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Cyclic Molecules of Uracil Bridged with Carbon Atoms

Dr. Kuljit Kaur

Post graduate Department of Chemistry, Khalsa College, Amritsar, Punjab, India

ABSTRACT

This review article provides information about the use of Uracil to synthesize various cyclic architects which bridges through carbon atoms.

Keywords: Uracil, macrocycle, pyrimidine-2,4-dione

I. INTRODUCTION

The mirroring of biological processes is 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.[1,2] Nucleic acids play an important role in determining the nature and functions of organisms and in controlling various metabolic and biosynthetic processes. Uracil is one of the four constituents of nucleic acid - RNA.

DNA is store house of genetic information and RNA is carrier of information relating to biosynthetic processes. The genetic information in DNA is not only stored in the sequence of nucleic bases but is also stored in the form of helix structure. This helical conformation is imposed by anionic phosphodiester moieties and the fairly rigid sugar units through steric and electrostatic effects. In this duplex / triplex formation, the C2=O, N3-H and C4=O of pyrimidine bases by and large participate in hydrogen bonding interactions thus are mainly responsible for the stabilization of tertiary structures.

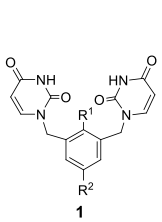
The uracil – the pyrimidine-2,4-dione is chemically pliable molecule. The facile deprotonation at nitrogen atoms provides numerous possibilities for alkylation and also these deprotonated species can coordinate with metal ions to provide numerous acyclic and cyclic structures. The present article discusses the cyclic molecules of uracil with bridged carbon atoms.

II. CYCLIC MOLECULES OF URACIL

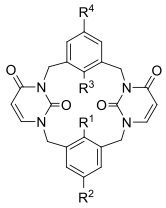
Tetrameric calix[2]uracil[2]arenes **2**, having similar or different substitution profiles in both arenes, were obtained by PTC catalysed condensations of 1,3-bis(bromomethyl) benzene derivatives with 1,3-bis[(1-uracilyl)methyl]benzene derivatives **1** obtained in turn by selective N-1 alkylation of 2,4-bis(trimethylsilyloxy)-pyrimidine with 1,3-bis(bromomethyl)benzene derivatives.[3] X-ray, variable temperature ^{1}H 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 CH_2 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.



1

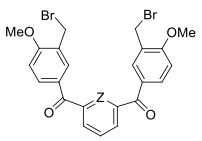


2

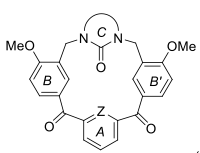
	R^1	R^2	R^3	R^4
(a)	H	H	H	H
(b)	OMe	Me	H	H
(c)	H	H	OMe	Me
(d)	OMe	Me	OMe	Me
(e)	OMe	Me	OAc	Me
(f)	OAc	Me	OMe	Me
(g)	OAc	Me	OAc	Me
(h)	OAc	t-Bu	OAc	t-Bu
(i)	OAc	H	OAc	H
(j)	OH	Me	OH	Me
(k)	OH	Me	OH	NO_2

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 attatched 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.

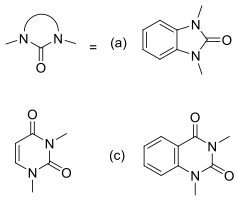
Calix[n]arenes **4** and **5** marked for having two carbonyl bridges, one cyclic urea and three arenes or two arenes and one pyridine units have been conveniently synthesized by condensation of the respective cyclic ureas with trimeric precursor **3.** The ^{1}H NMR splitting patterns of methylene signals 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[4].

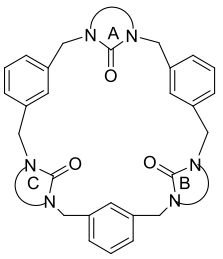


3; Z = CH or N



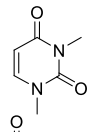
4; Z = CH
5; Z = N



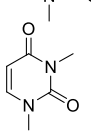


6-8

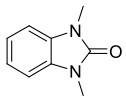
6; A, B, C =



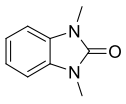
7; A, B =



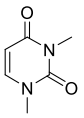
C =



8; A, B =

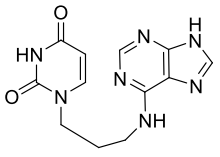


C =

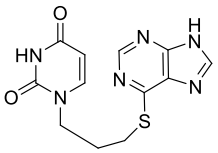


Energy minimization of heterocalixarenes **6-8** showed that two imide carbonyls were directed inwards cavity and the third one was placed outside. But on complexation with an ammonium cation, all three carbonyl moieties were directed inwards and formed H-bonds with H_3N^+– and the complexes were stabilized by -30 to 50 kJ $mole^{-1}$ in comparison with the parent heterocalixarene. Both in liquid-liquid and liquid-solid extraction studies, these heterocalixarenes selectively extracted $H_3N^+Bu^t$ picrate over K^+ picrate and the compound **7** showed highest selectivity.[5]

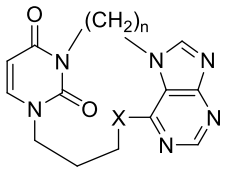
Uracil based macrocycles **11a-d** were synthesized by cyclization of **9** and **10** by treatment with α,ω-dibromoalkane and potassium carbonate in DMSO under high dilution conditions[6]. X-ray analysis of **11c** showed purine and the pyrimidine rings incline by dihedral angle of 50.4° with each other. The bond lengths and bond angles of the planar two rings are about the same values as those of 6-methylthiopurine[7] and 1,3-dimethyluracil[8].



a; X = NH, n = 3
b; n = 4
c; X = S, n = 3
d; n = 4



9 **10**

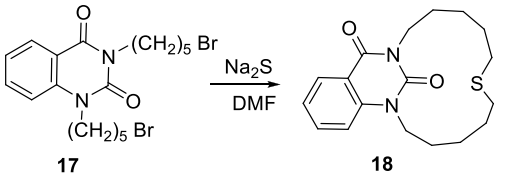


a; X = NH, n = 3
b; n = 4
c; X = S, n = 3
d; n = 4

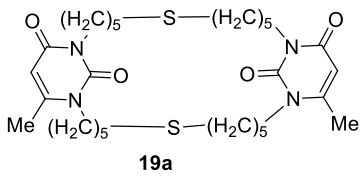
11

Cyclisation of 1,3-bis(ω-bromoalkyl)-5-bromouracil with *p*-methoxybenzylamine or sodium sulfide in PTC catalysed condensation resulted in formation of macrocycles **12-14** containing heteroatoms in

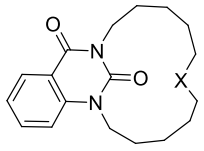
bridges.[9] During this synthesis, an unusual conversion of 5-bromouracil ring to hydantoin was observed. Macrocycle **12a** with *m*-xylyl group was synthesized in 4% only with 8% of hydantoin macrocycle **13**. Replacing *m*-xylyl to pentyl spacer resulted in macrocycle **12b** (13%). Cyclisation in the presence of Na_2S led to macrocycles **14a-b**. In their ^1H 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 δ 3.20-5.70 region attributed to folded conformation and exhibited slow conformational change on NMR time scale.



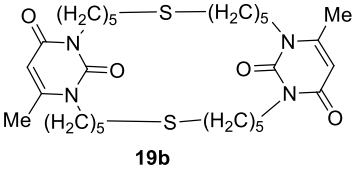
17 18



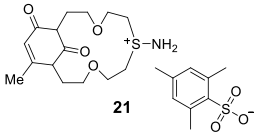
19a



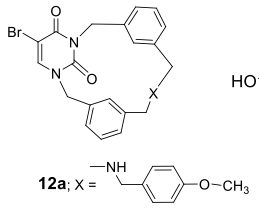
20a; X = SO
20b; X = SO_2



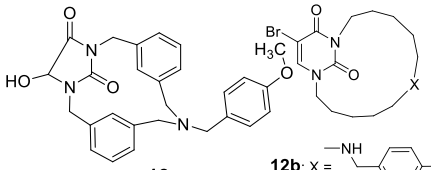
19b



21



12a; X =

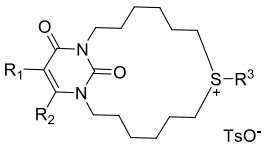


13

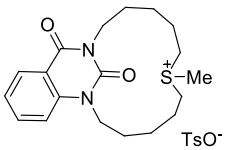
12b; X =

14a; X = S

14b; X = S

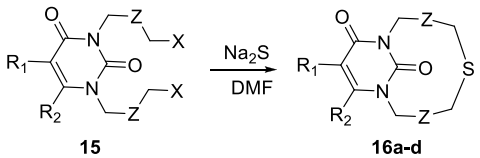


22



23

Reactions of dihalides **15** with Na_2S in DMF at 100-110 °C afforded a series of pyrimidinophanes **16a-d** with various numbers of methylene groups or ethoxyethyl fragments.[10] 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 CH_2Cl_2 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.

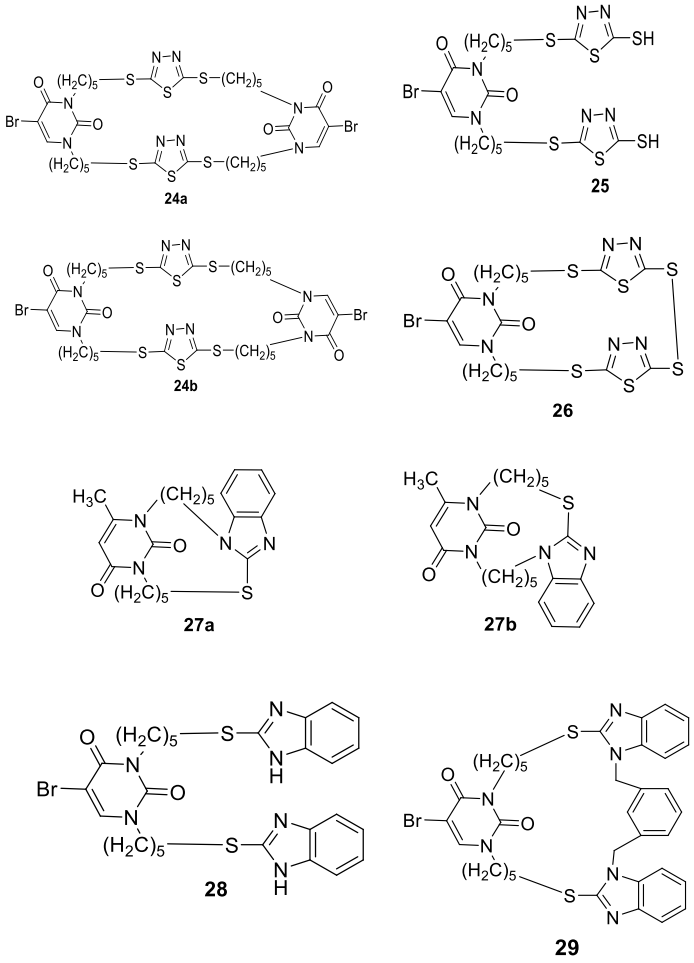


15 16a-d

a R1 = H, R2 = Me, Z = CH2OCH2, X = Cl (28%)
b R1 = H, R2 = Me, Z = (CH2)4, X = Br (24%)
c R1 = C10H21, R2 = Me, Z = (CH2)4, X = Br (19%)
d R1 = NO2, R2 = H, Z = (CH2)3, X = Br (13%)

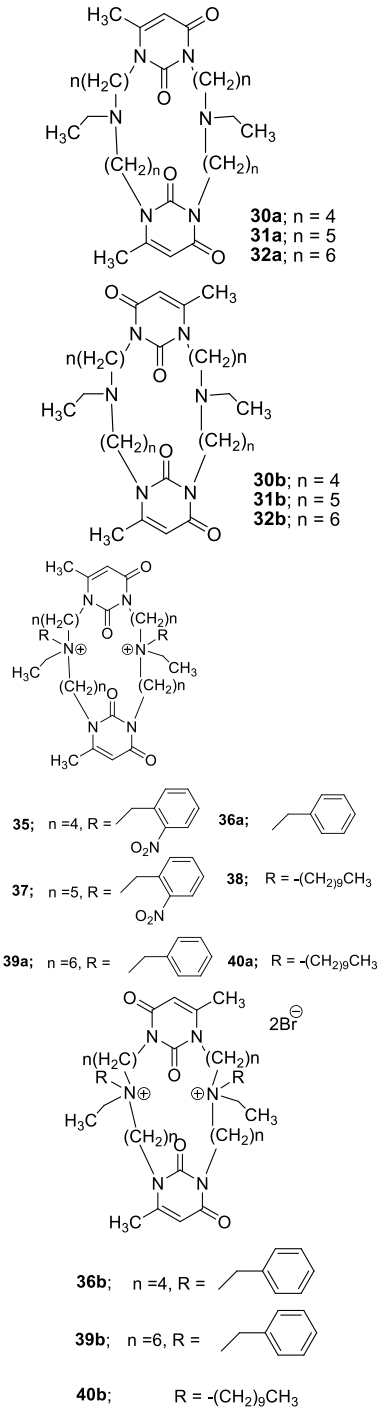
Reactions of 1,3-bis(bromopentyl)-5(6)-substituted uracils with different heterocycles like 2-mercapto-5-methyl-1,3,4-thiadiazole, 2,5-dimercapto-1,3,4-thiadiazole, 2-mercaptoimidazole, and 2-mercaptobenzimidazoles resulted in a series of acyclic compounds and isomeric heterocyclophanes.[11] Macrocycles **24a** and **24b** were isolated as mixture and two isomers could not be separated. Dithiazole **25** was oxidized to heterocyclophane **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.

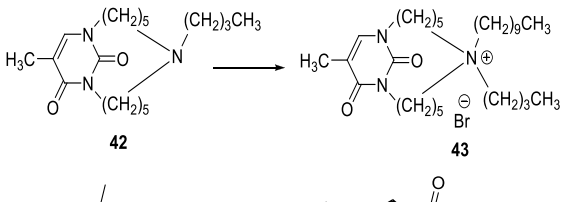
The reactions of 1,3-bis(α,ω-bromoalkyl)-6-methyluracils with 1,3-bis(α,ω-ethylaminoalkyl)-6-methyluracils or 1,3-bis(bromopentyl)thymine with butylamine afforded pyrimidinophanes **30-31** containing one or two uracil units and nitrogen atoms in bridging polymethylene chains.[12] In some cases individual 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 in macrocycles



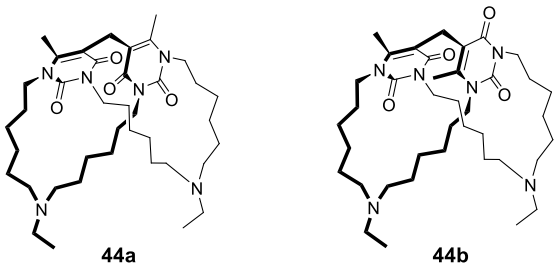
did not affect their activity. The reaction of mixture of **32a** and **32b** with benzyl bromide or n-decyl bromide afforded the mixture of isomers **39a** and **39b**, **40a** and **40b**, respectively. Antibacterial and antifungal activity of pyrimidinophanes increased with the increase in polymethylene 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.

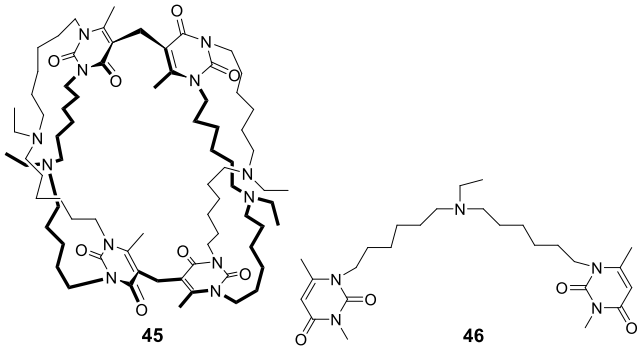
Pyrimidinocyclophane **42,** obtained by the reaction mixture of n-butylamine and 1,3-bis-(bromobromopentyl)thymine (**41**), on quaternization with n-decyl bromide gave macrocycle **43**.



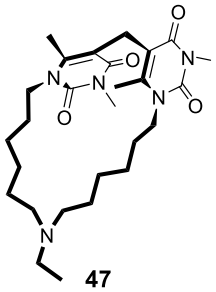
42 **43**



44a **44b**

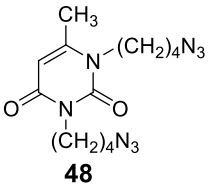


45 **46**

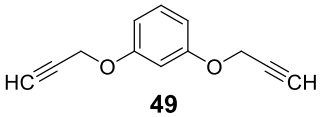


47

Trans-isomer **30b** on reaction with paraformaldehyde under acidic conditions gave cryptand-like pyrimidinophane **44a** with an intramolecular methylene spacer in almost quantitative yield[13]. 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.



48



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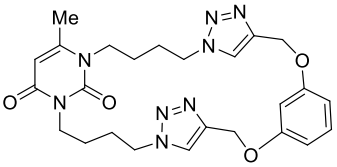

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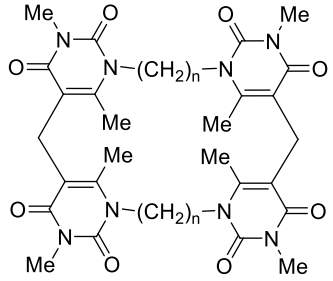

51a-d

a; n = 3; b; n = 4; c; n = 5; d; n = 6

1,3-Dipolar cycloaddition[14] 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.[22] 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.

III. CONCLUSION

It is crystal clear from the above discussed reports that uracil is chemically and structurally versatile molecule which can lead to the formation of varied number of cyclic architects.

IV.REFERENCES

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