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HETEROCALIXARENES. (REVIEW)

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Heterocalixarenes, i.e. heterocycle-based calixarenes, are interesting as receptors of a variety of molecules and ions. These compounds are described with regard to their syntheses, reactivity, and inclusion properties. In the presentation of benzoxazine-based calixarenes attention is paid to their chirality.

Keywords: benzoxazine, furan, inclusion properties, pyridine, resorcarenes.

Heterocalixarenes or calixhetarenes belong to the family of calixarenes [1-8], compounds intensively studied due to their interesting chemical and physicochemical properties as well as their application possibilities. Calixarenes contain phenol units, while heterocalixarenes are built from heterocyclic moieties, i.e. they are heterocycle-based.

Another class are heteracalixarenes, i. e. aza- [9, 10], oxa- [11, 12] and thiacalixarenes [13, 14], in which bridges between phenol units contain heteroatoms N, O, or S. Also known are calixarenes with appended heterocyclic moieties; they do not build the receptor cavities [15]. One should mention here also resorcarenes, built from resorcinol units [16, 17], and cavitands [18-20] resulting from the bridging of resorcinol hydroxyl groups of neighboring aromatic rings.

In this review, heterocalixarenes built from pyridine moieties and from other heterocycles are described in the first and second parts, and in the third part those built from benzoxazine units are presented, with special attention paid to their chirality. Calixpyrroles are a large class of heterocalixarenes for which many works are reported [21-23]; therefore, these compounds are reviewed elsewhere [24].

1. HETEROCALIXARENES WITH PYRIDINE UNITS

In order to obtain calixarenes **1** built from pyridine moieties, bridged at the 3 and 5 positions, the reactions of 2,6-dihydroxypyridine with aldehydes in acidic medium were performed [25]. The increased temperature and time of reactions allow one to avoid the formation of configurational isomers (Scheme 1).

The reaction of calix[4]pyrrole **2** with dichlorocarbene, generated from sodium trichloroacetate, involving pyrrole ring expansion, leads *via* mono-, di-, and trichloropyridine species **3**, **4** and **5** to chloropyridine-based calix[4]arenes **6**, bridged at the 2 and 6 positions [26, 27] (Scheme 2). The chlorine atoms are present in positions a or b.

One should mention here also macrocycle **7**, a specific receptor of tricarboxylate anions, obtained in a simple, one-step procedure from 3-bromomethylpyridinium bromide by neutralization with $NaHCO_3$ and subsequent extraction with dichloromethane [28]. Anions of tricarboxylic acids **8-12** have been used as guests (Scheme 3).

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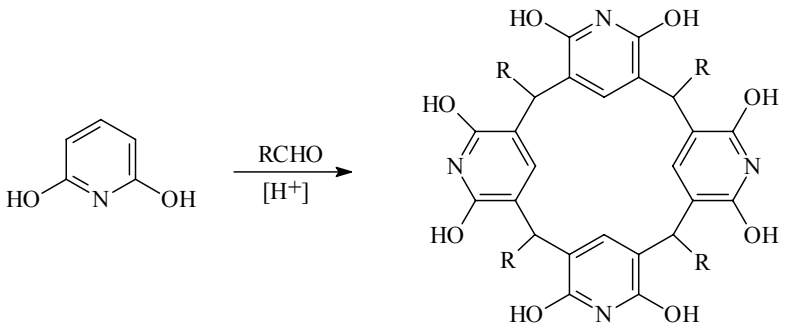
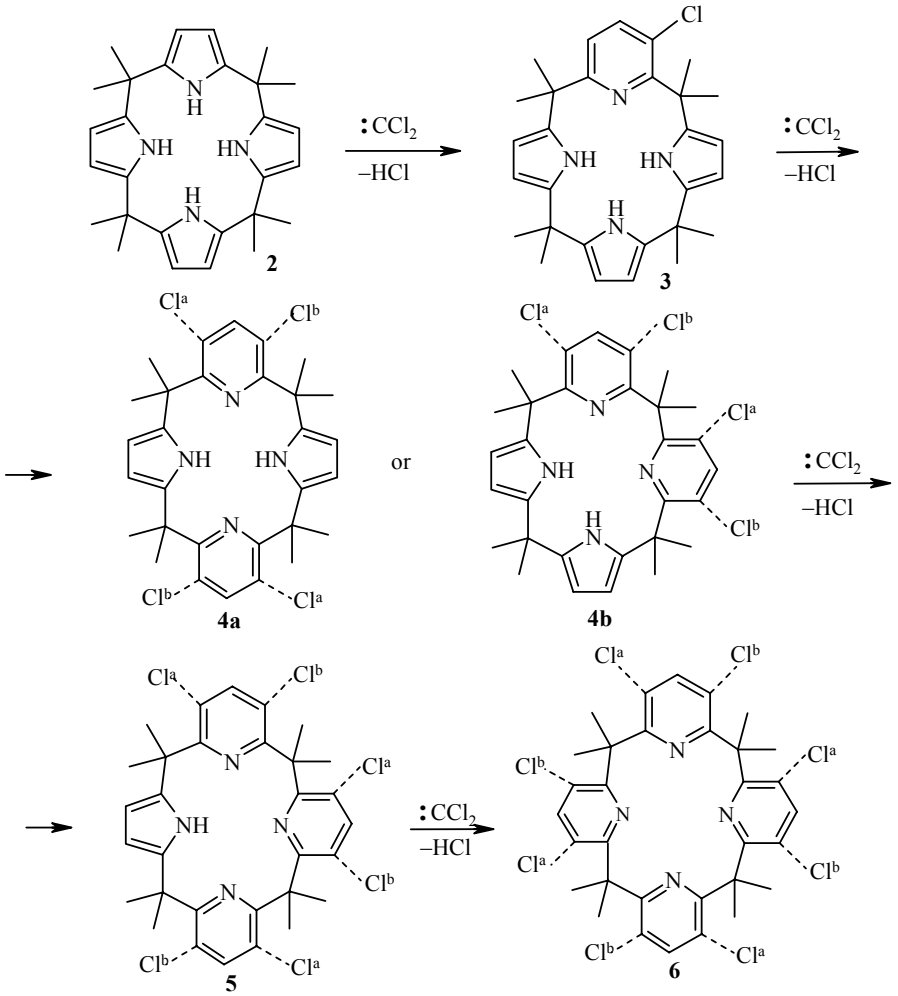
Scheme 1



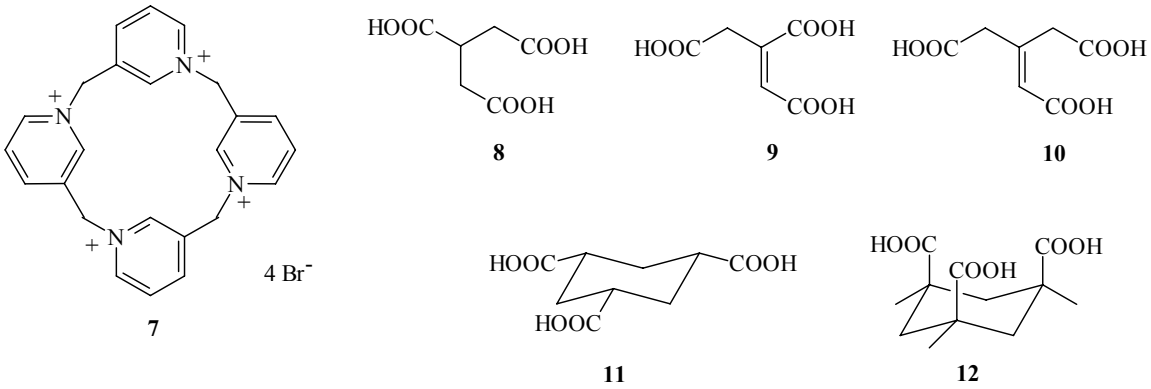
1

R = Me, *n*-Bu, 2-methylpropyl, *n*-$C_{11}H_{23}$, Ph, 4-$C_6H_4NO_2$

Scheme 2



Scheme 3



2. HETEROCALIXARENES WITH OTHER HETEROCYCLES

The furan-based calixarene **13** was obtained by condensation of furan with acetone. This compound (as a diene) was subjected to a Diels–Alder reaction with benzyne (as a dienophile), generated by the pyrolysis of benzenediazonium-2-carboxylate. The formed cycloadduct **14** was catalytically hydrogenated to give monoadduct **15** which was aromatized by acid-promoted dehydration with TsOH in toluene affording **16** [29].

The bis-adducts of **13** with benzyne **17** and **18** hydrogenated in a similar way afforded **19** and **20**, aromatized into **21** and **22**, respectively [29]. It was established that the bis-adduct **17** has a more opened-up cavity than **18**. Also the tris-adduct **23** is known (Scheme 4).

The Diels–Alder reaction of **13** with DMAD gave the mono-adduct **24** and four isomeric bis-adducts **25-28** [29].

The selective hydrogenation of the olefinic units which do not bear the ester functions gives compounds **29-33**. They have been subjected to the thermally promoted retro Diels–Alder reaction resulting in furan-based calixarenes in which the furan rings involved in cycloadditions contain carboxylate groups in the 3 and 4 positions. The retro Diels–Alder reaction was performed by pyrolysis at 220°C; in these processes from **29** the furan-based calixarene **34** was obtained, **30** and **31** afforded compound **35**, while **32** and **33** gave **36**. The carboxylate groups of the synthesized derivatives may be modified, for example, hydrolyzed or transesterified.

It should be pointed out that furan-based calixarenes in which the furan units contain dicarboxylate functions at the 3 and 4 positions cannot be obtained by the condensation of 3,4-furandicarboxylate due to the electron-withdrawing deactivating effect of these groups (Scheme 5).

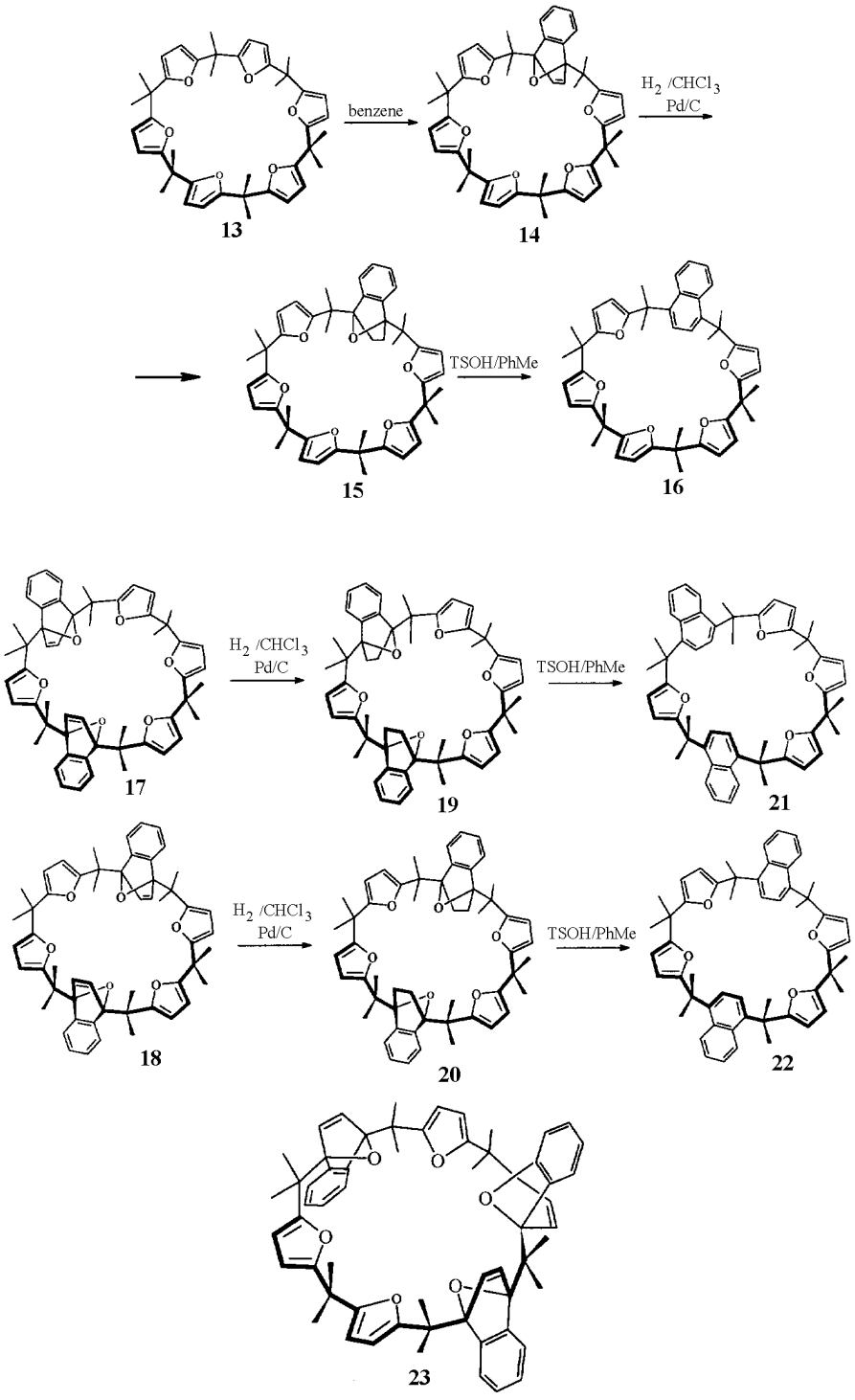
In order to obtain calixfuranopyrrole **37**, the condensation of its precursors **38** and **39** has been performed [30] (Scheme 6).

The reaction of pyrimidine **40** with bis(bromomethyl)benzenes **41** leads to compounds **42** which undergo subsequent cyclization with **41** to give calix[2]arenes **43a-f**; selected examples of **43** are presented (Scheme 7, ref. [31]).

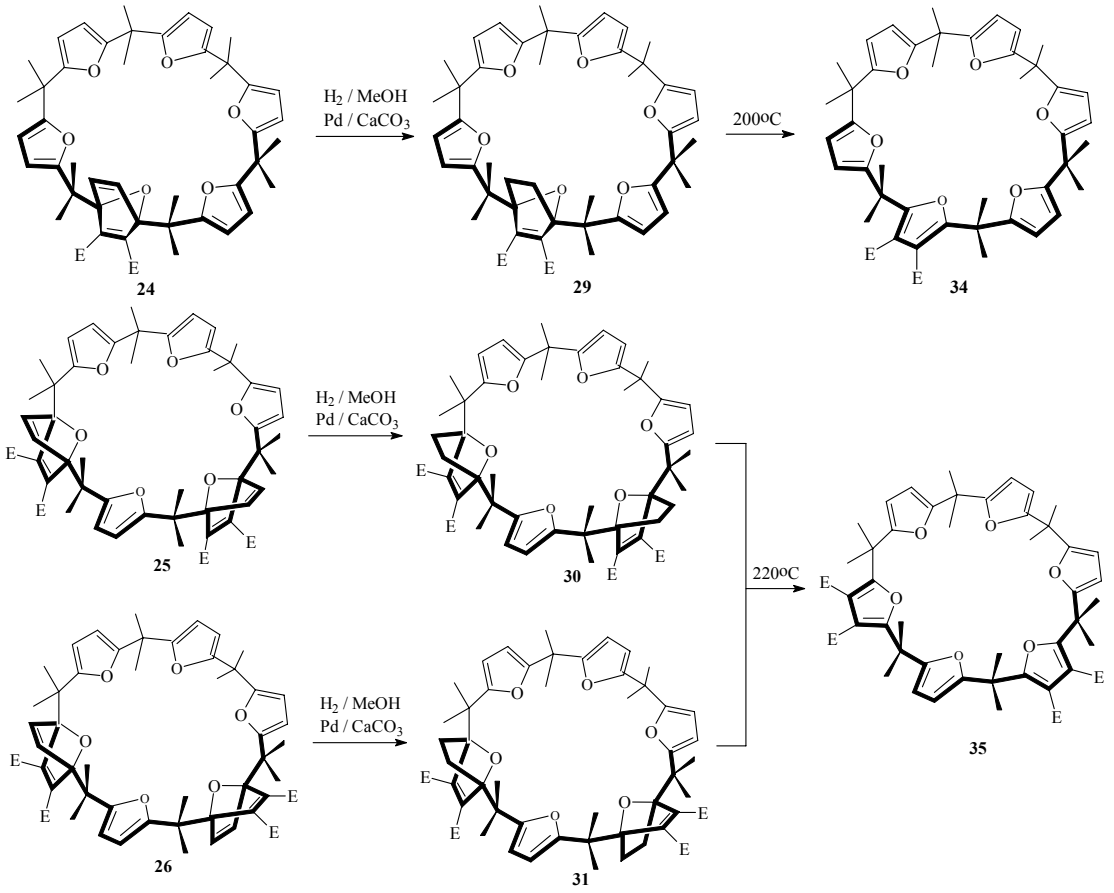
The titration of calixarene **43f**, possessing the chromogenic nitrophenol unit serving as one of the binding sites against metal acetates, results in the formation of 1:1 **43f**–metal acetate complexes, with preference for alkaline earth metal cations over alkali metal cations. It was observed that **43e** weakly binds acetonitrile and malonitrile.

Heterocalix[3]arenes containing cyclic ureido systems and linked by carbonyl groups in place of methylene spacers, **44-46**, have been synthesized as shown in Scheme 8, ref [32].

Scheme 4

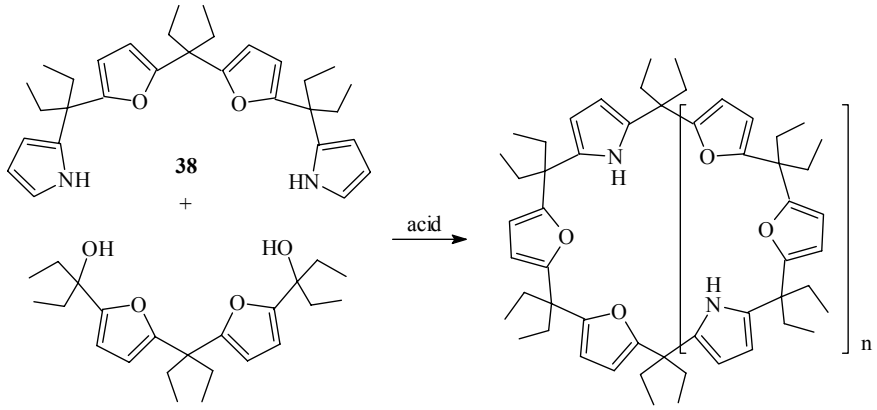


Scheme 5


H2 / MeOH
Pd / CaCO3
200ºC
H2 / MeOH
Pd / CaCO3
H2 / MeOH
Pd / CaCO3
220ºC
24
29
34
25
30
26
31
35

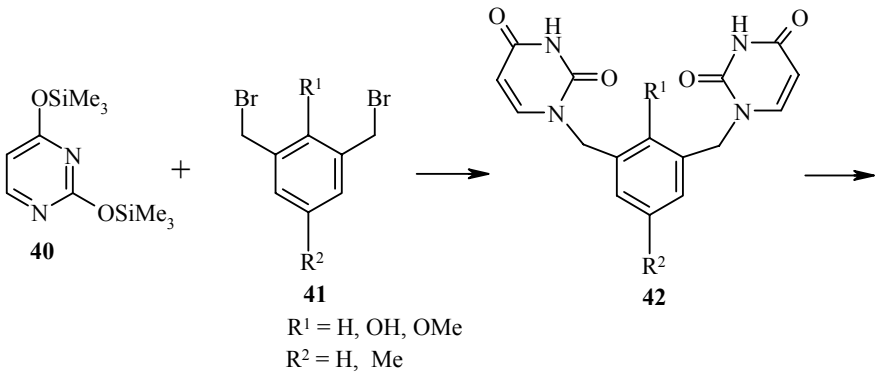
Scheme 5 (continued)

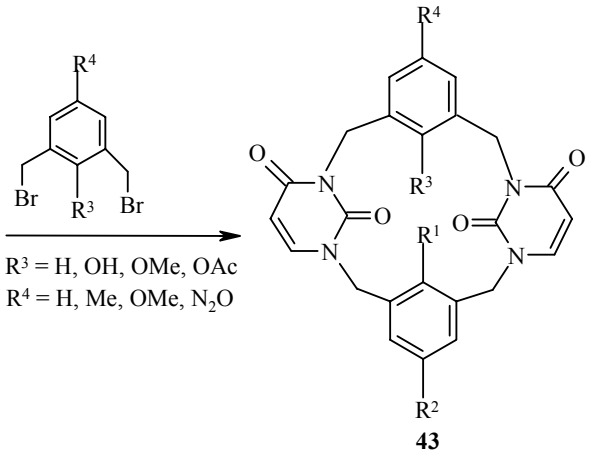
Scheme 6



39 37 *n* = 1, 3

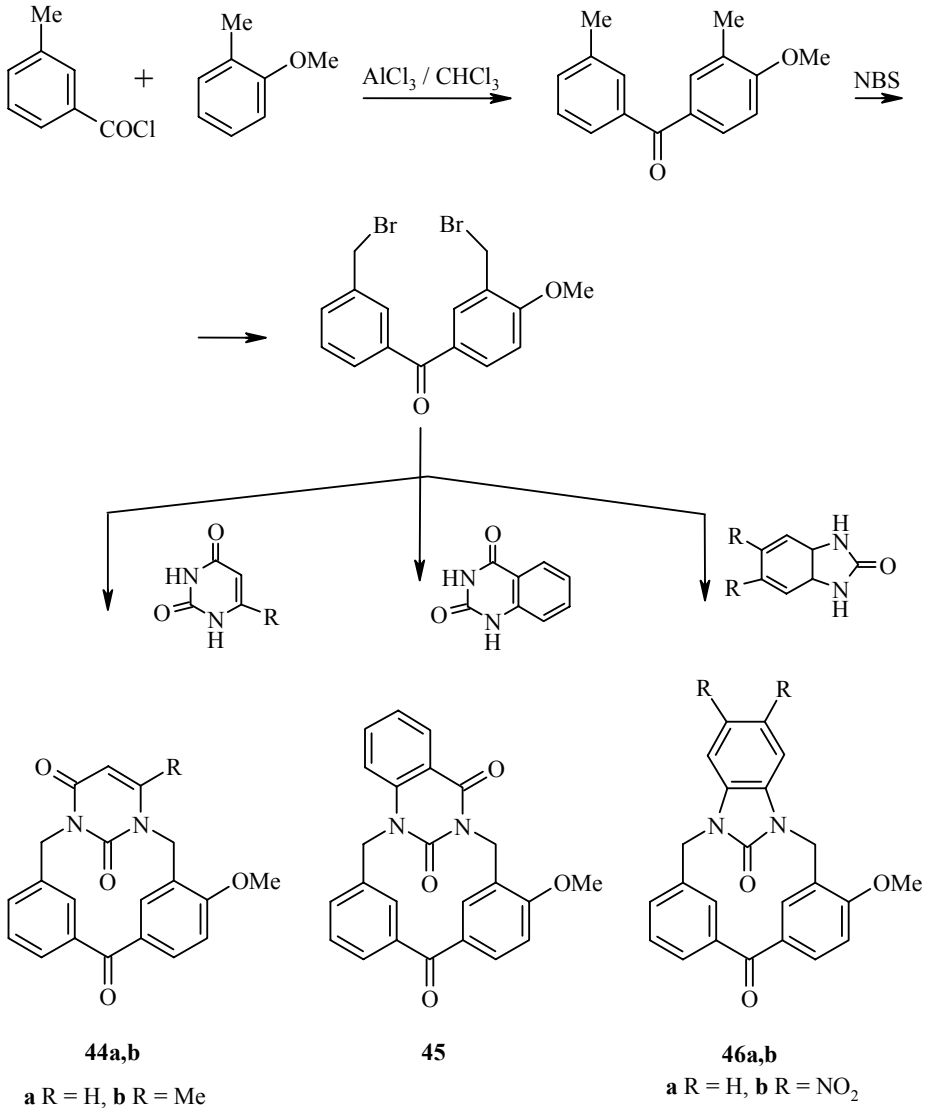
Scheme 7





		R^1	R^2	R^3	R^4
43	**a**	OMe	Me	H	H
	b	H	H	OMe	OMe
	c	OMe	Me	OMe	Me
	d	OMe	Me	OAc	Me
	e	OH	Me	OH	Me
	f	OH	Me	OH	NO_2

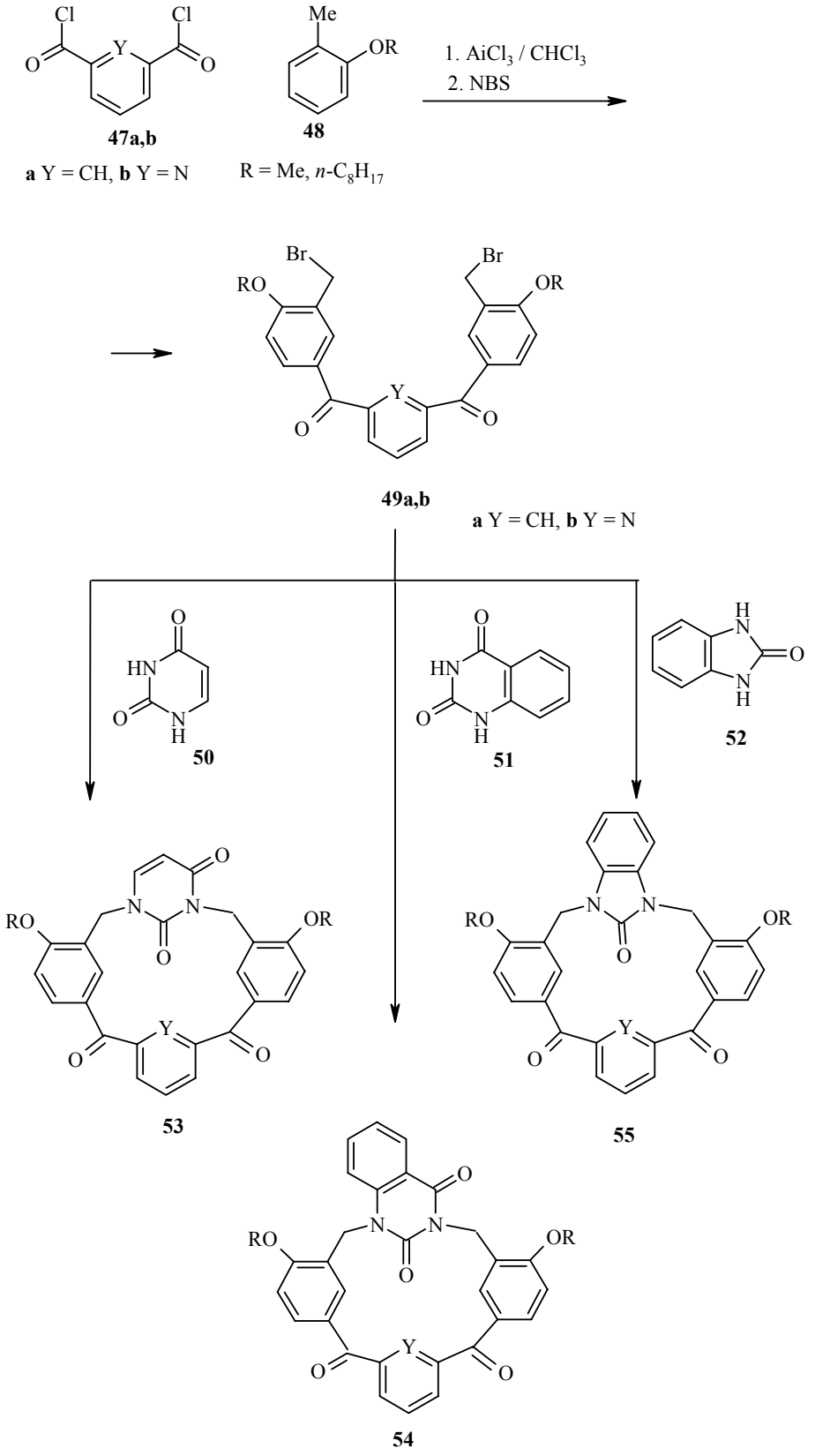
Scheme 8



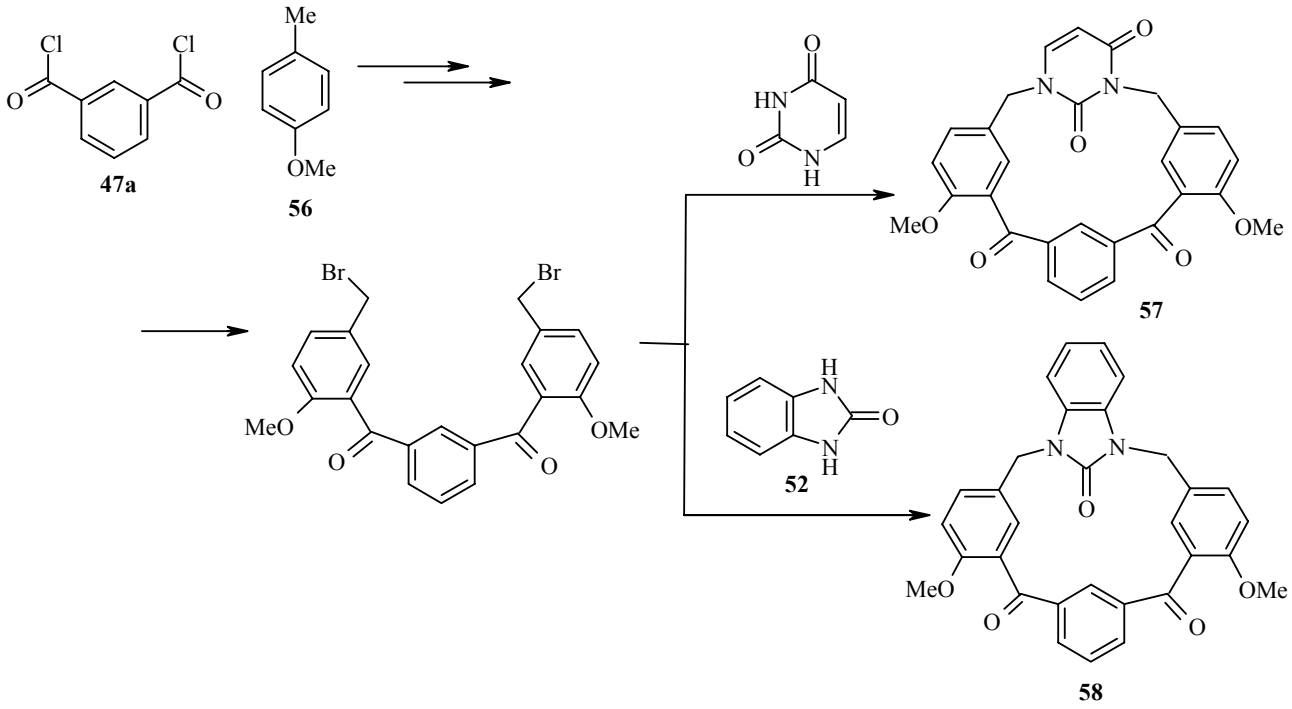
Similar calix[4]arenes bearing benzene or pyridine units have been obtained and their X-ray crystal structure and conformational analyses performed [33]. The synthesis begins with the Friedel–Crafts reaction of isophthaloyl dichloride **47a** or 2,6-bis(chlorocarbonyl)pyridine **47b** with 2-methylanisole **48**, followed by bromination with NBS. The cyclocondensation of the formed dibromide **49a**,**b** with uracil **50**, quinazolinedione **51,** and benzimidazolone **52** under solid-liquid phase-transfer catalytic conditions gave heterocalixarenes **53**-**55**. Analogous reactions of **47a** with 4-methylanisole **56** afforded compounds **57** and **58** (Scheme 9, ref. [33]).

Heterocalix[4]arenes **59a**,**b** and heterocalix[8]arenes **60a**-**d** containing benzimidazol-2-one moieties have been synthesized [34]; these latter form crystalline inclusion compounds with solvents: **60a**–toluene (1:3); **60b**–CH_2Cl_2 (1:1); **60c**–toluene–water (1:2:1); and **60d**–acetone–CH_2Cl_2 (1:1:1). It was observed that these hosts have higher complexing properties than conventional calix[8]arene **61**.

Scheme 9

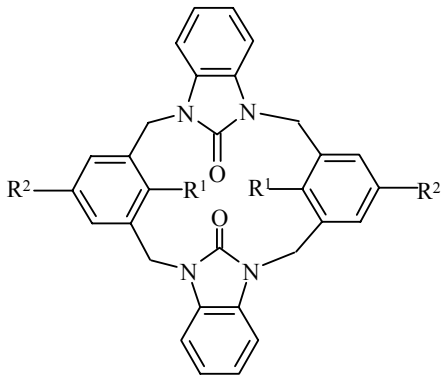

Cl
Cl
Y
O
O
47a,b
a Y = CH, b Y = N
Me
OR
48
R = Me, n-C8H17
1. AiCl3 / CHCl3
2. NBS
Br
RO
Br
OR
Y
O
O
49a,b
a Y = CH, b Y = N
HN
O
N
H
50
51
52
RO
OR
53
55
54

Scheme 9 (continued)



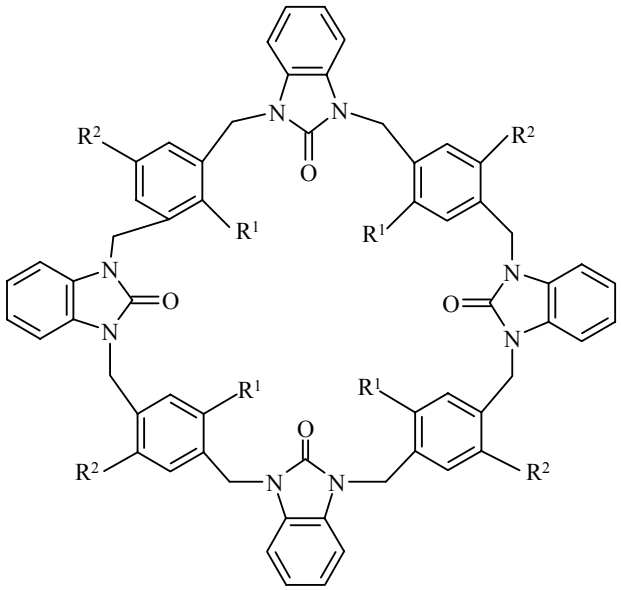
It was established that heterocalix[9]arene **62** forms with acetone and CH_2Cl_2 (1:2:2) inclusion complex (Scheme 10, ref. [35]).

Scheme 10



59a,b

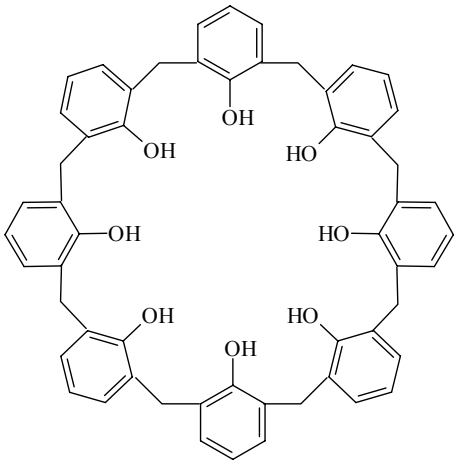
a R^1 = OMe, R^2 = H;
b R^1 = OMe, R^2 = *t*-Bu;



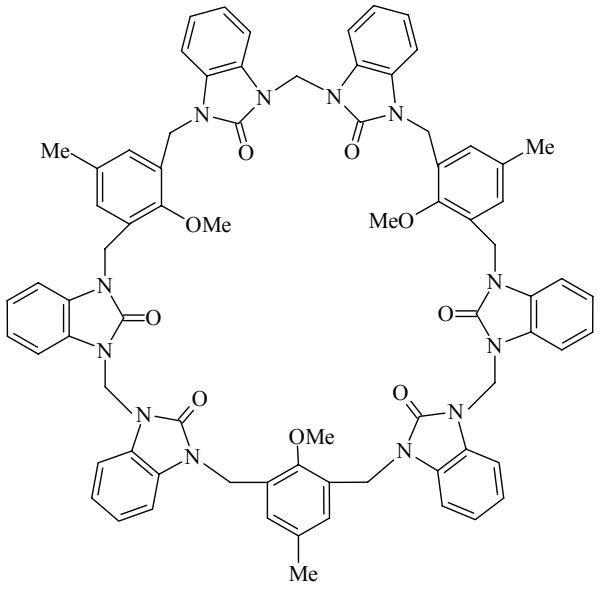
60a–d

a R^1 = OMe, R^2 = H; **b** R^1 = OMe, R^2 = *t*-Bu
c R^1 = OMe, R^2 = Ph; **d** R^1 = OH, R^2 = *t*-Bu

Scheme 10 (continued)



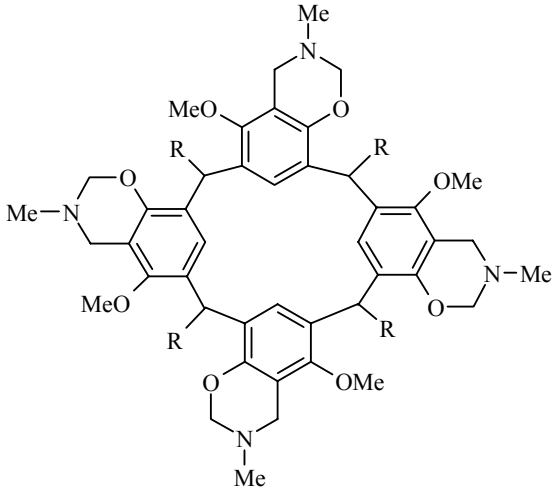
61



62

3. HETEROCALIXARENES WITH BENZOXAZINE UNITS

Numerous works concern chiral benzoxazine-based calixarenes [36-39], an example being the enantioselective synthesis of axially chiral enantiomerically pure **63** [37].



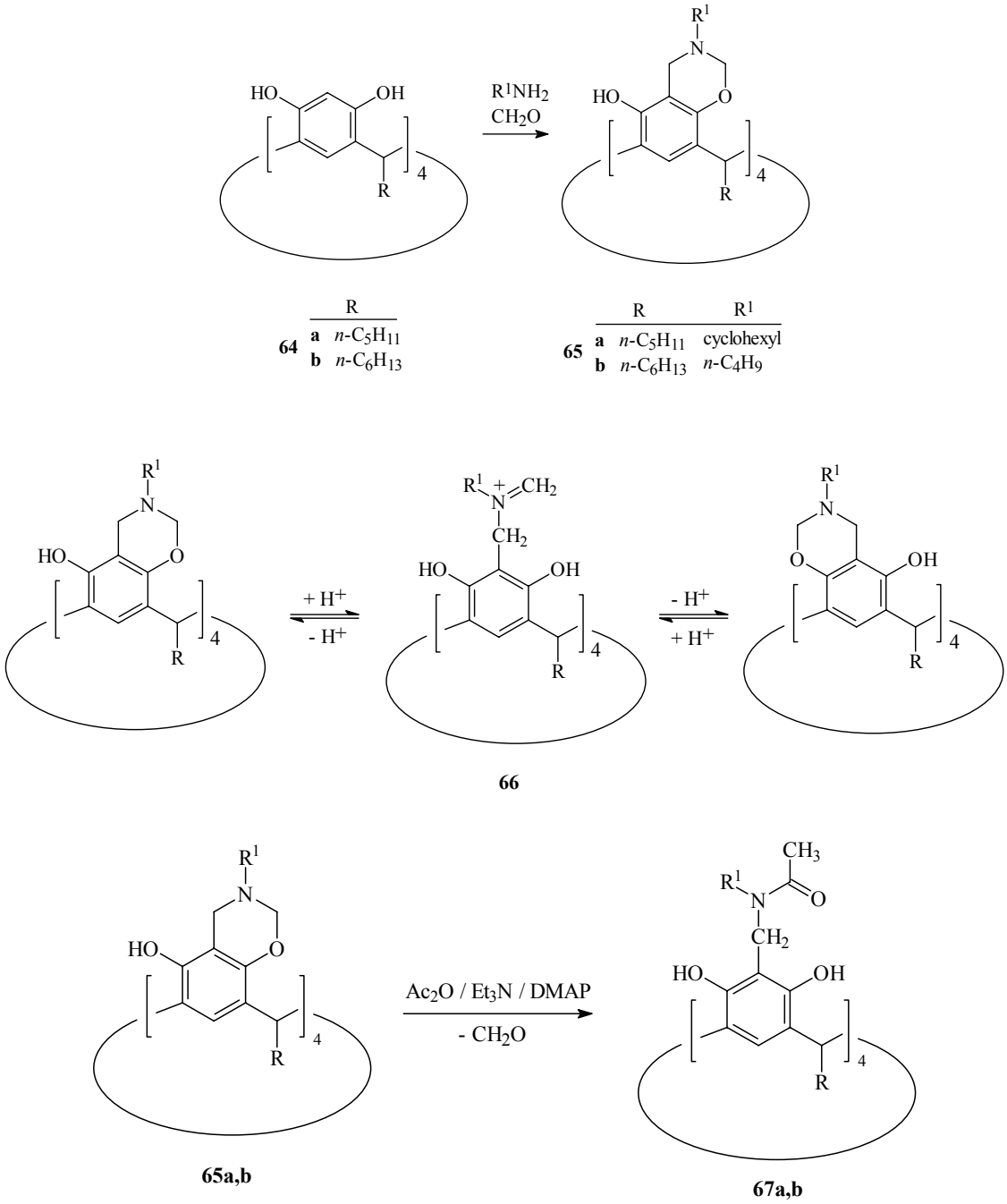
63

R = *n*-$C_{11}H_{23}$

The reaction of all-*cis* isomers of resorcarenes **64a**,**b** with primary amines and formaldehyde affords regioselectively C_4-symmetrical benzoxazine-based calixarenes **65a**,**b**, which are chiral host molecules with extended cavities [40].

The enantiomerization of **65a**,**b** catalyzed by traces of acid proceeds *via* immonium intermediates **66** [41]. It was observed that the reaction of **65a**,**b** with acetic anhydride results in the opening of the oxazine ring with the elimination of formaldehyde which leads to tetramides **67a**,**b**; the attempted acylation of the hydroxyl groups was not achieved (Scheme 11, ref. [41]).

Scheme 11



64

	R
a	*n*-C_5H_{11}
b	*n*-C_6H_{13}

65

	R	R^1
a	*n*-C_5H_{11}	cyclohexyl
b	*n*-C_6H_{13}	*n*-C_4H_9

66

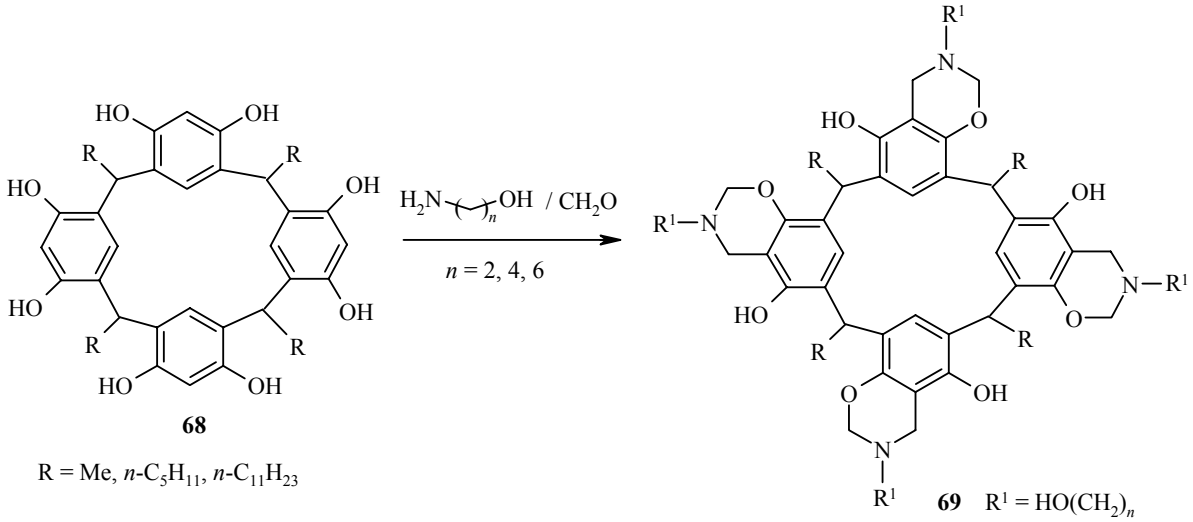
65a,b

67a,b

It should be mentioned that the tetrakis(O-methylation) of **65a**,**b** can be performed by treatment with *n*-butyllithium to deprotonate the hydroxyl group and using methyltriflate as a methylating reagent [37].

The condensation of resorcarenes **68** with amino alcohols and formaldehyde affords benzoxazine-based calixarenes **69** (Scheme 12, ref. [42]).

Scheme 12



68

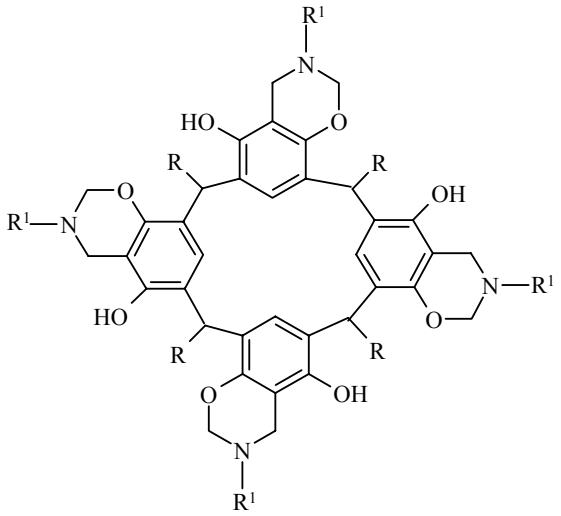
R = Me, *n*-C_5H_{11}, *n*-$C_{11}H_{23}$

69 $R^1 = HO(CH_2)_n$

It was observed that the chiral benzoxazine-based calixarene (**-**)-**70** undergoes the removal of formaldehyde molecule by treatment with hydrochloric acid in the *n*-propanol-water system to give resorcarene (**-**)-**71** [43]. This compound exists in the solid phase in a crown conformation; its crystallographic structure data are reported.

The HPLC enantiomeric resolution of inherently chiral benzoxazine-based calixarenes **72a-d** has been achieved, this experiment being proof of their chirality in solution (Scheme 13, ref. [40]).

It was established that chiral, lipophilic benzoxazine-based calixarene **73** forms Langmuir monolayers on water surfaces [44]. The Langmuir isotherm technique is a fast method for the estimation of enantioselection by chiral macrocyclic ligands forming Langmuir films on the water surface; this qualitative test gives information on the magnitude of enantioselection.

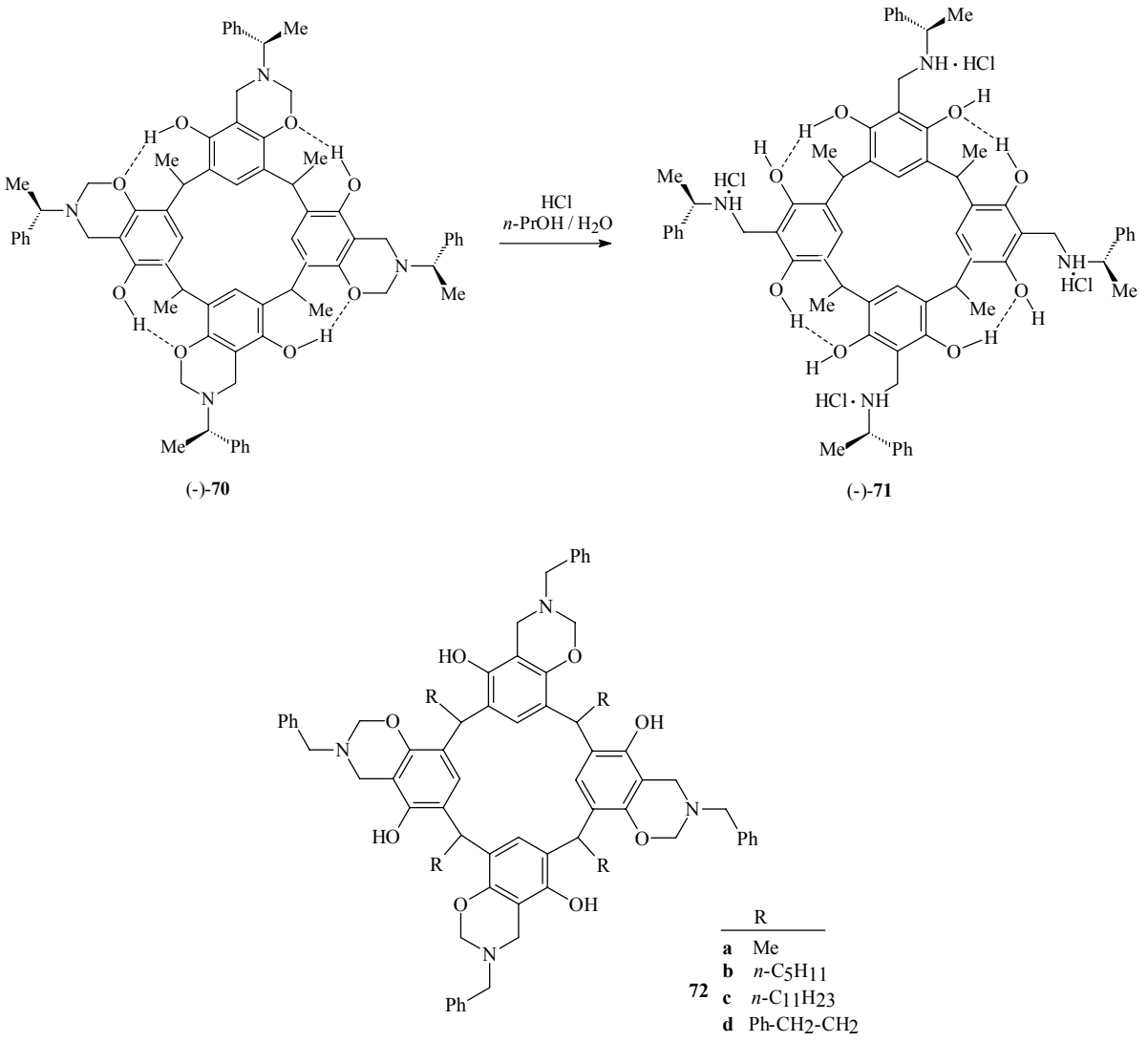


73

R = $C_{11}H_{23}$

R1 = PhCHMe

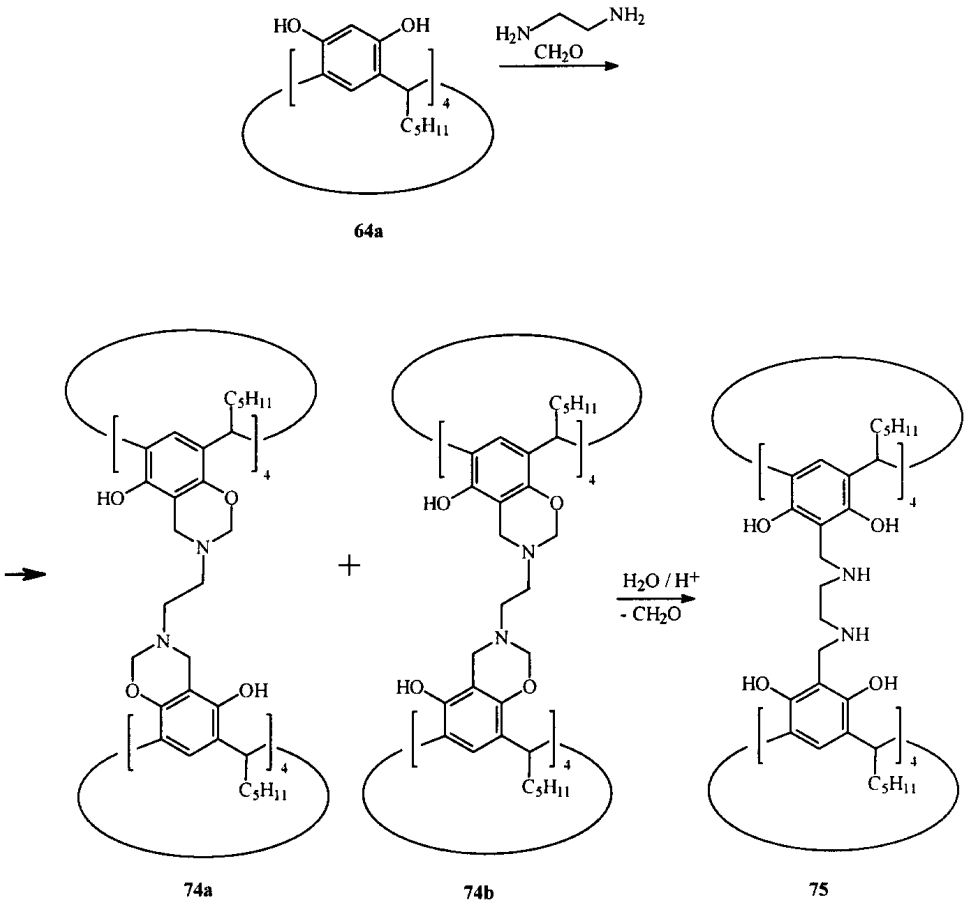
Scheme 13



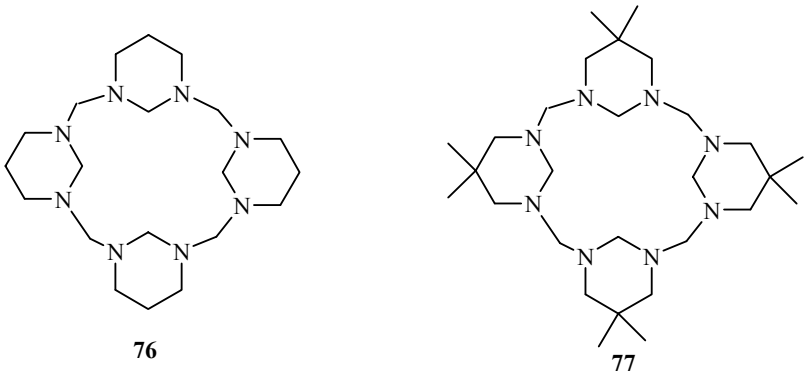
The condensation of resorcarene **64a** with ethylenediamine and formaldehyde under high dilution conditions affords the "dimer" **74** [45]. Two possible isomers, the chiral D_4-symmetrical **74a** and C_{4h}-symmetrical **74b**, could not be distinguished by NMR spectroscopy. It was observed that the cavities of both isomers collapse after some picoseconds because two resorcarene units adopt pinched cone conformations with C_2 symmetry. Due to this behavior, no inclusion compounds are formed [46]. The acid-catalyzed hydrolysis of **74** leads to oxazine ring opening resulting in the formation of secondary amine **75** (Scheme 14, ref. [45]).

In the review only selected examples of heterocalixarenes have been presented. One should mention here also polyazacompounds **76-79** with tetrahedrally situated nitrogen lone pair orbitals and high conformational flexibility [46], as well as the dione **80** [46] and annulenoid tetrathiafulvalenes **81** [47] (Scheme 15). Since many works dealing with calixarenes are reported [48-51] due to their application possibilities as receptors, especially in nuclear waste management, attention should also be paid to heterocalixarenes, as their analogues, which are not yet so much investigated. This topic is concerned with supramolecular chemistry [52-55], a rapidly developing research area of promising perspectives.

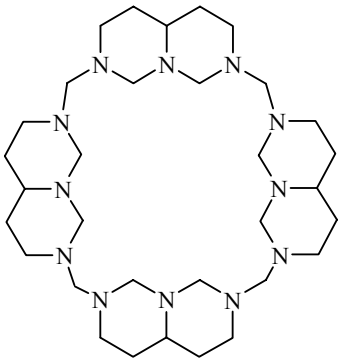
Scheme 14



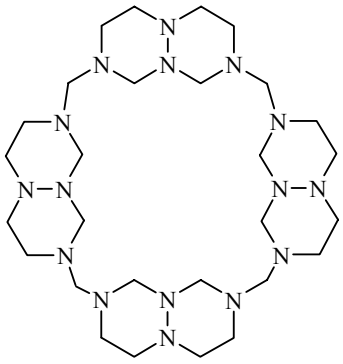
Scheme 15



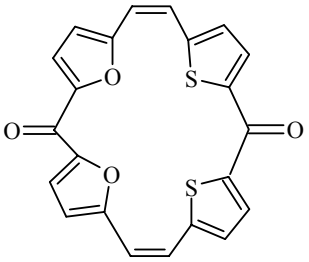
Scheme 15 (continued)



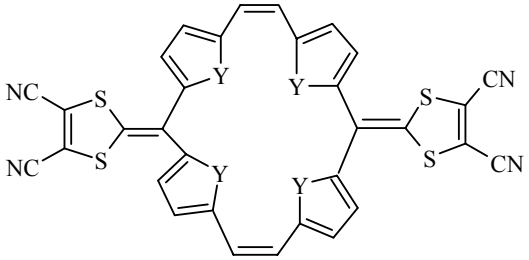
78



79



80



81

Y = O, S

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