions by methylene bridges and which when appropriately modified structurally, exhibit versatile binding character. Structural uniqueness, responsible for their molecular recognition status, is characterized by

(i) a core of aromatic rings (\( \pi \) - electron rich cavity) providing \( \pi \)-cation, \( \pi \)-\( \pi \), -CH...\( \pi \) etc. interactions, (ii) derivatization at rims generating varied possibilities of receptor designs capable of crown-type bindings and (iii) tunability of a cavity in respect to its size (\( n = 4,5,6... \)), depth, and conformation such as a cone, partial cone, 1,2- / 1,3- alternate geometry (Figure 1).

The replacement of phenolic unit(s) of calix[n]arenes 1 by heterocyclic ring(s), methylene bridge(s) by hetero atom(s) / or metal atoms constitute chemical entities now respectively designated as heterocalixarenes (e.g., 2 calix[4]pyrrole), heterocalixarenes (e.g., 3...}

Figure 1
thiacalix[4]arene\textsuperscript{4d} and metallacalixarenes\textsuperscript{4e} (Figure 2). Heterocycles as molecules of life\textsuperscript{5} are ubiquitous in biological functions because of their ability to undergo varied non-covalent interactions with ions as well as neutral species. Depending on the nature of the heterocyclic ring(s), heterocalixarenes can have both electron-rich (pyrrole) as well as electron-deficient (pyridine) $\pi$ – electron character of the cavity. The substitution and ring transformation profiles of constituent sub-heterocycles can assist in tuning the physico-chemical character of heterocalixarenes. Heteroatoms can also influence their binding character. With these additional features, heterocalixarenes are capable of providing a wider range of rational designs of synthetic receptors and consequent recognition events than calixarenes. Amongst heterocalix[n]arenes, the calix[4]pyrroles\textsuperscript{7} have found enormous applications in developing anion sensors. Other than pyrrole, number of other heterocycles viz. thiophene, furan, pyridine, imidazole, benzimidazole, indole, benzofuran, benz-1,3-oxazine, pyrimidine-2,4-dione, benzimidazol-2(1H)-one, quinazoline-1,4(1H,3H)-dione etc. have been used for developing heterocalixarenes\textsuperscript{6} with both electron-rich and electron-deficient cavities and their interactions have been studied with number of guests of neutral, cationic and anionic nature.

Structurally, metallacalixarenes constitute organo-inorganic hybrids where heterocyclic organic species with appropriately oriented donor nitrogens are linked in a self-assembled manner with inorganic metallic species to form functional entities which being positively charged can show anion-sensing ability. The presence of heterocyclic moieties and other functionalities (O, OH, NHR etc.) can induce interactions with additional metal ions. The metallacalixarenes have been represented as their molecular units with an inbuilt provision for abbreviated heterocyclic component(s) with binding sites. Thus, the representation of 4 above indicates that four (en)PtII linkers are joined to four uracil moieties at their 1,3 positions to form the cyclic tetramer. For forming metallacalixarenes, 1,3-heterocycles having at least two angularly disposed ligating nitrogens are employed and a prominent use has been made of nucleobases such as uracil, adenine, guanine, hypoxanthine etc. The model
heterocycles 2,2’-bipyrazine and 4,7-phenanthroline having similar inbuilt angular ligating character have also been used.

Uracil and thymine are the major constituents of nucleic acids RNA and DNA, respectively. Nucleic acids play an important role in determining the nature and functions of organisms and in controlling various metabolic and biosynthetic processes. DNA is store house of genetic information and RNA is carrier of information relating to biosynthetic processes. In 1953, the discovery of double helix structure of DNA through X-Ray crystallography by James Watson and Sir Francis Crick and their findings that only adenine –

The uracil / thymine – the pyrimidine-2,4-diones are chemically pliable molecules. The facile deprotonation at nitrogen atoms provides numerous possibilities for alkylation and also these deprotonated species can coordinate with metal ions to provide numerous acyclic and cyclic structures. In literature, metallacalixarenes with pyrimidines as aromatic core and metal ions as bridges between these heterocycles are known. However, there is not even a single report on the synthesis of heterocalixarenes based only on uracil moiety as the
aromatic core. In the present investigations, we have designed a simple protocol for the synthesis of calix[4]uracils where C4=O of each uracil points at the lower rim of the molecule. Before discussing the present research results, a brief account of literature reports on the uracil based cyclic molecular architectures lying in the categories of heterocalixarenes, metallacalixarenes and others has been presented.

Section 2.1 : Overview of uracil based cyclic molecular architectures

The literature reports have been presented in two categories with either carbon or with metal ion as bridge between two pyrimidine-2,4-dione moieties.

2.1.1. Uracil based cyclic molecular architects with carbon atoms as bridges

Tetrameric calix[2]uracil[2]arenes 2, having similar or different substitution profiles in both arenes, were obtained by PTC catalysed condensations of 1,3-bis(bromomethyl)benzene derivatives with 1,3-bis[(1-uracilyl)methyl]benzene derivatives 1 obtained in turn by selective N-1 alkylation of 2,4-bis(trimethylsilyloxy)-pyrimidine with 1,3-bis(bromomethyl)benzene derivatives.12 X-ray, variable temperature 1H NMR and molecular modeling studies showed that these heterocalixarenes, depending on the nature of the substituents on position-2 of the 1,3-phenylene rings attained an inward flattened partial cone, a cone or other flexible structures.

The X-ray structure of 2g showed an inward flattened partial cone conformation where the OAc of the flattened ring faced the π cloud of the second phenylene ring and experienced a C-H…π interaction. In the 2:1 complex of 2j with ethanol, two crystallographically independent molecules in the unit cell revealed a cone conformation and were bound with ethanol in an unusual 3-centered H-bonding at H of OH and CH2 with the C4=O of uracil of one molecule and at O of OH with the C5-H of uracil of second molecule. The compound 2j also formed crystalline complexes with methanol and ethylene glycol, loss of which turned crystals to amorphous powders, indicating H- bonded engineering of these crystals.
In the $^1$H NMR spectrum of 2g, a bridged CH$_2$ showed two AB quartets and one OAc appeared upfield. Similar profiles of $^1$H NMR spectra revealed inward flattened partial cone conformations in solution for all 2 having OAc or OMe at C-2 of phenylene attached at N-1, N-1 of uracil. But 2a, 2c and 2j which have H or OH at this site and showed broad signals for -CH$_2$-, have flexible structures in solution. However, their variable temperature $^1$H NMR studies showed the existence of two or more conformers which equilibrate at room temperature.

Calix[n]arenes 4 and 5 marked for having two carbonyl bridges, one cyclic urea and three arenes or two arenes and one pyridine units have been conveniently synthesized by condensation of the respective cyclic ureas with trimeric precursor 3. The $^1$H NMR splitting patterns of methylene signals of these heterocalixarenes revealed their variable flexibility depending on the nature of the cyclic ureas and on moving from benzimidazolone to uracil to quinazolone, the rigidity of the respective calixarenes increased"}
Energy minimization of heterocalixarenes 6-8 showed that two imide carbonyls were directed inwards cavity and the third one was placed outside. But on complexation with an ammonium cation, all three carbonyl moieties were directed inwards and formed H-bonds with H$_3$N$^+$- and the complexes were stabilized by -30 to 50 kJ mol$^{-1}$ in comparison with the parent heterocalixarene. Both in liquid-liquid and liquid-solid extraction studies, these heterocalixarenes selectively extracted H$_3$N$^+$Bu$^+$ picrate over K$^+$ picrate and the compound 7 showed highest selectivity.\(^\text{14}\)

Uracil based macrocycles 11a-d were synthesized by cyclization of 9 and 10 by treatment with 1,2-dibromoalkane and potassium carbonate in DMSO under high dilution conditions.\(^\text{15a}\) X-ray analysis of 11c showed purine and the pyrimidine rings incline by dihedral angle of 50.4\(^\circ\) with each other. The bond lengths and bond angles of the planar two rings are about the same values as those of 6-methylthiopurine\(^\text{15b}\) and 1,3-dimethyluracil\(^\text{15c}\).

Cyclisation of 1,3-bis(\(\alpha\)-bromoalkyl)-5-bromouracil with \(p\)-methoxybenzylamine or sodium sulfide in PTC catalysed condensation resulted in formation of macrocycles 12-14 containing heteroatoms in bridges.\(^\text{16}\) During this synthesis, an unusual conversion of 5-bromouracil ring to hydantoin was observed. Macrocycle 12a with \(m\)-xylyl group was synthesized in 4% only with 8% of hydantoin macrocycle 13. Replacing \(m\)-xylyl to pentyl spacer resulted in macrocycle 12b (13%). Cyclisation in the presence of Na$_2$S led to macrocycles 14a-b. In their \(^1\)H NMR spectra, all protons of the CH$_2$ groups at N-1 and N-3 atoms were observed as four doublets or four broadened multiplets in $\delta$ 3.20-5.70 region attributed to folded conformation and exhibited slow conformational change on NMR time scale.
Reactions of dihalides 15 with Na₂S in DMF at 100-110 °C afforded a series of pyrimidinophanes 16a-d with various numbers of methylene groups or ethoxyethyl fragments.¹⁷ The synthetic approach has also been extended to 1,3-bis(5-bromopentyl)quinazoline-2,4-dione 17 resulting in formation of macrocycle 18. X-ray structure of 18 revealed that torsion angles in the decamethylene bridge of pyrimidinophane 18 deviate significantly from 180°, and thus the polymethylene chain ‘hangs over’ the quinazoline unit. Oxidation of macrocycles 18 with hydrogen peroxide afforded sulfoxide 20a or sulfone 20b depending on the reaction conditions. Isomeric pyrimidinophanes 19a and 19b with different mutual arrangements of carbonyl groups C(4)=O at pyrimidine units have been synthesized. Amination of the S atom in pyrimidinophane 16a utilizing O-
mesitylenesulfonylhydroxylamine in CH₂Cl₂ led to macrocyclic salt 21, which was decomposed back to initial sulfide 16a on an attempt to convert it into sulfimine. Although pyrimidinophanes with S atoms in bridges do not react with alkyl halides, macrocycles 22 and 23 were synthesized by reaction of pyrimidinophanes 16b,c and 18 with methyl and nonyl esters of p-toluene-sulfonic acid.

Reactions of 1,3-bis(bromopentyl)-5(6)-substituted uracils with different heterocycles like 2-mercapto-5-methyl-1,3,4-thiadiazole, 2,5-dimercapto-1,3,4-thiadiazole, 2-mercaptoimidazole, and 2-mercaptobenzimidazoles resulted in a series of acyclic compounds and isomeric heterocyclophanes.18 Macrocycles 24a and 24b were isolated as mixture and two isomers could not be separated. Dithiazole 25 was oxidized to heterocyphoane 26 using triethylamine as a base. The ratio of heterocycle/ NaH/dibromide 2:4:1 gave two regioisomers 27a,b in yields 5, and 3%, respectively with other acyclic products. Compound 28 was cyclized to 29 in 17% yield.

Regioisomers demonstrated distinct UV-Vis absorbance and a hypochromic effect with respect to model compounds.

The reactions of 1,3-bis(α,ω-bromoalkyl)-6-methyluracils with 1,3-bis(α,ω-ethylaminoalkyl)-6-methyluracils or 1,3-bis(bromopentyl)thymine with butylamine afforded
pyrimidinophanes 30-31 containing one or two uracil units and nitrogen atoms in bridging polymethylene chains. In some cases individual geometric isomers of pyrimidinophanes differing in the mutual arrangement of the carbonyl and methyl groups at different pyrimidine rings were isolated e.g. 30a and 30b, 31a and 31b. Similarly, the reaction of 1,3-bis(6-bromohexyl)-6-methyluracil (33) with 1,3-bis(6-ethylaminohexyl)-6-methyluracil (34) gave isomeric pyrimidinophanes 32a and 32b. Quaternization of the bridging nitrogen atom with o-nitrobenzyl bromide, benzyl bromide, n-decyl bromide gave water-soluble pyrimidinophanes 35, 36a, 36b, 37, 38 which were evaluated for their antibacterial and antifungal activity. The arrangement of the carbonyl groups

\[
\begin{align*}
30a: & \quad n = 4 \\
31a: & \quad n = 5 \\
32a: & \quad n = 6
\end{align*}
\]

in macrocycles did not affect their activity. The reaction of mixture of 32a and 32b with benzyl bromide or n-decyl bromide afforded the mixture of isomers 39a and 39b, 40a and 40b, respectively. Antibacterial and antifungal activity of pyrimidinophanes increased with the increase in polymethylene N(pyr)-N-chain length and dramatically increased upon the introduction of n-decyl substituent at nitrogen spacer. Pyrimidinophanes with 5 and 6 methylene spacers in N(pyr)-N-chain and n-decyl substituent showed bacteriostatic, fungistatic, bactericidal, fungicidal activity comparable with standard antibacterial and antifungal drugs.
Pyrimidinocyclophane 42, obtained by the reaction mixture of n-butylamine and 1,3-bis-(bromobromopentyl)thymine (41), on quaternization with n-decyl bromide gave macrocycle 43.

Trans-isomer 30b on reaction with paraformaldehyde under acidic conditions gave cryptand-like pyrimidinophane 44a with an intramolecular methylene spacer in almost quantitative yield. Similar reaction of cis isomer 30a with paraformaldehyde gave cryptand-like pyrimidinophane 44b (42%) with the intramolecular methylene spacer, and pyrimidinophane 45 (52%) with intermolecular methylene spacers. For steric reasons, the mutual orientation of the uracil moieties in macrocycle 45 appears to be with an anti arrangement of the C4=O groups. Bis (3,6-dimethyluracil) derivative 46 underwent cyclization into pyrimidinophane 47 in 18% yield under these conditions.
1,3-Dipolar cycloaddition reaction of diazide 48 with diyne 49 afforded heterocyclophane 50. Reaction of α,ω-bis(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)alkanes with paraformaldehyde gave pyrimidinophanes 51a-d which contain four 3,6-dimethyluracil fragments, connected to each other by the methylene chains. The X-ray data revealed that the intermolecular π-π contacts between the 3,6-dimethyluracil fragments in the crystals of these compounds. Intramolecular stacking between the opposite uracil rings was observed for the macrocycles with trimethylene and hexamethylene chains, whereas there was no such interactions in pyrimidinophanes with tetramethylene chains.

2.1.2 Uracil based cyclic molecular architects with metal ions as bridges

Uracil based ‘Pt Blues’, cis-[(en)PtCl(UH-N1)] formed from (en)PtCl₂ and uracil (UH2), on reaction with aqueous silver nitrate gave [(en)Pt(UH-N1)H₂O]⁺ which tetramerized to cyclic complex [(en)Pt(UH-N1,N3)]₄⁺ (52) and crystallized as its nitrate salt. Though similar Pt²⁺, Pd²⁺ based cyclic products derived from the nucleobases guanine and theophylline were already reported, a clear-cut analogy of such a self-assembled chemical entity with a classical calixarene was drawn by Lippert for the first time. He assigned these systems the nomenclature ‘metallacalixarenes’. This contribution has focused attention and visibility on this category of organo-inorganic hybrid receptor systems in which the metal-binding endocyclic sites are invariably nitrogen atoms preferably meta oriented. The
tetranuclear product 52 in its X-ray structure depicts a 1,3-alternating arrangement in which oppositely placed uracil pairs have identical orientation with their O(2) groups on the same side. The hydrogen bonds between O(2)–O(4) of adjacent uracil units impart stability to this arrangement. In its crystals, tetranuclear cations are stacked producing a long channel and nitrate anions connect the cations via H-bonds involving NH2 of (en). In solution, 53 through rotation around a Pt–N bond by the uracil moiety through the annulus, achieves cone conformation 53 (1H NMR, X-ray). This phenomenon is influenced both by the pH and the presence of additional metal ions (Figure 3). In aqueous NaOH at pH 8, 53 forms its freely water-soluble alkali adduct 54 which on heating at 40 °C is partially (66%) converted to cone conformation 55. This equilibrium is dependent on the nature of the base employed.

**Figure 3** Effect of pH on conformational changes between 52 and 53.

Using Mg(OD)2, 100% conversion to cone conformer 55 is observed. The adduct 55 on acidification affords 53 (cone conformation of 52) where its four C(2)–OH units act as proton donors and acceptors as in classical calixarenes. Despite its four-fold positive charge, metallacalixarenes 52 and 53 exhibit high basicity of the exocyclic O and react with metal cations in various stoichiometries depending on the nature of the metal ion and the original conformation of the metallacalixarene. 1,3-Alternate conformer 52 coordinates to four additional divalent metal ions to give octanuclear complexes28. The X-ray structures of these complexes show that the 1,3-alternate conformation of 52 is retained in the octanuclear
complexes. In each one of these complexes, the uracil ring binds with four metal centers and carries Pt\(^{2+}\) at N(1), N(3) and M at O(2), O(4) of two adjacent dianionic moieties. The uracil rings at opposite side are not exactly parallel. The spatial disposition of the four heterometals in the molecular box is 1,3-alternate, with a displacement of \(\sim 1.9\)\(\AA\) from the plane defined by the four platinum centers. Similarly, 1,3-alternate conformer 52 with cis-Pt\(^{II}\)(NH\(_3\))\(_2\) and (en)Pt\(^{2+}\) salts undergoes deprotonation of UH moieties to form \([(\text{en})\text{PtU}(\text{en})]/(\text{NH}_3)_2]\(^{4+}\)\(_2\) which in the presence of an excess of NaCl or NaCN lose Pt units bound to O(4) and O(2). Despite the high thermodynamic stability of free [Pt(CN)]\(^{4-}\), the platinum units bound to N(1) and (N3) are not dissociated. In the presence of excess AgNO\(_3\), 52 forms an octanuclear complex \([(\text{en})\text{Pt(UH)Ag}]/(\text{NO}_3)_8 - 4\text{H}_2\text{O}\), which from its partially resolved X-ray structure has been assigned a pinched cone conformation where four AgI centers bind to the uracil O(2) donor atoms of the four uracil monoanions. On addition of NaCl, all four AgI dissociate to give 53. However, the cone conformer of \([(\text{en})\text{Pt(UH-N1,N3)}]/(\text{NO}_3)_3\)\(^{4+}\), i.e. 53, on addition of one equivalent of Zn\(^{2+}\), Be\(^{2+}\), or La\(^{3+}\) salts undergoes deprotonation from four uracil units to form \([(\text{en})\text{PtU}/\text{ZnSO}_4)](56a), \([(\text{en})\text{PtU}/\text{Be}]^{2+}\) (56b) and \([(\text{en})\text{PtU}/\text{La}/(\text{NO}_3)_3\) (57) (Figure 4).\(^{29}\)\(^{1}\)H NMR and ESIMS show that in the case of complexes 56a and 56b, the two exocyclic O atoms of the two base constituents are bridged by metal and the other two O are H-bonded via a coordinated water molecule thus stabilizing the cone conformation. In the case of 57, the tetradendate binding of La\(^{3+}\) to a cone conformer with nitrate anion binding at the exo side of the La\(^{3+}\) has been suggested by \(^{1}\)H NMR and mass spectral data.\(^{29}\) Metallacalixarenes 53 and 56 having a cone conformation are capable of binding with RSO\(^{-}\)\(^{3-}\) (R = aliphatic or aromatic) anions in water. These associations arise due to a cooperative effect between well-structured hydrophobic cavities and electrostatic interactions between positively charged cavities and the anionic guest.\(^{29}\) In 57, coordination of La\(^{3+}\) to the cone causes flattening of the cavity incapacitating it for guest inclusion. All complexes with 1,3-alternate conformations and Pt\(_4\)Ag\(_4\) complex having a pinched cone conformation, despite their high positive charge do not incorporate anions because of the narrowness of the inner cavity. In unique distinction from classical calix[4]arene which is isolated in a cone conformation, the uracil–Pt based metallacalixarene 52 is isolated in a 1,3-alternate conformation and has a high affinity for metal ions despite its positively charged nature. Its cone conformer 53 as well as its further derived positively charged complexes 56 bind anions also.\(^{29}\) The host–anion complexation is maximized when the stability of the metalated species is optimized. Thus 56a shows maximum interactions with anions at pH \(\sim 7.4\) and remains
stable between pH 3 and 8 and 56b shows anion complexation only at pH 5, a pH range in which 56b is stable. The cis-platin analog [(dpk)PtCl₂], prepared by treating 2,2u-dipyridylketone (dpk) with K₂PtCl₄, on reaction with AgNO₃ and subsequently with uracil or thymine gave pentanuclear Pt²⁺ complexes [(dpk)₂(dpkOH₂)₂Pt₅(U)₃](BF₄)(NO₃)₃-8H₂O, [(dpk)₂(dpkOH₂)₃Pt₅(U)₃](PF₆)(NO₃)₃,9H₂O, and [(dpk)₂(dpkOH₂)₃Pt₅(T)₃](ClO₄)₂(NO₃)₂.8H₂O. Here, the three dianionic nucleobases are bridged through three Pt²⁺(2), Pt²⁺(3), and Pt²⁺(5) centers chelated to (dpkOH₂) to form the trinuclear calix[3]arene segment. The other two Pt²⁺ centers are coordinated to the oxygen atoms of nucleobases, the other potential metal-binding sites. Pt²⁺(4) is bound through O(2) oxygens of nucleobases and Pt²⁺(1) is bound through O(4) oxygens of nucleobases. As a result, one nucleobase coordinates to four Pt²⁺ centers utilizing all N- and O- donor atoms and two other nucleobases coordinate to three Pt²⁺ centers.

**Figure 4** Schematic presentation of cone conformers of (a) 56 and (b) 57.

The modified nucleobase H₂L₁, generated in situ from 2-thiouracil-4-aldehyde and diethylene triamine, undergoes self-assembly with cobalt⁴⁺ trifluoromethane sulfonate to form a tetrameric species [Co(L₁)]₄(⁴⁺)(CF₃SO₃)₄ .8H₂O. In this complex four nitrogen atoms including the N(1) of uracil are coordinated to one cobalt whereas the other uracil N(3) and S are bound to an adjacent Co³⁺. The cyclic tetramer constitutes a highly extended form of metallacalixarene where the uracil nitrogen atoms are linked through Co³⁺. It elaborates a columnar cavity at its centre with adjacent Co–Co separation of 5.54 Å.

Uracil-based ditopic donor building block 58 self-assembled, following deprotonation of the two N3 positions, with square-planar cis-Pt⁴⁺L₂ entities to produce open “molecular boxes” (59, 60) which represent hybrids between classical organic calix[4]arenes and metallacalix[4]arenes. Cis-Pt⁴⁺(PPh₃)₂ and Pt⁴⁺(2,2’-bpy) (with PPh₃ = triphenylphosphine and
2,2′-bpy = 2,2′-bipyridine). 59 represents a cycle, consisting of two cis-Pt(PPPh₃)₂ moieties and two dianions of 58, with their N₃ sites deprotonated and binding to the Pt atoms with the four uracil rings adopting a 1,3alternate conformation. The two Pt atoms and the two C atoms of the methylene bridges are co-planar. The uracil rings are almost perpendicular to this plane (79.3(2)° and 78.9(2)°). A unique feature of mettallacalix[n]arenes containing bridging pyrimidine nucleobases is their propensity to use the exocyclic groups as metal binding sites, thereby producing higher nuclear clusters. This feature was observed on reaction of 58 with [Pt(2,2′-bpy)(H₂O)₂]²⁺ in water resulting in formation of (59). Each Pt is simultaneously bonded to a deprotonated N₃ position of 58 and to a O₄ site. As in 59, the uracil moieties retain the transoid orientation of the N(1)CH₃ groups and the overall 1,3alternate conformation of the uracil rings. The main structural difference between 59 and 60 is that the calixarene core in 60 is more extended as compared to 59. So, depending on the steric requirements of the co-ligands L at the Pt⁺⁺, two (59) or four (60) metal entities can be accommodated, leading to neutral (59) or cationic (60) complexes.

The pyrimidine nucleobase cytosine (H₂C) (61) is structurally closely related to uracil and also forms “mettallacalix[n]arenes” when treated with square-planar cis₃M⁺⁺ entities (M = Pt, Pd; a = NH₃ or a₂ = diamine). The number of possible linkage isomers for a given n and the number of possible rotamers can be substantially reduced if a “directed” approach is pursued. This principle has been demonstrated33 by allowing cis-[Pt(NH₃)₂(H₂C-N₃)₂]²⁺ (62) to react with (en)Pd⁺⁺ to give cycles of (N₁,N₃Pt⁺⁺N₃,N₁Pd⁺⁺)ₓ (with x = 2 or 3).

Treatment of cis-[Pt(NH₃)₂(HC-N₁)₂] (63; HC = monoanion of cytosine) with (bpy)Pd⁺⁺ (bpy = 2,2′-bipyridine) gave Pt₂Pd₂ cycle cis-{[Pt (NH₃)₂(N₁-HC-N₃)₂Pd (bpy)]₂}⁻(NO₃)₄·13H₂O (64) with the coordination sites34 of the metals inverted; hence, platinum is bonded to N₁ and palladium is bonded to N₃ sites. The addition of (bpy)Pd⁺⁺ to 64 led to the
formation of Pd₄Pt₂ complex (66) in which the exocyclic N4H₂ groups of the cytosine ligands have undergone deprotonation and chelate four more (bpy)Pd⁺ entities through the O₂ and N4H sites. With a large excess of (bpy)Pd⁺ over 64 (4:1), cis-(NH₃)₂Pt⁺ is eventually substituted by (bpy)Pd⁺ to give the Pd₈ complex. The linkage isomer of 64, cis-[(Pt(NH₃)₂-(N3-HC-)₂Pd (bpy))₂] (NO₃)₄·9H₂O (65), has been structurally characterized. The acid/base properties of cis-[(Pt(NH₃)₂-(H₂C-N1)₂] (63) have been determined and compared with those of the corresponding N3 isomer. The complexation of AgCl by 63 is also reported. It binds Ag⁺ through its available N3 site resulting in the formation of a coordination polymer. The two cytosine bases are attached to Ag⁺ in a roughly linear coordination and display a mutually oriented gauche-like conformation (dihedral angle between two cytosine rings was 81.58°).
2.1.3 References


149

CHAPTER 2 – Section 2.2


2.2.1 Introduction

To understand complex modes of recognition of biological receptors, investigations on structurally simpler models of receptors is an area of contemporary research.\textsuperscript{1,2} Heterocycles due to their diverse array of electron densities available on the heteroatoms and electron-rich / deficient nature of the heterocyclic ring provide unlimited opportunities for their interactions with wide variety of guests. Amongst heterocycles, pyrimidine-2,4(1H,3H)-diones (uracil, thymine etc.) are the most versatile for creating supramolecular architectures both in living systems\textsuperscript{3} and synthetic models.\textsuperscript{4} The H-bonding interactions in the Watson–Crick model\textsuperscript{3} provide the basis of double/multiple strand DNA and the metal ion interactions of phosphate groups stabilize these strands. The metal ion-π interactions of the heterocyclic rings and charge-electron interactions with the heteroatoms of nucleic bases lead to the stabilization of single strands and stimulate their catalytic processes.\textsuperscript{5,6} Advances in X-ray structure resolutions have provided further an insight into the nucleic base–metal ion interactions.

Structurally, uracil is a small molecule with number of functional moieties built in viz. enaminone (N1-C6=C5-C4=O), amide, vinylogous amide (C6=C5-C4=O-N3), urea (N1-C2=O-N3) etc. The resonating structures i-iii (Figure 1) of uracil suggest increased electron density on C4=O due to contribution of electron density from amide, vinylogous amide and enaminone moiety and specifying the scope of its interactions with metal ions, whereas other contributing structures iv and v create enhanced electron density on C2=O (urea oxygen).

Localised complexation of alkali metal ions by DNA / RNA apart from their function as counter ion for the charge neutralization of nucleic acids plays an important role in the stabilization of multistranded nucleic acid structures and substructures. Theoretical calculations of charge density distribution in nucleobases\textsuperscript{7} as well as electrostatic potentials\textsuperscript{8}
in the unsubstituted bases have suggested O(2), O(4) of these bases to be intrinsic metal ion binding sites. According to *ab initio* computation, Na\(^+\) binding to neutral uracil is expected to take place via both O(2) and O4 oxygen atoms.\(^9\) The X-ray crystal structure analysis of mono and dinucleotides containing uracil/thymine bases reveals that alkali metal ions directly interact with O2 oxygen atoms.\(^10\) The O4 site usually is involved in H-bonding with complementary base pair. Metal ion binding to the O4 position of the neutral pyrimidine-2,4-dione was first observed in two adducts of HgCl\(_2\) with uracil and 5,6-dihydrouracil.\(^11\) Later this binding pattern was proven to be relevant for a series of main group and transition metal compounds of N1 blocked model nucleobases.\(^12\) Metal coordination to deprotonated N3 position leaves residual basicity at the exocyclic oxygen atoms, notably O4, established through vibrational spectroscopy and potentiometry.\(^13\) As a consequence, the exocyclic oxygen atoms in metal – N3 coordinated complexes become generally better donors than in unmetalated neutral base. In year 2009, Lippert\(^14\) reported the utilization of only C4=O (not C2=O) and N3 atoms of uracil to form hybrids between calixarenes and metallacalixarenes. The molecular structure of this hybrid metallacalixarene acquired 1,3-alternate conformation (Figure 2).

**Figure 2** Molecular structure of hybrid calixarene with three phenyl groups attached to phosphorous atom omitted for clarity (reproduced from Dalton Trans. 2009, 9120).

The exclusive metal coordination to nucleobase sites such as exocyclic oxygen atoms of thymine (T-O4) or uracil (U-O4) base and extensive hydrogen bonding between the M aqua cations and bases is responsible for the stabilization of multistranded nucleic acid structures. The feasible model of Na\(^+\) binding to the thymine which is relevant with respect to thymine quartets in nucleic acids has been represented in Figure 3. This model represents the role of
O2 and O4 in coordination of Na⁺ resulting in favourable orientation of the N1 alkyl groups, one of the basic requirements for the existence of quartet structures.\textsuperscript{15}

The X-ray structure determination of an adduct [Na(1-MeUH)\textsubscript{4}] [AuCl\textsubscript{4}] (Figure 4) isolated from 1-methyluracil and Na[AuCl\textsubscript{4}] reveals the existence of almost planar (dihedral angle 5.3° between upper and lower rings) uracil quartet found in RNA tetraplex. The four 1-MeUH rings are bound via their exocyclic O4 oxygens to a single centrosymmetric Na⁺ within atomic distance being 2.336(7) Å (upper rings) and 2.301(8) Å (lower rings).\textsuperscript{16} There is a 14.6° angle between the NaO(4)\textsubscript{4} and AuCl\textsubscript{4} planes.

The structures of the 2:1 complexes of uracil : mercuric chloride, and dihydrouracil (a minor base of tRNA): mercuric chloride as determined by X-ray data illustrated that mercury atoms are held by chlorine bridges with the octahedral coordination completed by the oxygen atoms, O(4) of inversion-related bases\textsuperscript{11}. Dendritic macromolecules consisting of polynucleobases are capable of complexation with metal ion through heteroatoms of the nucleobases. Poly nucleobase consisting of uracil units (LuU-Obn) with the number of nucleobase layers 2-4 has been synthesized. The compound in Figure 5 has been found to form 1:1 complex with La\textsuperscript{3+}. The decrease in integral area of free C4=O band at 1665 cm\textsuperscript{-1} points towards predominant involvement of C4=O in complexation. This is possibly due to the high coordination ability of C4=O oxygen due to the presence of conjugated double bond.\textsuperscript{17}
Pyrimidine nucleic bases through metal ion complexation and intramolecular hydrogen bonding result in the building of diverse self assembled supramolecular architectures. A cyclic tetranuclear, nucleobase complex of (en)PtI18, [(en)Pt(UH-N3N3)].4(NO3)4 (Figure 6i)18, a metal analogue of calix[4]arene displays close similarity to calix[4]arene as far as overall geometry and conformational behaviour is concerned.19 It adopts 1,3-alternate conformation in solid state, which on deprotonation in solution adopts a cone conformation assigned on the basis of X-ray structure.

![Figure 6](image-url)

The replacement of metal ion coordination by covalent bonds results in supramolecular structures placing subheterocyclic urea oxygen towards the cavity (Figure 6ii and 6iii). We have earlier reported20 uracil based heterocalix[4/6]arenes where only half of aryl rings of the calix[4/6]arenes are replaced by the uracil moiety and other half are constituted by the m-phenylene rings. Here, C-2 oxygen constitutes the lower rim of the calixarene and is directed towards the cavity whereas C-4 carbonyl oxygen remains on the periphery. Heterocalix[6]arene 4 selectively extracted23 H3N+Bu' picrate over K+ picrate, both in liquid-liquid and liquid-solid extraction studies.

2.2.2 Present Design

In the present research work, we planned to synthesize calix[4]uracil derivatives with all the C4=O groups placed in one direction thereby making the four carbonyl groups to cooperatively bind with the metal ions. These C4=O atoms are expected to provide desirable electron rich character to bind with the electron deficient or positively charged species. Similar type of metallacalix[4]uracil21 with two Pt metals bridging between the N-3 nitrogen atoms of two methylene bis uracil derivatives is known. (Figure 2)

In order to have insight into the three dimensional structure of calix[4]uracil, its structure was optimized (Figure 7) using DFT approach at B3LYP/6-31G level of calculations using

![Figure 7 B3LYP/6-31G optimized structure of calix[4]uracil with all N1 substituted by methyl group.](image)

have a distance of 7Å between two arene rings, which is reduced to 6.0-6.2 Å units in case of calix[2]uracil[2]arene due to shorter N-C distances in comparison with C-C distances. The DFT - B3LYP/6-31G optimized structure of calix[4]uracil (Figure 7) shows that cavity is square with each side having a dimension between 5.0-5.2 Å. Therefore, as expected, calix[4]uracils are significantly smaller in size than the conventional calix[4]arenes.

The following synthetic strategy was planned to synthesize calix[4]uracil derivatives (Figure 8). Calix[4]uracil could be synthesized by cycloalkylation of 5,5′-methylenebis[1-alkyl-2,4(1H,3H)]pyrimidinedione (A) with 5,5′-methylenebis[3-bromomethyl-1-alkyl-2,4(1H,3H)]-pyrimidinedione (B). In turn, 5,5′-methylenebis[1-alkyl-2,4(1H,3H)] pyrimidinedione (A) could be synthesized by condensation of 1-alkyluracil with formaldehyde and (B) could be synthesized by bromomethylation of A with paraformaldehyde. 1-Alkyluracils (1-alkylpyrimidine-2,4(1H,3H)-diones) could be easily synthesized from the commercially available uracil. The details of the synthesis of these calix[4]uracils have been discussed here.
2.2.3 Synthesis of 1-alkyl-pyrimidine-2,4-diones (3) and their reactions with aldehydes

Pyrimidine-2,4(1H,3H)-dione (uracil) (1) on stirring with hexamethyldisilazane (HMDS) and chlorotrimethyl silane at 120 °C gave 2,4-bis(trimethylsiloxy)pyrimidine (2). On refluxing 2 with benzyl chloride in 1,2-dichloroethane using iodine as catalyst gave 1-benzyl-2,4(1H,3H)-pyrimidinedione (3a) (Scheme 1), 87%, m.p. 160 °C (Lit. m.p. 167 °C\textsuperscript{24a}, 179-180 °C\textsuperscript{24b}, 173-174 °C\textsuperscript{24c}), FAB Mass m/z 203 (M\textsuperscript+ +1). Its \textsuperscript{1}H NMR spectrum shows a 2H singlet at δ 4.94 (2H, NCH\textsubscript{2}), two 1H doublets at δ 5.74 (H-5) and 7.12 (H-6) along with the aromatic protons between δ 7.31-7.42 (5H, ArH) and exchangeable NH at δ 9.01. In its \textsuperscript{13}C NMR spectrum, the presence of nine signals confirms the presence of nine magnetically non-equivalent carbon atoms in this molecule. These spectral data corroborate the structure 3a for this compound. Similarly, 2 on refluxing with different alkyl halides viz. hexyl, octyl, dodecyl, octadecyl halides gave respective 1-alkylpyrimidine-2,4(1H,3H)-diones 3b-3e (Scheme 1). All these compounds have been characterized by \textsuperscript{1}H, \textsuperscript{13}C NMR and mass spectral data.
1-Benzyl-2,4(1H,3H)-pyrimidinedione 3a on heating with paraformaldehyde (0.5 eq) in HBr-acetic acid (33%) in an oil bath at 120 °C and usual work-up and crystallization from acetonitrile gave 4a (75%), m.p. 260 °C, FAB mass m/z 416 (M⁺) (Scheme 2). In its ¹H NMR spectrum, the presence of two 2H singlet at δ 3.29 and δ 7.88, respectively due to the methylene group and uracil 6-H shows the connectivity of the methylene carbon with two uracil moieties at C-5. These data along with ¹³C NMR spectrum and elemental analysis corroborate the structure 4a for this compound. Similarly, 1-alkyluracils 3b-3e on reaction with paraformaldehyde in HBr-acetic acid (33%) gave 5,5’-methylenebis[1-(alkyl)pyrimidine-2,4(1H,3H)-diones 4b-4e.

![Scheme 2](image)

The presence of a substituent on one of the methylene carbon atom of the calix[4]uracils will lead to unsymmetrical calix[4]uracil derivatives. So, 5,5’-methylene(µ-aryl)bis[1-(hexyl) pyrimidine-2,4(1H,3H)-dione] derivatives were synthesized by the reactions of 1-alkyluracil derivatives with aromatic aldehydes. The reaction of 3b with naphthalene-2-carboxaldehyde (4) gave 5a (70%), m.p. 255 °C, FAB mass M⁺/m/z 531 (M⁺+1) (Scheme 3). The presence of a 4H triplet at δ 3.66 due to N₁-CH₂, two 1H singlet at δ 5.31 due to bridged CH and at δ 7.61 due to H-1 of naphthalene ring along with other aromatic signals in ¹H NMR spectrum confirms the structure 5a. These data along with ¹³C NMR, mass and elemental analysis corroborates the structure 5a for this compound.

Similarly, the reaction of 3b with naphthalene-1-carboxaldehyde gave 5b (70%), m.p. 255 °C, FAB mass M⁺/m/z 531 (M⁺+1). The presence of a 4H multiplet at δ 3.58 due to N₁-CH₂, a 1H singlet at δ 5.85 due to bridged CH along with other aliphatic and aromatic signals confirmed the formation of 5b. Similar reactions of 3b with 4-nitrobenzaldehyde and 3-nitrobenzaldehyde gave respective 5,5’-Methylene(µ-aryl)bis[1-(hexyl) pyrimidine-2,4(1H,3H)-dione derivatives 5c-5d (Scheme 3). ¹H NMR spectrum of 5c showed a 4H triplet at δ 3.69 due to N₁-CH₂ and a 1H singlet at δ 5.23 due to methine proton, two 2H doublets at
δ 7.40 and 8.14 and a 2H singlet at δ 7.20 due to uracil 6-H and confirm the formation of 5c. In $^1$H NMR spectrum of 5d, the presence of methine CH at 5.23, two signals at 7.29 (2H) and 8.07 (1H) due to uracil-6H and m-nitrophenyl group, respectively are the characteristic signals supporting the formation of 5d.

Scheme 3

5,5′-Methylenebis[1-benzylpyrimidine-2,4(1H,3H)-dione] (4a) on heating with excess of (CH$_2$O)$_n$ in HBr-acetic acid (33%) in an oil bath at 90 °C gave 6a (Scheme 4), (89%), white solid, m.p. 132 °C, FAB mass M$^+$ m/z 600, 602, 604 (1:2:1). The presence of two 4H singlets at δ 4.92 (N$_1$-CH$_2$) and 5.69 (N$_3$-CH$_2$) and two 2H singlets at δ 3.27 (5,5′-methylene) and 7.51 (uracil 6-H) along with 10 ArH in its $^1$H NMR spectrum shows that both N-3 nitrogen atoms of 4a have been bromomethylated under these reaction conditions. In its $^{13}$C NMR spectrum, the presence of one additional carbon signal due to CH$_2$ carbon in addition to signals of 4a, also corroborate the structure 5a for this compound. Similarly, the reactions of 5,5′-methylenebis[1-alkyl pyrimidine-2,4(1H,3H)-diones (4b-4e) with (CH$_2$O)$_n$ in HBr-acetic acid gave respective 5,5′-methylenebis[3-bromomethyl-1-alkylpyrimidine-2,4(1H,3H)-diones] 5b-5e in 70-85% yield.

For 4 and 6: a R = -C$_2$H$_5$; b R = -(CH$_2$)$_2$CH$_3$; c R = -(CH$_2$)$_3$CH$_3$; d R = -(CH$_2$)$_4$CH$_3$; e R = -(CH$_3$)$_3$CH$_3$
2.2.4 Synthesis of calix[4]uracil derivatives

The cycloalkylation of 5,5'-methylenbis[1-(phenylmethyl)pyrimidine-2,4(1H,3H)-dione] (4a) with 5,5'-methylenbis[3-bromomethyl-1-(phenylmethyl)pyrimidine-2,4(1H,3H)-dione] (6a) under phase transfer catalytic conditions (CH₃CN-K₂CO₃-TBAHSO₄) provided crude mixture which on column chromatography gave pure 7a (Scheme 5), (20%), white solid, m.p. 90 °C (acetonitrile), HRMS calcd. for C₄₈H₄₀N₈O₈ 856.2969, found 856.2711. Its ¹H NMR spectrum shows the presence of two 4H sharp singlets at δ 3.02 due to C₅-CH₂ and at δ 6.15 due to N₃-CH₂, an 8H broad signal at δ 4.92 due to N₁-CH₂ protons along with a 24H multiplet between δ 7.31- 7.42 due to the aromatic protons. The presence of two 4H singlet

![Figure 9. Effect of variable temperature on ¹H NMR spectrum of 7a (CDCl₃).](image-url)
each at δ 3.02 and δ 6.15 due to C₅-CH₂ and N₃-CH₂ protons along with other signals points to the formation calix[4]uracil 7a. Its ¹³C NMR spectrum shows the presence of three signals in aliphatic region and eight signals in the aromatic region and corroborates the structure 7a for this molecule. In order to evaluate the reason for broadening of N1-CH₂ signal, ¹H NMR spectrum of 7a was recorded at variable temperature between +20°C and -50°C (Figure 9).

In variable temperature ¹H NMR experiment on 7a, on lowering the temperature to 10 °C, the broad signal at δ 4.92 underwent further broadening and its integration was decreased to 3H protons only. This lowering of temperature did not affect the integration or shape of the N₃-CH₂ or C₅-CH₂ signals. On further lowering the temperature to -10°C, the signal was almost completely vanished. At temperature -20 °C, two broad signals reappeared at δ 4.48 and δ 5.50 which were converted to two doublets on lowering the temperature to -50 °C. At this temperature, again the integration of these signals was equivalent to eight protons, as desired for the calix[4]uracil 7a (Figures 9 and 10).

![Figure 10 ¹H NMR spectrum of 7a (CDCl₃) showing depletion in integration of N1-CH₂ signal at -10 °C.](image)

It appears that at room temperature N₁-CH₂ protons form hydrogen bond with C=O group and thus the rotation around N₁-CH₂ bond does not remain completely free. At low temperature (-50 °C), this rotation around N₁-CH₂ bond is restricted. One of the protons of N₁-CH₂ group forms H-bond with C2=O oxygen atom and other proton remains free. So, the
two magnetically non-equivalent protons couple with each other to give AB doublets at δ 4.48 and δ 5.50. Therefore rotation of benzyl group is restricted at lower temperatures, which splits the CH2 signal to two doublets. This conformational mobility at RT and locking at lower temperature is reversible as the broad signal at δ 4.92 reappeared on increasing the temperature to 20 °C. Probably, the rotation around N-3 CH2 and C-5 CH2 bonds in the periphery of the calix[4]uracil remains free even at -50 °C.

The cycloalkylation of 5,5’-methylenebis[1-(hexyl) pyrimidine-2,4(1H,3H)-dione] (4b) with 5,5’-methylenebis[3-bromomethyl-1-(hexyl) pyrimidine-2,4(1H,3H)-dione] (6b) under phase transfer catalytic conditions (CH3CN-K2CO3-TBAHSO4) provided crude mixture which on column chromatography gave pure 7b (Scheme 6), (18%), white solid, m.p. 90 °C, HRMS calcd. for C44H64N8O6Na: 855.4745, found 855.4739. Its 1H NMR spectrum (at 20°C) shows the presence of a 12H triplet at δ 0.9 due to –CH3 protons of hexyl chain, two broad signals at δ 1.28 and δ 1.64 due to CH2 protons of the chain, three 4H singlets each at δ 3.05 due to C5-CH2, at δ 6.07 due to N3-CH2 and at δ 7.19 due to uracil 6-H along with a 8H broad singlet at δ 3.69 due to N1-CH2 protons. The spectral data along with 12 signals in its 13C NMR spectrum confirm the formation of calix[4]uracil 7b.

![Scheme 6](image)

In variable temperature 1H NMR experiment of 7b (Figure 11), on lowering the temperature to 10 °C, the signal at δ 3.65 was further broadened and started dividing into two broad signals at 0 °C. At -30 °C, it was converted to two broad signals at δ 3.49 and δ 3.90 with integration of 4 protons each. On further lowering the temperature to -40 °C and -50 °C, each of these broad signals split into two multiplets. During lowering of temperature, the CH2 proton signals at δ 1.6 also started converted into two parts around 0 °C but as the temperature was lowered this new signal moved downfield up to δ1.8 but its contribution was
Figure 11. Effect of temperature on $^1$H NMR spectrum of 7b (CDCl$_3$).

decreased. However, unlike 7a where the integration of N$_1$-CH$_2$ protons was decreased on lowering the temperature up to 0 °C and then it reappeared, in case of 7b the integration of N$_1$-CH$_2$ protons was not affected by the temperature.

Similarly, the cycloalkylation of 5,5’-methylenebis[1-(octyl)-2,4(1H,3H)-pyrimidinedione] (4c) with 5,5’-methylenebis[3-bromomethyl-1-octyl]-2,4(1H,3H)-pyrimidinedione] (6c) gave 7c (Figure 12), (20%), MS calcd. for C$_{52}$H$_{80}$N$_8$O$_8$: 944.61 found 944.96. Its $^1$H NMR spectrum (at 20 °C) the N1-CH$_2$ (8H) protons appeared as broad singlet whereas other
protons appeared in multiplicities as expected for those protons. On lowering the temperature to -50 °C, this broad signal was converted to two multiplets at δ 3.51 and δ 3.92 with integration of 4H each (Figure 13).

Figure 13. Effect of temperature on $^1$H NMR spectrum of 7c (CDCl$_3$).

Figure 14. Effect of temperature on $^1$H NMR spectrum of 7d (CDCl$_3$).
Similarly, calix[4]uracil 7d was obtained in 20% yield, MS calcd. for C_{68}H_{112}N_{8}O_{8}: 1168.86, found 1168.07, by cycloalkylation of (4d) with (6d) (Figure 12). The presence of the desired aliphatic and aromatic signals in ¹H NMR and ¹³C NMR spectra confirmed the structure of 7d. The ¹H NMR spectrum of 7d also showed N1-CH₂ protons as broad signal at δ 3.69 which on lowering the temperature to -50 °C (Figure 14) was converted into two broad signals at δ 3.52 and 3.88. Additionally, some signals appeared at δ 4.73 which may be due to the presence of water only.

![Figure 15](image)

**Figure 15.** Effect of temperature on ¹H NMR spectrum of 7e (CDCl₃).

Calix[4]uracil 7e (Figure 15) with 18 carbon chain at N-1 position was synthesized by cycloalkylation of 4e with 6e. The presence of the desired aliphatic and aromatic signals in ¹H NMR and ¹³C NMR spectra confirmed the structure of compound 7e. In ¹H NMR (at 20 °C) spectrum of 7e, N1-CH₂ protons appeared as a 8H multiplet at δ 3.72, three 4H signals each appeared at δ 3.29 (C5-CH₂), δ 5.72 (N3-CH₂) and δ 7.43 (uracil-6H) (Figure 15) along with other aliphatic signals corresponding to 7e. On gradually lowering temperature from 20 °C to -50 °C, the N1-CH₂ signal which normally in case of 7a - 7d was split into two signals becomes broad but does not split but the singlets at δ 7.43 due to uracil 6-H and at δ 4.87 split into two signals each. Also, on lowering the temperature to -20 °C a broad signal appeared at
δ 5.13 which vanished as the temperature was further lowered to -50 °C. These could be assigned to unbound water molecules present in the solution. Also a broad 2H signal at δ 8.30 underwent gradual downfield shift on lowering the temperature and was finally shifted to δ 9.14 at -50 °C. This could be attributed to bound water molecule whose binding strength is increased on lowering the temperature and appears more downfield.

To study the effect of substituents present on the rim of the calix[4]uracil on conformational behaviour of the respective calix[4]uracil, we have synthesized unsymmetric calix[4]uracils 7f-7i. The cycloalkylation of 5,5’-(naphthalen-2-ylmethylene)bis[1-(hexyl)-2,4(1H,3H)-pyrimidinedione (5a) with 5,5’-methylenebis[3-bromomethyl-1-hexyl]-2,4(1H,3H)-pyrimidinedione (6b) under phase transfer catalytic conditions (CH₃CN-K₂CO₃-TBAHSO₄) gave 7f (Scheme 7), (20%), m.p. 180 °C, HRMS calcd. for C₅₄H₇₀N₈O₈ 958.5317, C₅₄H₇₀N₈O₈+Na: 981.5214, found 981.5209. The presence of a 2H doublet at δ 3.11 due to C5-CH₂, two broad signals between δ 3.4-3.8 due to N1-CH₂, a 1H singlet at δ 5.07 due to C5-CH, a 4H singlet at δ 6.15 due to N3-CH₂, two singlets at δ 7.22 and δ 7.57 due to 4H (uracil 6-H) and 1H (naphthalene 1-H), respectively along with signals due to hexyl chains and naphthalene moiety in its ¹H NMR spectrum and the presence of 23 signals in ¹³C NMR spectrum confirmed the formation of calix[4]uracil 7f. In variable temperature ¹H NMR experiment, two broad signals corresponding to N1-CH₂ protons were converted to at least five broad signals spread between δ 3.2 -4.2, on lowering the temperature to -50 °C. In this process, the singlet due to N3-CH₂ at δ 6.15 and at δ 7.22 due to uracil 6-H were split into two singlets and signals due to naphthalene rings also showed significant change in their chemical shifts. These results confirm that 7f attains number of conformations which are locked on decreasing the temperature.
Similarly, 5b on cycloalkylation with 6b gave calix[4]uracil 7g (Scheme 8) in 16% yield, m.p. 140 °C, HRMS calcd. for C_{54}H_{70}N_{8}O_{8}Na: 981.5214, found 981.5215. The ¹H NMR and ¹³C NMR spectral data confirmed the structure 7g for the compound. In its ¹H NMR spectrum at 20 °C (Figure 16) C5-CH₂ protons appeared as AB quartet at δ 3.12 and N1-CH₂ protons as broad signals between δ 3.60 – 3.95. On lowering the temperature to -50 °C, the singlet due to N3-CH₂ protons at δ 6.17 was split into two signals. The signals due to uracil 6-H at δ 7.23 and naphthalene protons between δ 7.36 - 7.45 and δ 7.59 - 7.83 remained unaffected by the temperature.

![Scheme 8](image)

**Figure 16.** Effect of temperature on ¹H NMR spectrum of 7g (CDCl₃).

Under same reaction conditions, 5c and 5d underwent cycloalkylation with 6b to give calix[4]uracils 7h and 7i (Scheme 9). In ¹H NMR spectrum of 7h, the presence of two 2H
doublets at δ 7.37 and 8.13 confirms the presence of p-nitrophenyl moiety and the appearance of bridged C5-CH as quartet at δ 3.10 shows the rigidity in the conformation of the structure. Other signals like C5-CH, uracil 6-H appeared as singlet at δ 4.93 and δ 7.21. These spectral data along with presence of 17 carbon signals in its 13C NMR spectrum confirm the structure 7h. In 1H NMR spectrum of 7i the presence of a triplet (δ 7.36), two doublets (δ 7.57 and δ 8.09) and a singlet at 7.97 due to one proton each confirm the presence of m-nitro phenyl ring and other signals due to calix[4]uracil confirm the formation of 7i.

Thus, calix[4]uracils due to bulk of the substituent at rim carbon show different conformational features as depicted by 1H NMR spectra of these compounds. However, 13C NMR spectra show discrete signals due to magnetically non-equivalent carbons. These results clearly define that the conformations in these molecules undergo fast inter-conversion.

2.2.5 Solid-Liquid extraction studies of calix[4]uracils.

In order to evaluate the metal recognition behaviour of these calix[4]uracils, the solid-liquid extraction25 of alkali and alkaline earth metal picrates using chloroform solution of calix[4]uracils 7a, 7b and 7f were performed. The extraction results (Table 1, Figure 17) show that 7a extracts Li+ picrate > 50 times more effectively than Na+, K+ and Mg2+ picrate but selectivity is lower against Ca2+, Sr2+ and Ba2+ picrates. The change in substituent at N-I in 7b does not affect the selectivity pattern. However, unsymmetric calix[4]uracil 7f probably due to its restricted conformations showed greater extraction of Li+ in comparison to symmetrical calix[4]uracils 7a and 7b. Also, 7f showed selective extraction of Ba2+ amongst alkaline earth metal ions.
Table 1. Extraction (%) of metal picrates by 7a, 7b and 7f.

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<th>Metal picrate</th>
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<th>7b</th>
<th>7f</th>
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<td>22.6</td>
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</table>

Figure 17. Graphical representation of % extraction of metal ions by 7a, 7b and 7f.

2.2.6 Geometry optimization of calix[4]uracil (7b) and its complexes with alkali metal ions

To have further insight into conformation of 7b and its mode of complexation towards alkali and alkaline earth metal ions, the geometry optimization of calix[4]uracil 7b and its complexes with alkali metal ions was performed using DFT method at B3LYP/6-31G level of calculations on Gaussian 09 programme. As earlier stated, geometry optimization of 7b shows that all the four C₄=O oxygen atoms can point to the lower rim and the N-1 alkyl substituents occupy upper rim positions (Figure 7). This conformation is conducive for its complexation with metal ions through four C-4 carbonyl oxygen atoms. The heat of formation of calix[4]uracil with Li⁺, Na⁺ and K⁺ shows that 7b preferably binds with Li⁺ over Na⁺ and K⁺ ions. These results are in consonance with order of extraction of metal picrates (Figure 18). (Table 2)
Figure 18. B3LYP/6-31G optimized structures of (a) 7b (b) 7b-Li⁺, (c) 7b-Na⁺ and (d) 7b-K⁺ complexes.

Table 2. Heat of formation of various complexes as determined using DFT calculation at B3LYP/6-31G level

<table>
<thead>
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<th>Compd.</th>
<th>Energy (kcal/mol) of complexes*</th>
<th>Energy (kcal/mol) (7b + M⁺) #</th>
<th>Heat of formation complex (kcal/mol)</th>
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<td>K⁺</td>
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* Determined for the complex  # calculated by addition of energy of 7b and metal ion
2.2.7 Metal templated synthesis of calix[4]uracils

The cycloalkylation of 5,5'-methylenebis[1-(alkyl)-2,4(1H,3H)-pyrimidinedione 4a-e with 5,5'-methylenebis[3-bromomethyl-1-alkyl)-2,4(1H,3H)-pyrimidinedione 6a-e in dry THF using LiH as base provided crude mixture which on column chromatography gave pure 7a-e, in 38-40% yields. In these reactions ~ 20% of unreacted 4a-e was also recovered. So, the presence of Li\(^{+}\) ions in the solution provided a template to form 7 in higher yields.

In conclusion, we have synthesized all uracil based calix[4]uracil derivatives. The presence of substituent at rim carbon has further diversified their structure. The variable temperature \(^1\)H NMR spectrum studies show that N1-CH\(_2\) proton shows interaction with C2=O oxygen atom in all the cases. The conformations of these calix[4]uracils are also affected by the length of the chain at N1 uracil moiety and substituent at the rim carbon. The extraction of metal picrates shows that these calix[4]uracil derivatives bind with Li\(^{+}\) preferentially over other alkali metal picrates. The use of Li\(^{+}\) as template increases the yield of these calix[4]uracils from 16-20% to 38-40%.

2.2.8 EXPERIMENTAL

GENERAL INFORMATION

All reagents were used as received. All reactions were performed by heating in an oil bath unless otherwise stated. TLC was performed on microslides pre-coated with silica gel ‘G’ containing calcium sulphate as binder or with silica gel HF-254, by dipping a pair of slides held back to back in slurry of adsorbent in chloroform – methanol (80:20). The plates were visualised by the UV fluorescence (\(\lambda_{\text{max}} = 254\) nm) and under I\(_2\) vapours. Proton magnetic resonance spectra (\(^1\)H NMR) and variable temperature \(^1\)H NMR spectra were recorded at 300 MHz. Carbon magnetic resonance spectra (\(^{13}\)C NMR) were performed at 75 MHz on JEOL AI using CDCl\(_3\) solution containing tetramethylsilane as an internal standard. Chemical shifts (\(\delta\)) are reported in parts per million (ppm), and are referenced to the residual solvent peak, which is generally deuterochloroform (\(^1\)H- \(\delta\) 7.26 and \(^{13}\)C- \(\delta\) 77.0 ppm), unless otherwise stated. The order of citation in parentheses is (1) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br s = broad singlet, vb = very broad, app = apparent), (2) coupling constant (\(J\)) quoted in Hertz, and (3) number of equivalent nuclei (by integration). Elemental analysis was performed on Flash EA-1112 series CHNS-O analyser.
instrument. Infrared (IR) spectra were recorded on FT-IR spectrometer using KBr as medium. Only significant absorptions ($\lambda_{\text{max}}$) are reported in wave numbers (cm$^{-1}$). HRMS were recorded on micro TOF-Q II using ESI as source type. Melting points were determined in open capillaries and are uncorrected.

**Synthesis of 3a-3e: General procedure**

A suspension of pyrimidine-2,4(1H,3H)-dione 1 (1.12 gm, 10 mmol) in hexamethyldisilazane (HMDS) (4.83 g, 25 mmol) and chlorotrimethyl silane (0.1 ml) was stirred at 120 °C. After the completion of silylation, excess HMDS was removed under vacuum and the reaction mixture was cooled to room temperature. Then 1,2-dichloroethane (20 ml), alkyl halide (15 mmol) and iodine (20 mg) (catalyst) were added and the reaction mixture was stirred at reflux temperature for 24 h. After the completion of the reaction (ttc), the reaction mixture was cooled and ethanol was added. The solid separated was filtered off and was re-crystallized from ethanol to get pure 3a-e.

1-(Phenylmethyl)-2,4(1H,3H)-pyrimidinedione (3a): white solid; 87%; mp 160 °C (CHCl$_3$);

![3a](image)

[found C, 65.00; H, 5.01; N, 13.76. C$_{11}$H$_{10}$N$_2$O$_2$ requires C, 65.34; H, 4.98; N, 13.85%; $\delta_H$ (300 MHz, CDCl$_3$+TFA): 4.94 (s, 2H, NCH$_2$), 5.72 (d, $J = 7.9$ Hz, 1H, C5-H), 7.17 (d, $J = 7.9$ Hz, 1H, C6-H), 7.31-7.42 (m, 5H, ArH); $\delta_C$ (75 MHz, CDCl$_3$+TFA): 52.30, 102.58, 128.16, 129.17, 129.37, 133.48, 146.04, 151.94, 166.19; FAB Mass m/z 203 (M$^+$+1).]

1-Hexyl-2,4(1H,3H)-pyrimidinedione (3b): white solid; 60%; mp 65 °C (CHCl$_3$);

![3b](image)

[found C, 60.96; H, 8.34; N, 14.12. C$_{10}$H$_{16}$N$_2$O$_2$ requires C, 61.20; H, 8.22; N, 14.27%; $\delta_H$ (300 MHz, CDCl$_3$): 0.89 (t, $J = 6.6$ Hz, 3H, CH$_3$), 1.32 (q, 8H, 4xCH$_2$), 3.71 (t, $J = 7.35$ Hz, 2H, NCH$_2$), 5.68 (d, $J = 7.8$ Hz, 1H, C5-H), 7.14 (d, $J = 7.8$ Hz, 1H, C6-H), 8.65 (s, 1H, NH); $\delta_C$ (75 MHz, CDCl$_3$): 13.8, 22.3, 26.0, 28.9, 31.2, 48.8, 102, 144.4, 150.9, 163.9; FAB mass M$^+$ m/z 198 (M$^+$).]

1-Octyl-2,4(1H,3H)-pyrimidinedione (3c): white solid; 75%; mp 60 °C (CHCl$_3$);

![3c](image)

[found C, 64.29; H, 8.84; N, 12.42. C$_{12}$H$_{20}$N$_2$O$_2$ requires C, 64.26; H, 8.99; N, 12.49%; $\delta_H$ (300 MHz, CDCl$_3$): 0.88 (t, $J = 6.9$ Hz, 3H, CH$_3$), 1.29 (br s, 12H, 6 x CH$_2$), 3.72 (t, $J = 7.5$ Hz, 2H, N1-CH$_2$), 5.71 (d, $J = 7.5$ Hz, 1H, C5-H), 7.15 (d, $J = 7.8$ Hz, 1H, C6-H), 9.28 (br s, 1H, NH, exchanges with D$_2$O);]
δC (75 MHz, CDCl3): 14.01, 22.52, 26.33, 28.96, 29.03, 31.62, 48.84, 101.98, 144.54, 151.00, 164.29.

1-Dodecyl-2,4(1H,3H)-pyrimidinedione (3d): white solid; 80%; mp 75 °C (CHCl3);

[found C, 68.21; H, 9.98; N, 9.96. C16H20N2O2 requires C, 68.53; H, 10.06; N, 9.99%]; δH (300 MHz, CDCl3): 0.88 (t, J = 6.6 Hz, 3H, CH3), 1.29 (br s, 20H, 10 x CH2), 3.71 (t, J = 7.5 Hz, 2H, N1-CH2), 5.69 (d, J = 7.8 Hz, 1H, C5-H), 7.14 (d, J = 7.8 Hz, 1H, C6-H), 8.72 (br s, 1H, NH, exchanges with D2O);

δC (75 MHz, CDCl3): 14.06, 22.60, 26.33, 28.9, 29.08, 29.25, 29.35, 29.44, 29.52, 31.82, 48.89, 101.99, 144.51, 150.79, 163.91.

1-Octadecyl-2,4(1H,3H)-pyrimidinedione (3e): white solid; 85%; mp 80 °C (CHCl3);

[found C, 72.32; H, 11.00; N, 7.66. C22H40N2O2 requires C, 72.48; H, 11.06; N, 7.68%]; δH (300 MHz, CDCl3): 0.88 (t, J = 7.2 Hz, 3H, CH3), 1.30 (br s, 32H, 16 x CH2), 3.71 (t, J = 7.5 Hz, 2H, N1-CH2), 5.70 (d, J = 7.8 Hz, 1H, C5-H), 7.15 (d, J = 7.8 Hz, 1H, C6- H); δC (75 MHz, CDCl3): 14.06, 22.60, 26.33, 28.97, 29.08, 29.25, 29.35, 29.44, 29.52, 31.82, 48.89, 101.99, 144.51, 150.79, 163.91.

**Synthesis of 4a-4e**: General procedure

The suspension of 1-alkyl-2,4-(1H,3H)-pyrimidinedione 3 (10 mmol) and paraformaldehyde (150 mg, 5 mmol) in HBr- acetic acid (33%) (12 ml) was stirred in an oil bath at 120 °C for 12 h. After completion of the reaction (tlc), the reaction mixture was cooled to room temperature and was then poured in to crushed ice. The solid separated was filtered off, washed with water and was crystallized from CH3CN to get pure 4. Similarly, reactions of 3b with aryl aldehydes viz. naphthalene-2-carboxaldehyde, naphthalene-1-carboxaldehyde, p-nitrobenzaldehyde and m-nitrobenzaldehyde gave respective 5a-d.

5,5′-Methylenebis[1-(phenylmethyl)-2,4(1H,3H)-pyrimidinedione (4a): white solid; 75%; mp 260 °C (CH3CN); [found C, 66.36; H, 5.04; N, 13.20. C23H26N4O4 requires C, 66.34; H, 4.84; N, 13.45 %]; δH (300 MHz, CDCl3+TFA): 3.29 (s, 2H, CH2), 4.94 (s, 4H, 2 x CH2), 7.24-7.36 (m, 10H, 2 x 5 ArH), 7.88 (s, 2H, 2 x uracil C6-H); δC (75 MHz, CDCl3 + TFA): 23.3, 56.3, 110.4, 127.3, 127.8, 128.4, 136.3, 142.3, 150.8, 163.7; HRMS calcd. for C23H26N4O4 416.1485, found 417.2527 (M+1).
5,5’-Methylenbis[1-(hexyl)-2,4(1H,3H) pyrimidinedione (4b): white solid; 80%; mp 225
°C (CH₃CN); [found C, 62.43; H, 7.94; N, 13.87. C₂₁H₃₂N₄O₄ requires C, 62.35; H, 7.97; N, 13.85%]; δH (300 MHz, CDCl₃): 0.89(t, J = 6.5 Hz, 6H, 2 x CH₃), 1.31 (bs, 12H, 6 x CH₂), 1.64 (s, 4H, 2 x CH₂), 3.26 (s, 2H, CH₂), 3.69 (t, J = 7.4 Hz, 4H, 2 x NCH₂), 7.42 (s, 2H, 2 x uracil-6-H), 8.36 (br s, 2 x NH, exchanges with D₂O); δC (75 MHz, CDCl₃): 13.9, 22.4, 23.6, 26.0, 29.0, 31.2, 48.8, 110.4, 143.2, 150.5, 163.8; FAB MS m/z 405 (M⁺+1).

5,5’-Methylenbis[1-(octyl)-2,4(1H,3H)pyrimidinedione (4c): white solid; 80%; mp 205
°C (CH₃CN); [found C, 65.23; H, 8.83; N, 12.37. C₂₃H₄₀N₄O₄ requires C, 65.19; H, 8.75; N, 12.16%]; δH (300 MHz, CDCl₃): 0.88(t, J = 6.6 Hz, 6H, 2 x CH₃), 1.28 (s, 20H, 10 x CH₂), 1.68 (s, 4H, 2 x CH₂), 3.27 (s, 2H, CH₂), 3.69 (t, J = 7.4 Hz, 4H, 2 x NCH₂), 7.43 (s, 2H, 2 x uracil-6-H), 8.78 (br s, 2H, 2 x NH, exchanges with D₂O); δC (75 MHz, CDCl₃): 14.1, 22.6, 23.6, 26.4, 29.1, 31.7, 48.8, 110.4, 143.3, 150.7, 164.3; HRMS calcd. for C₂₅H₄₂N₄O₄: 460.3050, found 461.4396.

5,5’-Methylenbis[1-(dodecyl)-2,4(1H,3H)pyrimidinedione (4d) white solid; 80%;
mp 182 °C (CH₃CN); [found C, 68.89; H, 9.67; N, 11.2. C₃₃H₆₀N₄O₄ requires C, 69.19; H, 9.85; N, 9.78%]; δH (300 MHz, CDCl₃): 0.88(t, J = 6.6 Hz, 6H, 2 x CH₃), 1.26 (bs, 36H, 18 x CH₂), 1.61 (bs, 4H, 2 x CH₂), 3.27 (s, 2H, CH₂), 3.69 (t, J = 7.5 Hz, 4H, 2 x NCH₂), 7.42 (s, 2H, 2 x uracil-6-H), 8.34 (br s, 2H, 2 x NH, exchanges with D₂O); δC (75 MHz, CDCl₃): 14.1, 22.7, 23.7, 26.4, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 48.8, 110.4, 143.3, 150.6, 164.0; MS calcd. for C₃₃H₆₀N₄O₄ 572.43; found 595.58 (M⁺+Na).

5,5’-Methylenbis[1-(octadecyl)-2,4(1H,3H)pyrimidinedione (4e): white solid; 80%;
mp 175 °C (CH₃CN); [found C, 72.82; H, 10.80; N, 8.01. C₄₅H₇₈N₄O₄ requires C, 72.93; H, 10.88; N, 7.56%]; δH (300 MHz, CDCl₃): 0.88(t, J = 6.6 Hz, 6H, 2 x CH₃), 1.25 (s, 60H, 30 x CH₂), 1.65 (s, 4H, 2 x CH₂), 3.27 (s, 2H, CH₂), 3.69 (t, J = 7.5 Hz, 4H, 2 x NCH₂), 7.42 (s, 2H, 2 x uracil-6-H), 8.31 (br s, 2 x NH, exchanges with D₂O); δC (75 MHz, CDCl₃): 14.1, 22.7, 26.4, 29.1, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 48.9, 110.4, 143.3, 150.5, 163.8.
5,5'-Methylene (2-naphthyl) bis[1-(hexyl)-2,4(1H,3H) pyrimidinedione (5a) :

white solid; 70%; m.p. 255 °C; [found C, 70.14; H, 7.24; N, 10.55. 
$C_{31}H_{38}N_4O_4$ requires C, 70.16; H, 7.22; N, 10.56%]; $\delta_H$ (300 MHz, 
CDCl$_3$): 0.85 (t, $J = 6.6$ Hz, 6H, 2 x CH$_3$), 1.25 (s, 12H, 6 x CH$_2$), 
1.60 (s, 4H, 2 x CH$_2$), 3.66 (t, $J = 8.3$ Hz, 4H, 2 x NCH$_2$), 5.31 (s, 
1H, CH), 7.12 (s, 2H, 2 x ArH), 7.31 (d, $J = 7.8$ Hz, 1H, ArH), 7.47 – 7.50 (m, 2H, 2 x ArH), 
7.61 (s, 1H, ArH), 7.76 - 7.84 (m, 3H, 3 x ArH), 8.34 (br s, 2H, 2 x NH); $\delta_C$ (75 MHz, 
CDCl$_3$): 13.9, 22.4, 25.9, 28.9, 31.2, 41.1, 49.0, 113.1, 126.1, 126.2, 126.3, 126.5, 127.5, 
127.8, 128.5, 132.4, 133.2, 136.3, 144.7, 150.4, 163.2; FAB mass M$^+$ m/z 531 (M$^+$+1).

5,5'-Methylene (1-naphthyl) bis[1-(hexyl)-2,4(1H,3H)-pyrimidinedione (5b) :

white solid; 70%; m.p. 255 °C; [found C, 70.32; H, 7.22; N, 10.55. 
$C_{31}H_{38}N_4O_4$ requires C, 70.16; H, 7.22; N, 10.56 %]; $\delta_H$ (300 MHz, 
CDCl$_3$): 0.83 (m, 6H, 2 x CH$_3$), 1.15 (s, 12H, 6 x CH$_2$), 1.63 (s, 4H, 2 
 x CH$_2$), 3.58 (q, $J = 6.6$ Hz, 4H, 2 x NCH$_2$), 5.85 (s, 1H, CH), 6.86 (s, 
2H, 2 x ArH), 7.28 -7.33 (m, 1H, ArH), 7.41 -7.51 (m, 3H, 3 x ArH), 7.77-7.89 (m, 3H, 3 x 
ArH), 8.37 (br s, 2 x NH); $\delta_C$ (75 MHz, CDCl$_3$): 13.9, 22.3, 25.7, 28.7, 31.1, 37.7, 48.9, 
112.9, 123.6, 125.0, 125.5, 125.9, 126.7, 128.3, 128.9, 130.6, 134.1, 134.8, 144.4, 150.4, 
162.8; FAB mass M$^+$ m/z 531 (M$^+$+1).

5,5'-Methylene (4-nitro) bis[1-(hexyl)-2,4(1H,3H) pyrimidinedione (5c) :

white solid; 70%; m.p. 240 °C; [found C, 61.66; H, 6.74; N, 13.00. 
$C_{27}H_{33}N_5O_6$ requires C, 61.70; H, 6.71; N, 13.32 %]; $\delta_H$ (300 MHz, 
CDCl$_3$): 0.87 (t, $J = 6.6$ Hz, 6H, 2 x CH$_3$), 1.27 (s, 12H, 6 x CH$_2$), 1.63 
(t, 4H, 2 x CH$_2$), 3.69 (t, $J = 7.2$ Hz, 4H, 2 x NCH$_2$), 5.23 (s, 1H, CH), 
7.20 (s, 2H, 2 x ArH), 7.40 (d, $J = 8.4$ Hz, 2H, ArH), 8.14 (d, $J = 6.9$ Hz, 2H, ArH), 10.65 (br 
s, 2H, 2 x NH, exchanges with D$_2$O); $\delta_C$ (75 MHz, CDCl$_3$): 13.9, 22.5, 26.0, 29.0, 31.2, 40.9, 
49.2, 111.9, 123.8, 128.7, 145.1, 146.9, 147.0, 150.3, 163.1; FAB mass M$^+$ m/z 526 (M$^+$+1).
5,5’-Methylene (3-nitro) bis[1-(hexyl)-2,4(1H,3H) pyrimidinedione (5d):

White solid; 70%; m.p. 220 °C; [found C, 60.70; H, 6.73; N, 13.30. C_{27}H_{35}N_{5}O_{6} requires C, 61.70; H, 6.71; N, 13.32%]; δH (300 MHz, CDCl₃): 0.87 (t, J = 6.6 Hz, 6H, 2 x CH₃), 1.25 (s, 12H, 6 x CH₂), 1.59 (s, 4H, 2 x CH₂), 3.71 (t, J = 6 Hz, 4H, 2 x NCH₂), 5.23 (s, 1H, CH), 7.29 (s, 2H, 2 x ArH), 7.48 - 7.57 (m, 2H, ArH), 8.07 (s, 1H, ArH), 8.13 (d, J = 7.8 Hz, 1H, ArH), 8.58 (br s, 2H, 2 x NH, exchanges with D₂O); δC (75 MHz, CDCl₃): 13.9, 22.4, 26.0, 28.9, 31.2, 40.6, 49.2, 111.8, 122.1, 122.6, 129.5, 134.0, 141.5, 145.0, 148.3, 150.1, 162.9; FAB mass M⁺ m/z 525 (M⁺).

Synthesis of 6a-6e: General procedure

A suspension of 4 (5 mmol) and paraformaldehyde (900 mg, 30 mmol) in HBr- acetic acid (33%) (12 ml) was stirred at 120 °C for 6-8 h. The reaction mixture was cooled to room temperature and was then poured in to crushed ice. The solid formed was filtered off and was washed with water. The crude sample was recrystallized from acetonitrile to obtain pure 6.

5,5’-Methylenebis[3-bromomethyl-1-phenylmethyl]-2,4(1H,3H)-pyrimidinedione (6a):

white solid; 89%; mp 132 °C (CHCl₃); δH (300 MHz, CDCl₃): 3.27 (s, 2H, CH₂), 4.92 (s, 4H, 2 x N1CH₃), 5.69 (s, 4H, 2 x N3CH₂), 7.31 – 7.41 (m, 10H, ArH), 7.52 (s, 2H, 2 x ArH); δC (75 MHz, CDCl₃): 25.1, 36.0, 52.7, 109.6, 128.0, 128.6, 129.1, 134.8, 141.8, 149.8, 161.6.

5,5’-Methylenebis[3-bromomethyl-1-hexyl]-2,4(1H,3H)-pyrimidinedione (6b):

white solid; 70%; mp 110 °C (CHCl₃); δH (300 MHz, CDCl₃): 0.89 (t, J = 6 Hz, 6H, 2 x CH₃), 1.32 (s, 16H, 2 x 4CH₂), 3.32 (s, 2H, CH₂), 3.75 (t, J = 7.35 Hz, 4H, 2 x N1CH₂), 5.70 (s, 4H, 2 x N3CH₂), 7.45 (s, 2H, 2 x ArH); δC (75 MHz, CDCl₃): 13.9, 22.4, 25.1, 26.0, 28.8, 31.2, 35.9, 49.9, 109.3, 142.2, 149.6, 161.8.

175
5,5’-Methylenebis[3-bromomethyl-1-octyl]-2,4(1H,3H)-pyrimidinedione (6c): White solid; 80%; mp 90 °C (CHCl₃); δH (300 MHz, CDCl₃): 0.88 (t, J = 6.9 Hz, 6H, 2 x CH₃), 1.28 (br s, 24H, 12 x CH₂), 3.32 (s, 2H, CH₂), 3.76 (t, J = 7.20 Hz, 4H, 2 x N1CH₂), 5.70 (s, 4H, 2 x N3CH₂), 7.46 (s, 2H, 2 x ArH); δC (75 MHz, CDCl₃): 14.0, 22.6, 25.1, 26.4, 27.0, 27.6, 29.1, 31.7, 41.6, 49.7, 109.9, 140.9, 151.1, 163.4.

5,5’-Methylenebis[3-bromomethyl-1-dodecyl]-2,4(1H,3H)-pyrimidinedione (6d): White solid; 80%; mp 90 °C (CHCl₃); δH (300 MHz, CDCl₃): 0.88 (t, J = 6.6 Hz, 6H, 2 x CH₃), 1.26 (br s, 36H, 18 x CH₂), 1.66 (s, 4H, 2 x CH₂), 3.32 (s, 2H, CH₂), 3.75 (t, J = 7.20 Hz, 4H, 2 x N1CH₂), 5.70 (s, 4H, 2 x N3CH₂), 7.45 (s, 2H, 2 x ArH); δC (75 MHz, CDCl₃): 14.1, 22.7, 25.1, 26.4, 28.9, 29.1, 29.3, 29.4, 29.5, 29.6, 31.9, 36.0, 50.0, 109.3, 142.2, 149.7, 161.8.

5,5’-Methylenebis[3-bromomethyl-1-octadecy]-2,4(1H,3H)-pyrimidinedione (6e): White solid; 70%; mp 110 °C (CHCl₃); δH (300 MHz, CDCl₃): 0.88 (t, J = 6.6 Hz, 6H, 2 x CH₃), 1.25 (s, 56H, 28 x CH₂), 1.62 (s, 4H, 2 x CH₂), 3.32 (s, 2H, CH₂), 3.73 (t, J = 6.9 Hz, 4H, 2 x N1CH₂), 5.70 (s, 4H, 2 x N3CH₂), 7.46 (s, 2H, 2 x ArH); δC (75 MHz, CDCl₃): 14.1, 22.7, 26.4, 28.9, 29.1, 29.3, 29.4, 29.5, 29.7, 31.9, 36.0, 50.0, 109.3, 142.2, 149.6, 161.8.

Synthesis of calix[4]uracils 7a-7i: General procedure

To the solution of 4 (3.0 mmol) in dry CH₃CN (400 ml) were added K₂CO₃ (0.829 g, 6.0 mmol), 6 (3 mmol) and TBAHSO₄ (0.03 mmol) (catalyst). The reaction mixture was stirred at 80 °C for 24 h. The suspended solid was filtered off and was washed with acetonitrile. The combined filtrate was distilled off and residue was purified by silica gel (100-200 mesh) column chromatography using hexane – CHCl₃ mixtures as eluents to isolate pure 7.
**Calix[4]uracil (7a)**: White solid; 20%; mp 90 °C (CHCl₃); δ_H (300 MHz, CDCl₃): 3.02 (s, 4H, 2 x C₅-CH₂), 4.92 (bs, 8H, 4 x N1-CH₂), 6.15 (s, 4H, 2 x N₃-CH₂), 7.31 - 7.42 (m, 24H, ArH); δ_C (75 MHz, CDCl₃): 27.6, 48.1, 52.2, 109.2, 128.0, 128.3, 129.0, 135.6, 141.6, 151.5, 161.7; HRMS calcd. for C₄₈H₆₁N₈O₈: 856.2969, found 856.2711.

**Calix[4]uracil (7b)**: White solid; 18%; mp 265 °C (CHCl₃); δ_H (300 MHz, CDCl₃): 0.9 (t, J = 6.9 Hz, 12H, 4 x CH₃), 1.28 (br s, 24H, 12CH₂), 1.64 (br s, 8H, 4 x CH₂), 3.05 (s, 4H, 2 x C₅-CH₂), 3.69 (br s, 8H, 4 x N1-CH₂), 6.07 (s, 4H, 2 x N₃-CH₂), 7.19 (s, 4H, uracil 6-H); δ_C (75 MHz, CDCl₃): 13.9, 22.5, 26.2, 27.4, 29.0, 31.3, 47.7, 49.7, 108.4, 142.0, 151.1, 161.8; HRMS calcd. for C₄₈H₆₁N₈O₈: 832.4847, C₄₈H₆₁N₈O₈⁺ Na⁺: 855.4745, found 855.4739.

**Calix[4]uracil (7c)**: White solid; 18%; mp 280 °C (CHCl₃); δ_H (300 MHz, CDCl₃): 0.89 (t, J = 6.8 Hz, 12H, 4 x CH₃), 1.29 (m, 28H, 14CH₂), 1.64 (m, 8H, 4 x CH₂), 1.77 (br s, 12H, 6 x CH₂), 3.05 (s, 4H, 2 x C₅-CH₂), 3.70 (bs, 8H, 4 x N1-CH₂), 6.07 (s, 4H, 2 x N₃-CH₂), 7.19 (s, 4H, uracil 6-H); δ_C (75 MHz, CDCl₃): 14.0, 22.5, 26.5, 27.1, 29.0, 29.1, 29.2, 31.7, 49.9, 108.6, 142.4, 151.1, 162.0; MS calcd. for C₅₂H₇₄N₈O₈: 944.6099, found 944.9614.

**Calix[4]uracil (7d)**: White solid; 20%; mp 120 °C (CHCl₃); δ_H (300 MHz, CDCl₃): 0.87 (t, J = 6.5 Hz, 12H, 4 x CH₃), 1.26 (br s, 72 H, 36 x CH₂), 1.58 (br s, 8H, 4CH₂), 3.05 (s, 4H, 2 x C₅-CH₂), 3.69 (br s, 8H, 4 x N1-CH₂), 6.07 (s, 4H, 2 x N₃-CH₂), 7.19 (s, 4H, uracil 6-H); δ_C (75 MHz, CDCl₃): 14.1, 22.7, 26.6, 29.1, 29.2, 29.3, 29.6, 31.9, 49.7, 108.5, 142.1, 151.1, 161.8; MS calcd. for C₆₈H₁₁₂N₈O₈: 1168.8603, found 1168.0762.
**Calix[4]uracil (7e)**: White solid; 20%; mp 85 °C (CHCl₃); δ_H (300 MHz, CDCl₃): 0.88 (t, J = 6.3 Hz, 12H, 4 x CH₃), 1.25 (br s, 120H, 60 x CH₂), 1.61 (br s, 8H, 4 x CH₂), 3.29 (s, 4H, 2 x C₅-CH₂), 3.71 (q, J = 8.6 Hz, 8H, 4 x N1-CH₂), 5.72 (s, 4H, 2 x N3-CH₂), 7.43 (s, 4H, uracil-6-H); δ_C (75 MHz, CDCl₃): 14.1, 22.6, 24.4, 26.4, 28.9, 29.1, 29.3, 29.4, 29.5, 29.6, 31.9, 48.8, 49.9, 109.5, 142.2, 149.8, 161.9.

**Calix[4]uracil (7f)**: white solid; 20%; mp 180 °C (CHCl₃); δ_H (300 MHz, CDCl₃): 0.85 (s, 12H, 4 x CH₃), 1.28 (m, 24H, 12CH₂), 1.58 (br s, 8H, 4 x CH₂), 3.11 (q, 2H, C₅-CH₂), 3.68 (br s, 8H, 4 x N1-CH₂), 5.07 (s, 1H, C₅CH), 6.15 (s, 4H, 2 x N3-CH₂), 7.22 (s, 4H, ArH), 7.46 (m, 2H, ArH). δ_C (75 MHz, CDCl₃): 13.9, 22.5, 26.1, 27.5, 28.9, 31.2, 42.9, 47.8, 49.8, 108.4, 126.0, 126.2, 126.6, 127.2, 127.4, 128.0, 128.2, 132.2, 133.2, 134.4, 136.2, 151.1, 161.9; HRMS calcd. for C₅₄H₇₀N₈O₆: 958.5317, C₅₄H₇₀N₈O₆ +Na⁺: 981.5214, found 981.5209.

**Calix[4]uracil (7g)**: white solid; 16%; mp 140 °C (CHCl₃); δ_H (300 MHz, CDCl₃): 0.89 (s, 12H, 4 x CH₃), 1.29 (br s, 24H, 12 x CH₂), 1.62 (br s, 8H, 4 x CH₂), 3.12 (m, 2H, C₅-CH₂), 3.60 (br s, 8H, 4 x N1-CH₂), 5.55 (s, 1H, C₅CH), 6.17 (s, 4H, 2 x N3-CH₂), 7.23 (s, 4H, ArH), 7.36 - 7.45 (m, 4H, ArH), 7.59 - 7.83 (m, 3H, ArH); δ_C (75 MHz, CDCl₃): 13.9, 22.5, 26.1, 27.6, 29.0, 31.2, 40.0, 47.9, 49.7, 123.8, 125.6, 126.5, 127.0, 128.0, 128.8, 130.2, 133.8, 134.4, 159.6, 161.8; HRMS calcd. for C₅₄H₇₀N₈O₆: 958.5317, C₅₄H₇₀N₈O₆ +Na⁺: 981.5214, found 981.5215.

**Calix[4]uracil (7h)**: white solid; 20%; mp 197 °C (CHCl₃); δ_H (300 MHz, CDCl₃): 0.87 (s, 12H, 4 x CH₃), 1.29 (br s, 24H, 12CH₂), 1.60 (br s, 8H, 4CH₂), 3.10 (q, 2H, C₅-CH₂), 3.60 (br s, 8H, 4 x N1-CH₂), 4.93 (s, 1H, C₅CH), 6.12 (s, 4H, 2 x N3-CH₂), 7.21 (s, 4H, ArH), 7.37 (d, J = 8.7 Hz, 2H, ArH), 8.13 (d, J = 8.7 Hz, 2H, ArH); δ_C (75 MHz, CDCl₃): 13.9, 22.5, 26.1, 28.9, 31.2, 43.2, 47.8, 49.7, 50, 108.5, 123.7, 129.6, 144.0, 146.8, 146.9, 151.0, 161.8; HRMS calcd. for C₅₀H₆₇N₉O₁₀: 953.5011, C₅₀H₆₇N₉O₁₀ +Na⁺: 976.4909, found 976.4910.
Calix[4]uracil (7i): white solid; 20%; mp 155 °C (CHCl₃); δH (300 MHz, CDCl₃): 0.86 (s, 12H, 4 x CH₃), 1.30 (br s, 24H, 12 x CH₂), 1.61 (br s, 8H, 4 x CH₂), 3.11 (q, 2H, C₅-C₂H), 3.71 (bs, 8H, 4 x N1-CH₂), 4.97 (s, 1H, C₅H), 6.13 (s, 4H, 2 x N3-CH₂), 7.22 (s, 4H, ArH), 7.36 (t, J = 8 Hz, 1H, ArH), 7.57 (d, J = 8 Hz, 1H, ArH), 7.97 (s, 1H, ArH), 8.09 (d, J = 8 Hz, 1H, ArH); δC (75 MHz, CDCl₃): 13.9, 22.5, 26.2, 28.9, 31.3, 33.9, 47.8, 49.7, 50.0, 108.5, 123.3, 129.6, 134.7, 141.1, 143.9, 148.3, 151.0, 161.8; HRMS calcd. for C₅₀H₇₇N₉O₁₀: 953.5011, C₅₀H₇₇N₉O₁₀+Na⁺: 976.4909, found 976.4911.

Synthesis of calix[4]uracil 7a-e using lithium cation as template: To the suspension of LiH (0.047 g, 6.0 mmol) in dry THF (400 ml), the solution of 4a (1.21 g, 3.0 mmol) (THF 50 ml) was added under N₂ and reaction mixture was stirred for 1h. Then solution of 6a (1.81 g, 3 mmol) was added and reaction mixture was allowed to stir at 70 °C for 24 h. The suspended solid was filtered off and was washed with THF (10 ml). The combined filtrate was distilled off and the residue was purified by silica gel (100 - 200 mesh) column chromatography using hexane - CHCl₃ mixtures as eluents to isolate pure 7a in 38% yield. Similar reactions of 4b-4e with respective 6b-6d gave respective calix[4]uracils 7b-7e in 38-42% amounts.

Extraction studies

The solid metal picrate²⁵ (1 eq.) was added to a chloroform solution (2 ml) of calix[4]uracil 7 (1 mM) and was shaken in centrifugal tube for 5 min and was allowed to equilibrate for 2h. The mixtures were then centrifuged. An aliquot (1 ml) from chloroform layer was diluted to 10 ml with acetonitrile. UV absorption was measured against CHCl₃-CH₃CN solution (1:9) at 374 nm and % extraction was calculated using earlier reported epsilon values. In case of barium picrate, chloroform from aliquot was removed and residue was diluted to 10 ml using distilled water and absorbance of this solution was recorded at 355 nm.
Table 3. Extinction coefficients (ε) of metal picrates in CH$_3$CN and H$_2$O.

<table>
<thead>
<tr>
<th>Metal picrate</th>
<th>Extinction coefficient (ε) in CH$<em>3$CN at $\lambda</em>{\text{max}}$ 374 nm</th>
<th>Extinction coefficient (ε) in H$<em>2$O at $\lambda</em>{\text{max}}$ 355 nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li$^+$</td>
<td>18600</td>
<td>15500</td>
</tr>
<tr>
<td>Na$^+$</td>
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<td>15200</td>
</tr>
<tr>
<td>K$^+$</td>
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<td>15000</td>
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<tr>
<td>Mg$^{2+}$</td>
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</tr>
<tr>
<td>Ca$^{2+}$</td>
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<tr>
<td>Ba$^{2+}$</td>
<td>-----</td>
<td>27000</td>
</tr>
<tr>
<td>Sr$^{2+}$</td>
<td>29500</td>
<td>27300</td>
</tr>
</tbody>
</table>

Theoretical studies

The geometry optimizations for the ground states of calix[4]uracils and their metal complexes were performed, using density functional theory (DFT) at the B3LYP/6-31G level of theory using Gaussian 09 programme.