Syntheses, structures and interactions of heterocalixarenes

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Abstract

This account provides a summary of a chapter on Heterocalixarenes in *Advances in Heterocyclic Chemistry*. The parent article (2005AHC67) constitutes 116 references, 30 X-ray structures and 189 chemical structures about heterocalix[*n*]arenes possessing varied heterocycles viz. furan, thiophene, pyridine, imidazole, benzimidazole, indole, benzofuran, benz-1,3-oxazine, pyrimidine-2,4-dione, benzimidazol-2(1*H*)-one, quinazoline-1,4(1*H*,3*H*)-dione, etc.

Keywords: Heterocalixarenes, synthesis, X-ray structures, conformations, supramolecular interactions

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1. Introduction

Molecular recognition involving multimolecular entities formed between chemical species of complementary topology through non-covalent interactions is a phenomenon at the core of biology and chemistry.[1] To understand complex modes of recognition of biological receptors, investigations on structurally simpler models of synthetic receptors are an area of contemporary research activity. The calixarenes **1** – the third generation synthetic receptors, on modification by

tuning the size, depth or conformation of their π-e rich cavity (fig. 1) and by derivatisation at rim(s), provide receptors with targeted properties.[2,3] The replacement of their phenolic unit(s) by heterocycle(s), constitute heterocalixarenes classified according to the category of the subcycle(s). The nature of subcycle(s) reveals electron rich or deficient cavity and varied transformation profiles for these systems. Thus a range of rational designs of heterocalixarene receptors, with possibilities of wider range of noncovalent interactions and consequent recognition events than calixarenes, can be envisaged. The nomenclature of heterocalixarenes takes cognisance of the nature and number of core subcycles and bridge substituents and the sizes of calixarenes and linear oligomers are also denoted as Cn and Ln. Recently, calix[*n*]pyrroles have been the subject of many reviews,[4-6] but the parent article[7] constitutes the first review on other heterocalixarenes and consists of 116 references, 30 X-ray structures and 189 chemical structures. In the parent article[7] heterocalix[*n*]arenes possessing varied heterocycles viz. furan, thiophene, pyridine, imidazole, benzimidazole, indole, benzofuran, benz-1,3-oxazine, pyrimidine-2,4-dione, benzimidazol-2(1*H*)-one, quinazoline-1,4(1*H*,3*H*)-dione etc. have been reviewed. The three dimensional structures and conformational behaviour of these heterocalixarenes have been discussed in number of cases. The interactions of these host molecules with the guests have been also presented.

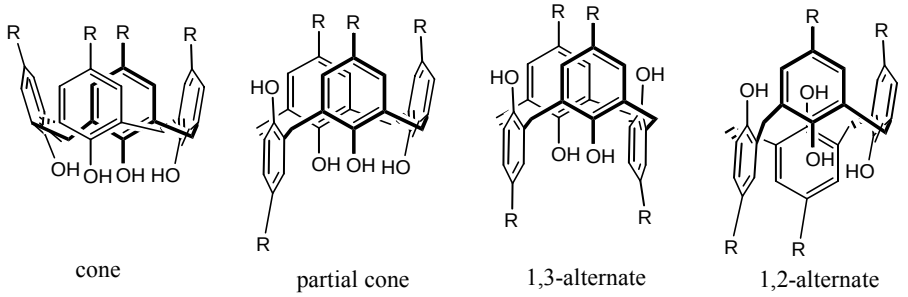
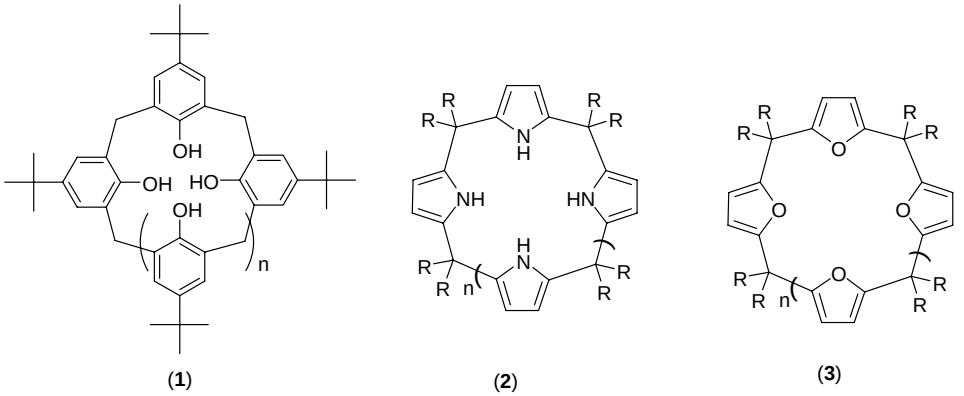


Figure 1

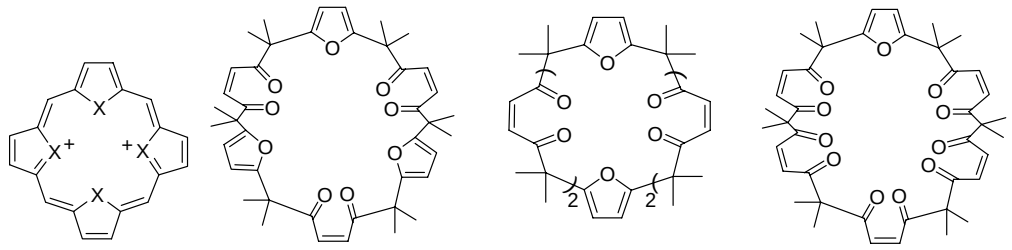
2. Calix[*n*]furans and their hybrid systems



Calix[*n*]furans **3**, are the earliest entries amongst heterocalixarenes. Their single step syntheses by acid catalysed cyclocondensations of furyl alcohols and reactions of furan with carbonyl compounds, provide mixtures of Cn and Ln and are confined mainly to C_4 systems. However, in some cases, reaction parameters have been optimised to procure targeted Cn or Ln. The two step directed synthesis of C_4 to C_9, by cyclocondensations of precursors Ln with carbonyl compounds, has been facilitated by the availability of a compendious method for both odd and even membered linear oligomers up to L_9. It involves reactions of combinations of metalated furan or its oligomers with appropriate electrophilic carbamoyl derivatives of furan or oligomers and subsequent Me_2Zn-$TiCl_4$ induced conversion of carbonyl to isopropyl linkers. Since variation of core sub-heterocycles would further tune the binding character of resulting hybrid heterocalixarenes, a host of such systems containing combinations of furan, pyrrole, thiophene and bipyrrole as well as bridge substituents have been obtained by acid catalysed condensations of appropriate linear oligomers in (3+1),(2+2),(3+2),(3+ketone) and (4+2) combinations.

As receptors, calix[*n*]furans and hybrid C_4 systems reveal some unique metal cation binding modes. As compared with calix[*n*]furans, calix[*n*]tetrahydrofurans, show better cation binding abilities which are influenced by the cavity size and bridge substituents. Calix[*n*]furans constitute precursors for many otherwise inaccessible cyclic entities including heterocalix[*n*]arenes due to the chemical pliability of furan ring. The reactions of calix[4]furan **3** (n = 1, R = Me) with H_2S and H_2Se constitute the only syntheses of calix[4]thiophene and its selena analog. DDQ oxidation of these systems provide dicationic aromatic O, S, Se bridged [18]annulenes **4** (X = O, S, Se), the analogs of porphyrin.

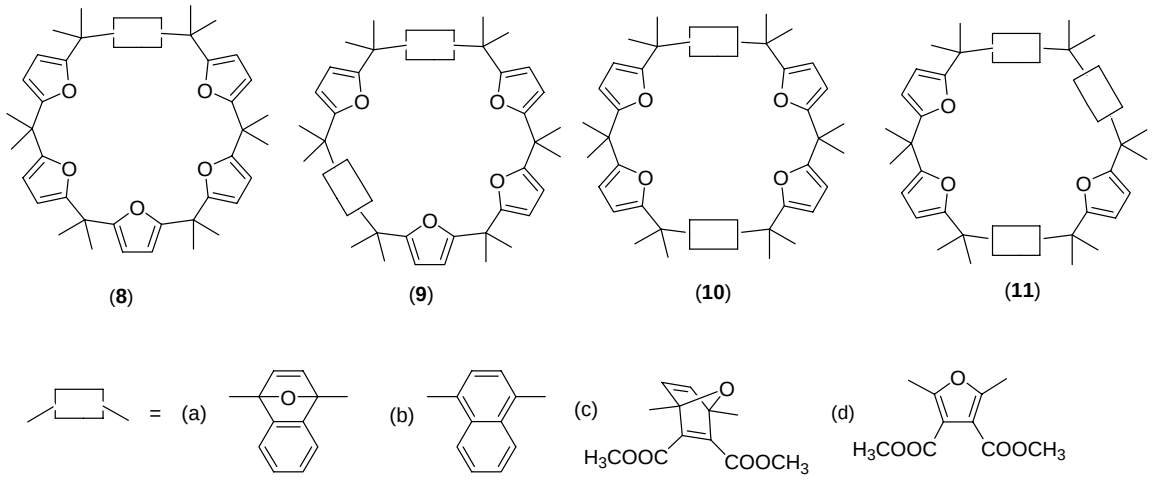
The oxidative cleavage of calix[*n*]furans with different stoichiometries of *m*-CPBA provides macrocycles **5-7** containing varied ratios of furan and 1,4-dione units which are precursors of many otherwise inaccessible calix[*n*]pyrroles particularly β-unsubstituted calix[5]pyrrole **2** (n = 2, R = Me), homocalix[*n*]isopyrazoles and hybrid heterocalix[*n*]arenes. Also cyclophanes having varied combinations of furan and isothiazole rings have been formed from calix[*n*]furans.



(**4**) (**5**) (**6**) (**7**)

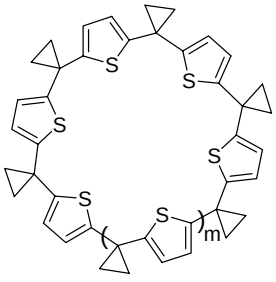
Diel-Alder adducts of furan(s) of calix[*n*]furans provide some unique chemical entities. Benzyne adds on **3** (n = 3, R = Me) in varied stoichiometric proportions to form adducts **8a-11a** which undergo hydrogenation and acid catalysed dehydration to form **8b-11b** where one or two furan rings of precursor **3** (n = 3, R = Me) are replaced by 1,4-naphthyl units. However, in case

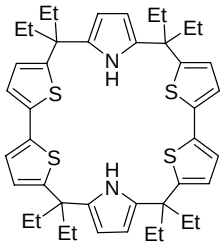
of **3** (n = 1, R = Me), only the monoadduct undergoes hydrogenation and acid catalysed dehydration but bis adducts fail to do so due to their structural rigidity. The flexible bis-adduct of benzyne and furanocyclophane containing two furan and two 1,4-dione units easily forms cyclophane having two 1,4-naphthyl and two furan units. Dimethyl acetylenedicarboxylate and **3** (n = 3, R = Me) form mixture of 7-oxabornadiene containing adducts **8c-11c**. The 7-oxabornadiene unit(s) of these adducts smoothly undergo retero Diel-Alder reaction to form hybrid heterocalixarenes **8d-11d** having furan(s) bearing ester groups at 3 and 4 positions, a substitution profile which cannot be achieved otherwise.

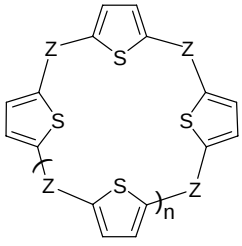


3. Calix[*n*]thiophenes

L_2 of thiophene bearing substituents at the bridged carbon, due to steric strain, undergo facile acid catalysed condensations with carbonyl compounds to form calix[4]thiophenes. The chemical transformation mode involving sodium sulphide induced conversion of 1,4-butadyne chromophores provides a structurally intriguing category of calix[*n*]thiophenes **12** possessing cyclopropylidene bridges. A number of hybrid and heteroatom bridged calix[*n*]thiophenes viz. **13-17** are reported.



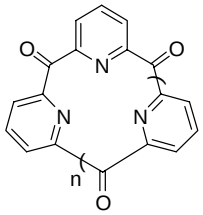




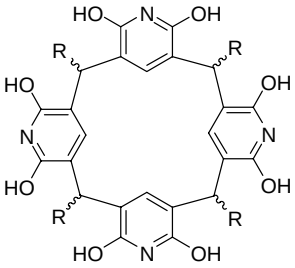
(14) Z = -S-, n =1
(**15**) Z = -Si(Me)$_2$-, n =1
(**16**) Z = -Si(Me)$_2$-, n = 2
(**17**) Z = -PPh-, n =1

4. Calix[*n*]pyridines and related systems

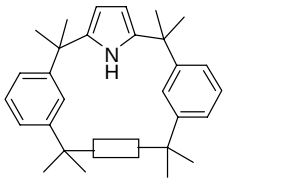
Calix[*n*]pyridines, having π-e deficient N electron rich pyridine units in their core are synthesized by cyclocondensation and pyrrole ring homologation of appropriate precursors. Only octahydroxycalix[4]pyridines (**19**) having nitrogens at the upper rims have been formed by electrophilic procedure involving reactions of 2,6-dihydroxypyridine with aldehydes. Using nucleophilic reactions of 2-lithiopyridine derivatives with 6-carbethoxy/cyanopyridine derivatives and lithioacetonitrile with 2-bromopyridine derivatives followed by transformations at the bridge(s) provide ketonic calix[3]pyridine and calix[4]pyridine systems **18** (n = 1, 2). The influence of pyridine in generating unprecedented reactivity at bridge carbons is evident from the formation of a hemiketal at one ketone of **18** (n = 1), on crystallisation from methanol and a dimer from its analog having $–CH_2-$ in place of one carbonyl bridge. A sulphur bridged calix[3]pyridine was formed by intermolecular condensation of 6-chloropyridine-2-thione.

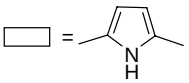


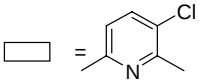
(**18**)



(**19**)



(**20**) 

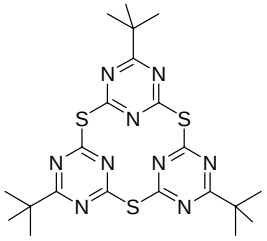
(**21**) 

The ring expansion of pyrrole(s) of easily available **2** (n = 1, R = Me) to pyridine(s), provide calix[4]pyridine and hybrid calix[n]pyrrole[m]pyridine systems. The dichlorocarbene insertion performed in varied stoichiometric proportions provide all possible octamethylcalix[*n*]3-chloropyridine[m]pyrrole systems (n + m = 4). The transition metal assisted reactions of **2** (n = 1, R = Me) with carbon monoxide result in homologation of up to two pyrrole rings to pyridines having even alkyl and alkenyl groups, with high selectivity and controlled regiochemistry. The reaction of dichlorocarbene with octamethylcalix[2]-benzene[2]pyrrole (**20**) gave octamethylcalix[2]benzene[1]3-chloropyridine[1]pyrrole (**21**) which elaborates a flattened partial cone conformation in the solid state.

5. Triazine based Heterocalixarenes

Calix[*n*]triazines represent another class of electron-deficient heterocalixarenes as the electronic complement to the π-basic calixarenes and as recognition systems for electron rich guests. S-linked calix[3] triazine**,** has been obtained from 2,4-dichloro-6-t-butyl-1,3,5-triazine and sodium

sulphide. Calix[3]triazine (**22**) shows high degree of mobility but calix[3]triazine[3]arene (**23**) due to intramolecular H-bonding shows poor mobility for interactions with guest molecules.



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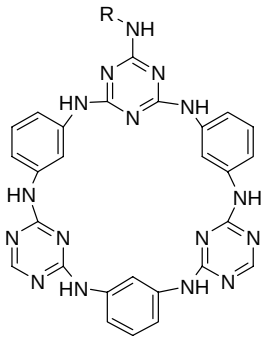
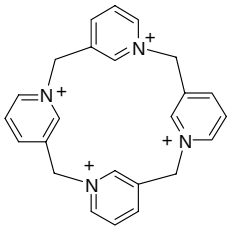


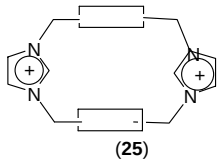
(**23**)

6. Cationic and Betaine Heterocalixarenes

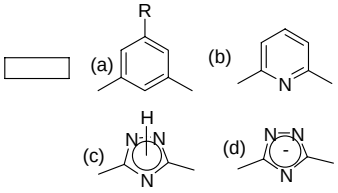
Calix[4]pyridinium tetracation system also represents electron-deficient heterocalixarenes. The self N-alkylation of 3-bromomethylpyridine generated *in situ* from its hydrobromide gave hydrated tetrabromide of **24**. The dicationic heterocalixarenes **25**, possessing two 1,3-imidazolium rings and two sub-cycles from amongst 1,3-phenylene; 2,6- pyridine; 3,5-(1,2,4)-triazole rings and a combination of phenylene and triazole rings, have been synthesized. The deprotonation of triazole(s) provide mono and bis-betaines such as **25d** which constitute unconventional heterocalixarenes having both π-rich and π-deficient heteroaromatic moieties. **25.b**$(Br^-)_2$, on treatment with ammonium hexafluorophosphate forms **25.b** $(PF_6)_2$ which on reaction with Ag_2O affords dimeric silver carbene complex. By using (5+1) and (5+3) combinations enlarged hexameric and octameric analogous heterocalixarenes have been formed.



(**24**)

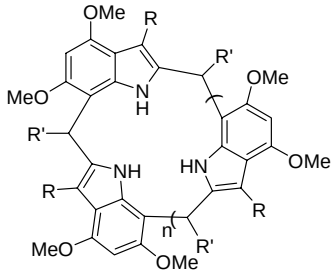


(**25**)



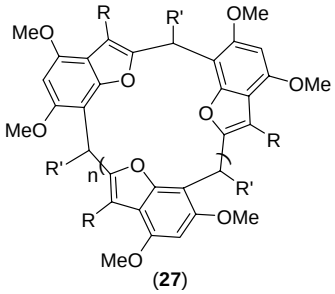
7. Calix[*n*]indoles and calyx[*n*]benzofurans

Calix[*n*]indoles and calix[*n*]benzofurans having π- electron rich cavities are synthesized by electrophilic reactions at electron rich 2,7- positions of indoles and benzofurans. The phosphoryl chloride or acid catalysed reactions of aromatic aldehydes with 3-substituted-4,6-dimethoxyindole and similar reactions of such indoles as well as their dimers having hydroxymethyl and hydroxybenzyl group(s) at 2 and / or 7 position(s) as such or with an appropriate complementary indole based component, give symmetrical 2,7- linked calix[3]indoles **26** (n = 1). For triggering cone conformations in these predominantly flattened partial cone systems, attempts at their organization through H- bonding by having amidomethine bridges have met with limited success. Unsymmetrically linked calix[3]indoles have been obtained from C2 linked dimeric indole systems having hydroxymethyl group at 7- positions and 3-aryl-2,6-dimethoxyindoles. Acid catalysed dimerisation of bis-hydoxymethyl derivatives of dimers of above substituted indoles form various calix[4]indoles **26** (n = 2).



(**26**)

R' = H, Ar
R = Me, Ar etc.



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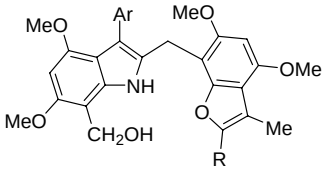


(**28**)

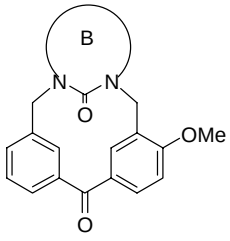
3-Substituted-4,6-dimethoxybenzofurans react with aldehydes to give both symmetrically **27** (n =1) and unsymmetrically linked calix[3]benzofurans and their ratio is influenced by the nature of 3- substituents. 3-t-Butyl-4,6-dimethoxybenzofuran and formaldehyde form calix[4]benzofuran **27** (n = 2, R = Bu^t, R^1 =H). 2-Hydroxymethyl derivatives of above benzofurans, on treatment with acid and K-10 clay respectively form symmetrically and unsymmetrically linked calix[3]benzofurans but when benzylic or secondry alcoholic groups are present at position 2, on treatment with acid corresponding **27** (R = Ph, R^1 = H, Aryl, Me, CONHR, COOMe etc.) are formed. The hybrid dimeric alcohol **28** (R = H) on treatment with acid forms a symmetrically linked hybrid heterocalixarene calix[1]indole[2]benzofuran. Here, the initially formed linear tetramer cleaves to parent heterocyclic units which recombine to form the product. The dimeric alcohol **28** (R = CH_2OH) by condensation with appropriate second component has been used in procuring hybrid C_3 and C_4 systems.

Calix[4]benz-1,3-oxazines are obtained from resorc[4]arenes by Mannich reaction with formaldehyde and a primary amine including chiral ones in a stereoselective manner. The back

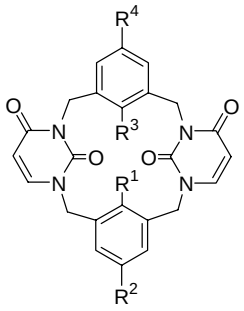
conversion of a diastereomerically pure system provides a unique practical approach for an axially chiral enantiomerically pure resorc[4]arene.

8. Cyclic urea-based heterocalixarenes

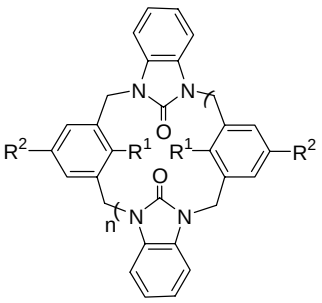
Heterocalixarenes having biologically ubiquitous urea unit embedded in perhydro or conjugated heterocyclic component(s) elaborate unique binding and conformation characters. The bisanions of cyclic ureas in which urea moiety is capped with $(CH_2)_2$, $(CH_2)_3$ and $–CH_2$-N(Bu^t)-CH_2 units react with 1,3-bis(bromomethyl)benzene to form perhydro cyclic urea based heterocalixarenes. Trimeric heterocalixarenes **29** (B = a, uracil; b, benzimidazol-2-one; c, quinazolin-2,4-dione) have been formed by condensations of cyclic ureas with dihalide of the benzophenone segment. **29b** $(H_2O)_{0.5}$ shows a unique network of H-bonds involving three of the four CH of each benzimidazolone, imide O, carbonyl O and water. The strong H-bonding of water to four molecules of **29b** is responsible for engineering its crystal. The tetrameric calix[2]uracil[2]arenes **30**, having similar or different substitution profiles in both arenes have been obtained from 1,3-bis[(1-uracilyl)methyl] benzene derivatives and 1,3-bis(bromomethyl)benzene derivatives. Depending on the nature of substituents on position 2 of 1,3-phenylene rings, **30** attain inward flattened partial cone, cone or other flexible structures. **30** (R^1, R^3 = OH; R^2, R^4 = Me) forms a 2:1 complex with ethanol which shows an unusual H-bonding at H of its OH and CH_2 with C_4=O of one uracil molecule and O of its OH with C5-H of uracil of second molecule. The calix[2]benzimidazolone[2]arenes **31** (n = 1) and octameric systems **31** (n = 3) have been formed by high dilution and template induced condensations of 1,3-bis(bromomethyl)benzene and the trinuclear segment component of **31** (n = 1). The compounds **31** (n = 3) reveal unique molecular shapes and interactions with a variety of solvent molecules.



(**29**)



(**30**)

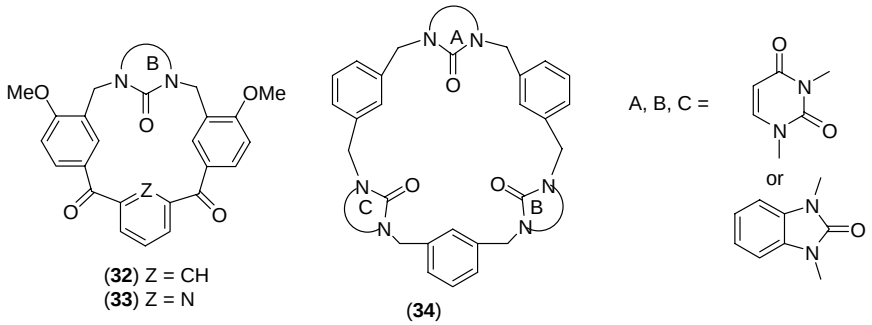


(**31**)

The tetrameric systems **32** and **33** (B = a: benzimidazolone; b : uracil; c : quinazolin-2,4-dione), marked for having two carbonyl bridges, one cyclic urea and three arenes or two arenes and one pyridine nuclei have been synthesized by condensations of respective cyclic ureas with dihalides of trimeric precursors. The compound **32a** forms with benzene an inclusion complex

(1:1) revealing its face to face π-π interaction with benzimidazolone which in turn shows π-π interaction with isophthaloyl ring of symmetry related molecule.

Heterocalixarenes **34a-d**, designed for RNH_3^+/ K^+ binding selectivity, were synthesized by condensations of trinuclear systems, 1,3-bis[(1-uracilyl)methyl]benzene and 1,3-bis[(2-oxobenzimidazolyl)methyl]benzene derivatives with appropriate dibromides. A rare odd membered C9 sized hetero[6]benzimidazolone[3]arene system has been reported and it shows unique binding with acetone and dichloromethane.



(**32**) Z = CH
(**33**) Z = N

(**34**)

Like a jewel in a ring, a hetero atom can provide physicochemical value in a heterocycle. Similarly, replacing phenolic unit(s) in the structural core of calixarenes by heterocyclic unit(s) generates similar effect in heterocalixarenes. Of the numerous possible structural designs, except for the oldest heterocalixarene – calix[4]pyrrole, only a few have been synthesized and even fewer have been structurally elaborated and evaluated for their receptor and related characters. In addition to single or multistep synthetic approaches, their facile procurement by heterocyclic transformations on some easily available heterocalixarenes opens up a unique practicable and pliable mode of forming many otherwise inaccessible inspiring new chemical entities including heterocalixarenes and demands exploration. Thus, it is left to human imagination as to how many such systems await investigation to develop newer chemical entities of potential use for human welfare.

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