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CALIXPYRROLES AND RELATED COMPOUNDS

Wanda Śliwa

Institute of Chemistry and Environmental Protection, Pedagogical University
al. Armii Krajowej 13/15, 42-201 Częstochowa, Poland
e-mail: w. sliwa @ wsp. czest. pl

Abstract- The chemistry of calixpyrroles and related compounds is reviewed. Calixpyrroles, including examples of expanded species are presented along with calixphyrins. Synthetic approaches, binding properties and application possibilities of the above compounds are described.

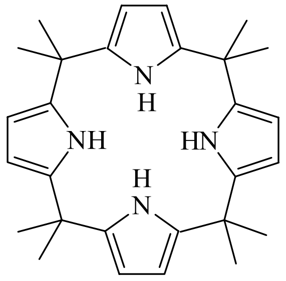
1. Introduction
2. Calixpyrroles
3. Calixphyrins
4. Conclusion

1. INTRODUCTION

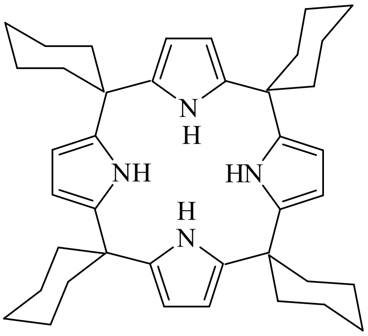
Calixarenes, promising receptors of small molecules or ions are a topic of an intense research. [1-5] Calixpyrroles, [6-11] a class of the above compounds, containing pyrrole units instead of phenolic ones are of a special interest as readily accessible binding agents for anions, [12-15] transition metal ions [16,17] and neutral species. [18,19] Receptors for anions are far less studied than those for cations. Since anions play a crucial role in chemistry [20] and biology,[21] the design of such compounds is of an importance. In the paper selected examples of calixpyrroles and calixphyrins are presented.

2. CALIXPYRROLES

Calixpyrroles, i.e. octaalkylporphyrinogens are synthesized by condensation of pyrrole with appropriate ketones in the presence of acid catalyst, e.g. **1** and **2** are obtained from pyrrole and acetone or cyclohexanone, respectively.[12]



1



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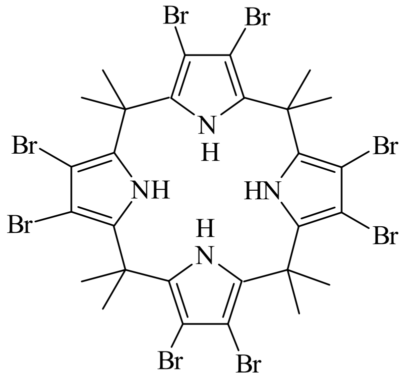
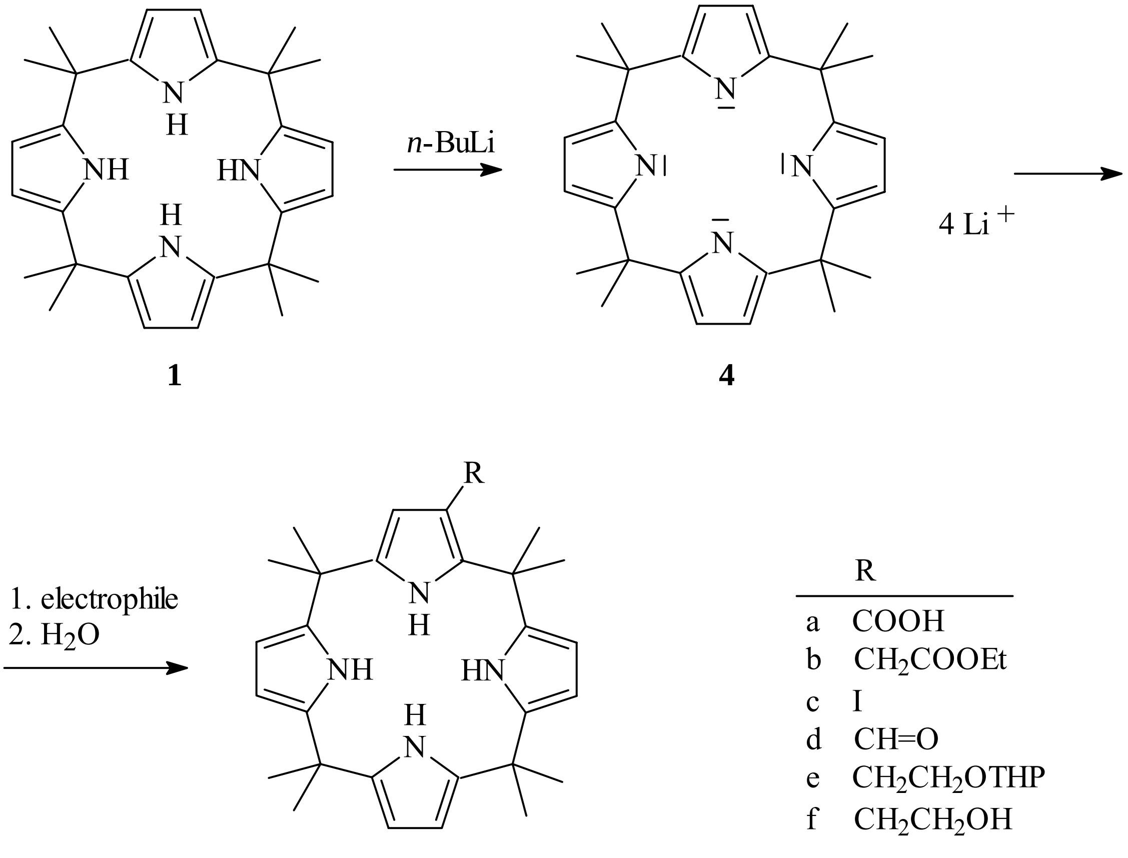


3

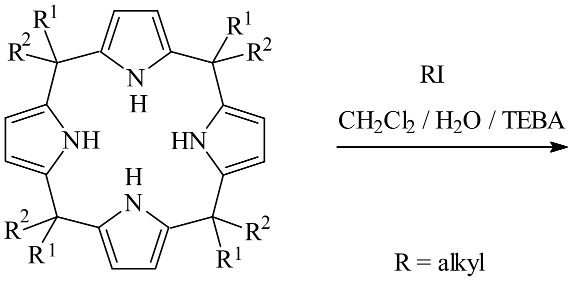
Functionalization of calixpyrroles is easy, for example the synthesis of **3** involves the bromination of **1** with NBS.[12] Calix[4]pyrroles serve for construction of colorimetric [22] and fluorescent [23] anion sensor systems , and anion selective electrodes. [24]

Lithiation of **1** leads to the lithiated species (**4**) which was subjected *in situ* to the addition of electrophiles. Reactions of **4** with carbon dioxide, ethyl bromoacetate, chloroiodide, *N*-formylpiperidine and 1-bromo-2-(tetrahydropyranyloxy)ethane afforded **5a**-**e**. The treatment of the derivative (**5e**) with *p*-toluenesulfonic acid gave compound (**5f**). [6]



	R
a	COOH
b	CH_2COOEt
c	I
d	CH=O
e	CH_2CH_2OTHP
f	CH_2CH_2OH

The alkylation of calix[4]pyrroles (**6a**) with alkyl iodides under phase transfer conditions leads to tetra-*N*-alkylated compounds (**6b**).[25]

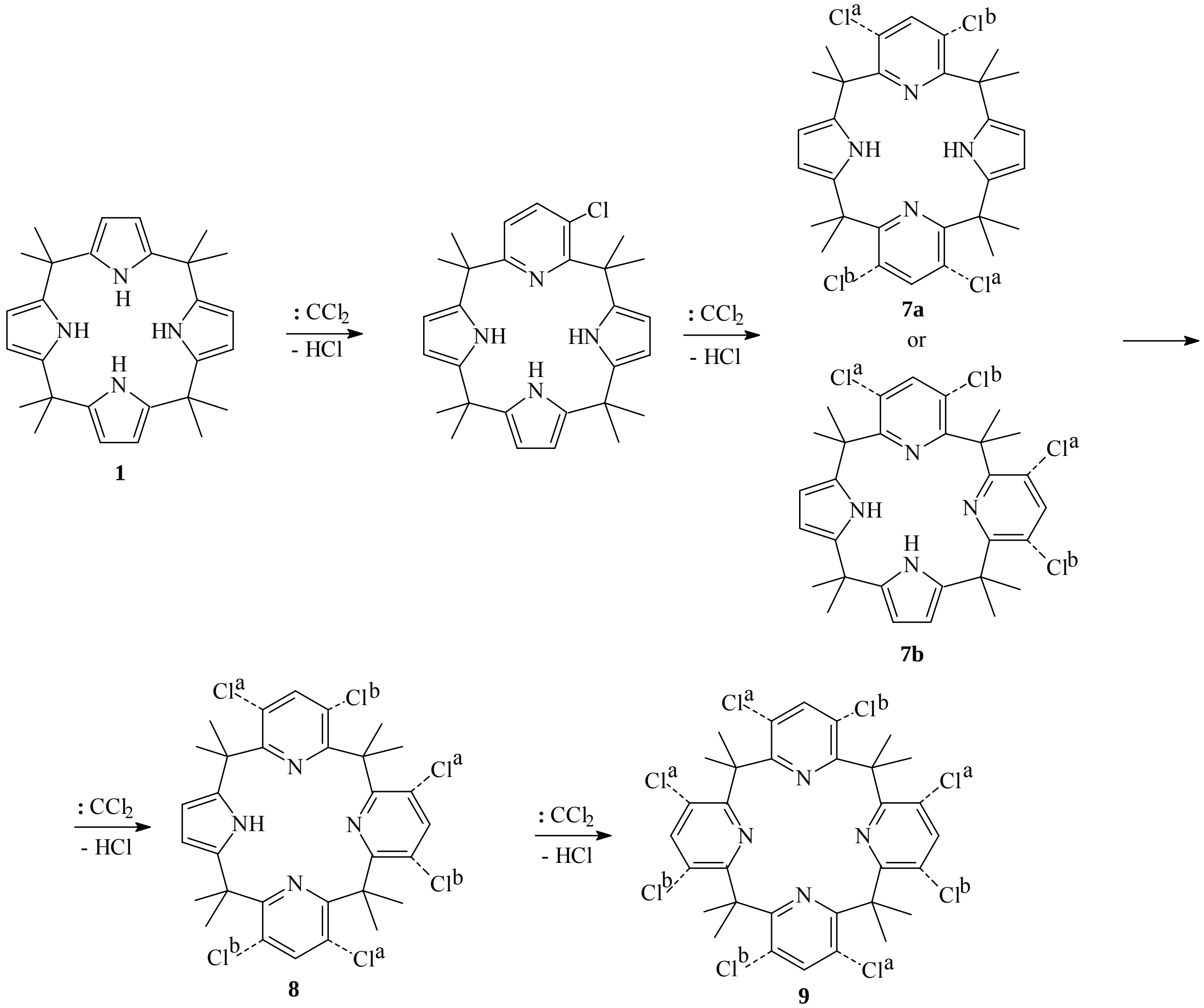


6a

$R^1 = R^2 = Me$
$R^1, R^2 = (CH_2)_4, (CH_2)_5$

6b

The ring expansion of calix[4]pyrrole (**1**) affording in a facile procedure calixpyridinopyrroles (**7a,b** and **8**) and calixpyridine (**9**) proceeds as follows.[26]



1

7a

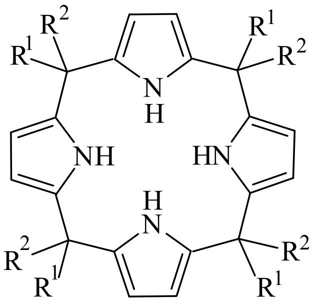
7b

8

9

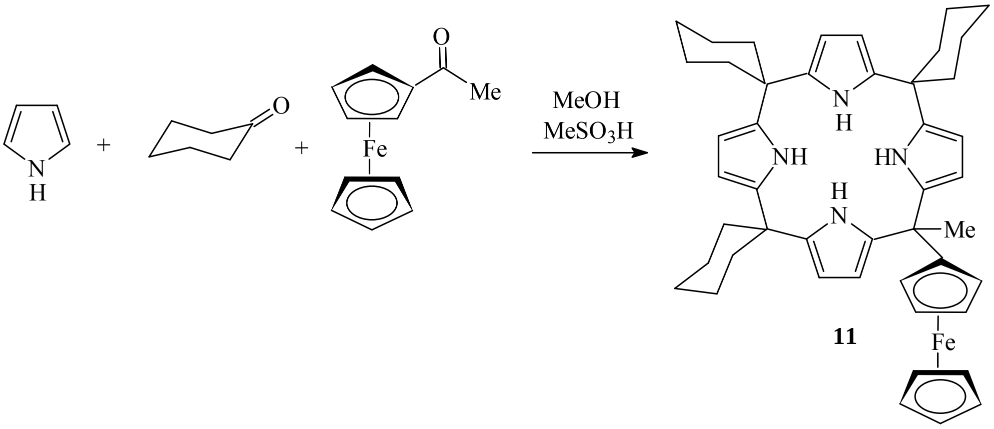
The chlorine atoms may be in position a or b, but not both

Calixpyrroles, e.g. **1** or **10** [12] form 1:1 complexes with F$^-$ and Cl$^-$ anions. [13]



1 $R^1 = R^2 = Me$
10 $R^1, R^2 = CH_2(CH_2)_3CH_2$-

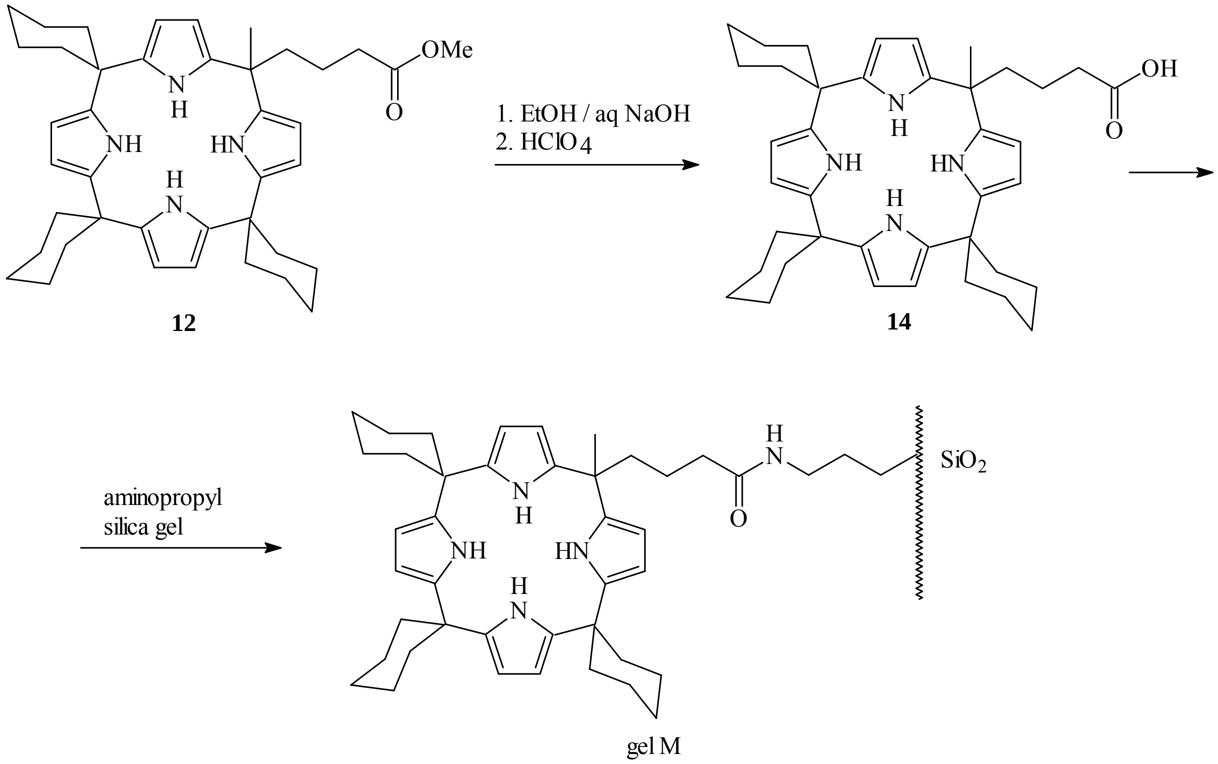
In these complexes calix[4]pyrroles (**1**) and (**10**) adopt the cone conformation with the anion situated above the cone and forming four hydrogen bonds with the four pyrrole NH groups.[21] However, **1** and **10** give with neutral molecules, e.g. alcohols and amides, 1:2 complexes.[21] In the conformational study of anion-binding properties of calixpyrroles the quantum mechanics density functional theory was used.[21]
In the search for anion receptors containing ferrocene unit,[27] compound (**11**) has been synthesized by condensation between pyrrole, cyclohexanone and acetylferrocene.[28]



11

Using ^1H NMR analysis in DMSO-d_6 / acetonitrile-d_3 (1:9 v/v) it was found that **11** binds F$^-$, Cl$^-$ and $H_2PO_4^-$ ions in this solvent mixture and may serve as electrochemical sensor for anions. A direct coordination mechanism is proposed, involving ferrocene CH and calixpyrrole NH hydrogen-bonding interactions with the anion.[27] It was established that **11** adopts the 1,3-alternate conformation in the solid state.[29,30]
Studying calix[4]pyrroles in the aspect of their properties of binding anionic and neutral species, two calix[4]pyrrole-modified silica gels have been prepared.[15] The process begins with the synthesis of **12** and **13**. Calixpyrrole (**12**) was obtained from pyrrole, cyclohexanone and methyl-4-acetylbutyrate in one step; **13** was synthesized from pyrrole, acetone, n-butyllithium and ethyl bromoacetate in two steps. Compounds (**12**) and (**13**) were hydrolyzed to give calix[4]pyrrole monoacids (**14**) and (**15**), respectively.

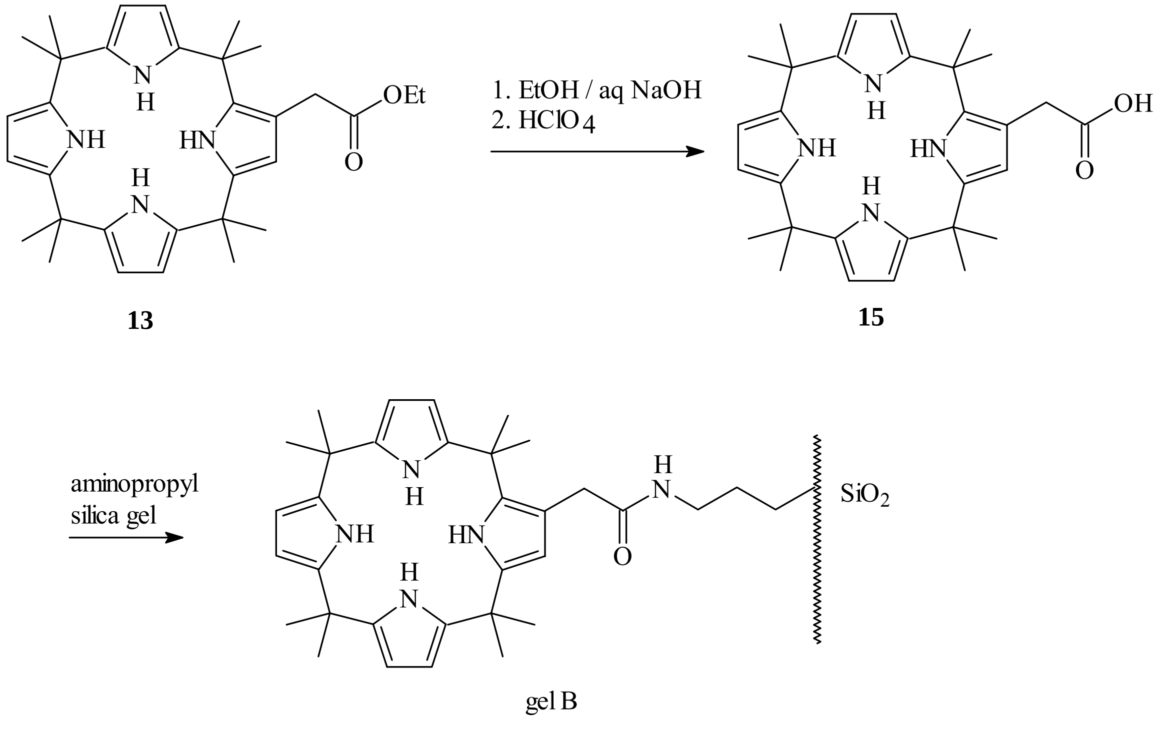
Coupling of **14** and **15** with aminopropyl silica gel gave two silica gel solid supports: gels M (*meso*-hook) and B (*β*-hook).



12

14

gel M

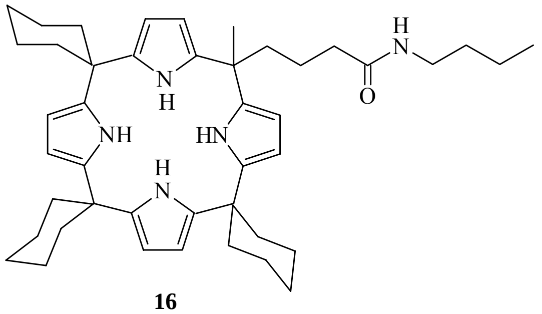


13

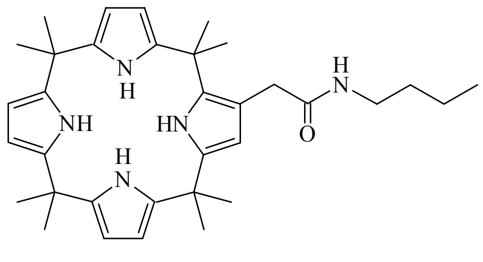
15

gel B

Calix[4]pyrroles (**16**) and (**17**) served as model compounds for the study of anion-binding properties of gels M and B.



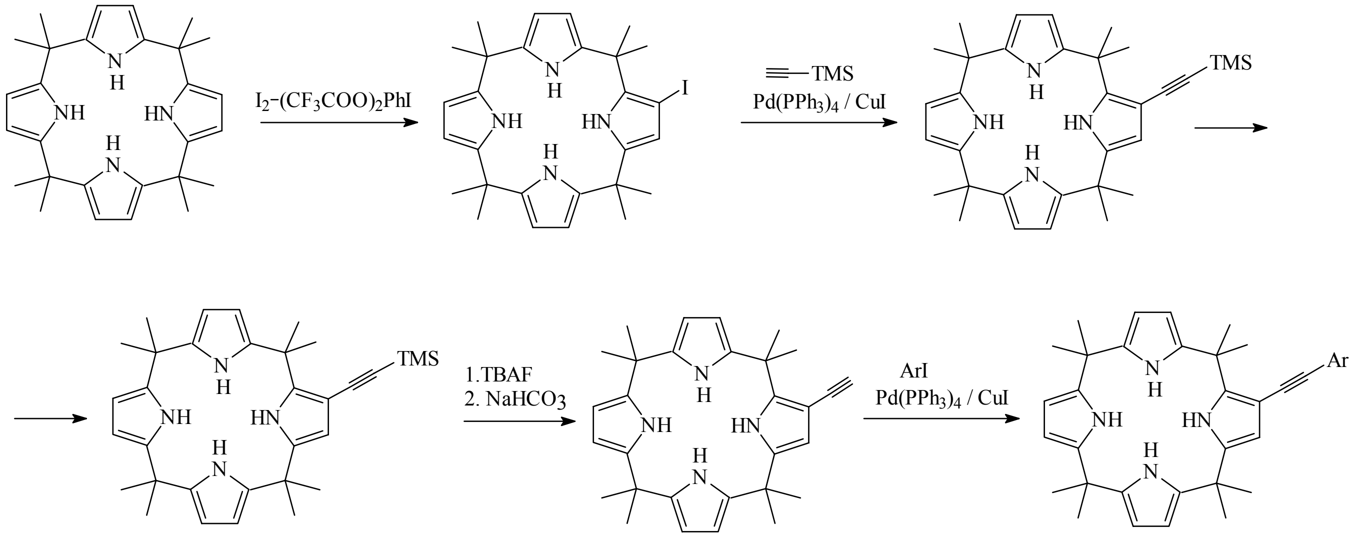
16



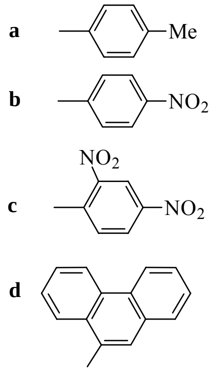
17

It was established that both gels M and B selectively bind fluoride, chloride, bromide, hydrogensulfate and dihydrogenphosphate anions, and gel M binds also benzoate, benzenesulfonate and Cbz protected amino acids, for example serine, glutamine and alanine, as well as phosphorylated derivatives of adenine. Gels M and B may also bind neutral species, for example polyfluorobiphenyls, serving as models of toxic polychlorobiphenyls. The above results show that gels M and B may be used as solid supports for the HPLC separation of N-protected amino acids, nucleotides, oligonucleotides and perfluorinated biphenyls.[15]

The following reactions lead to compounds (**18a-d**).[31]



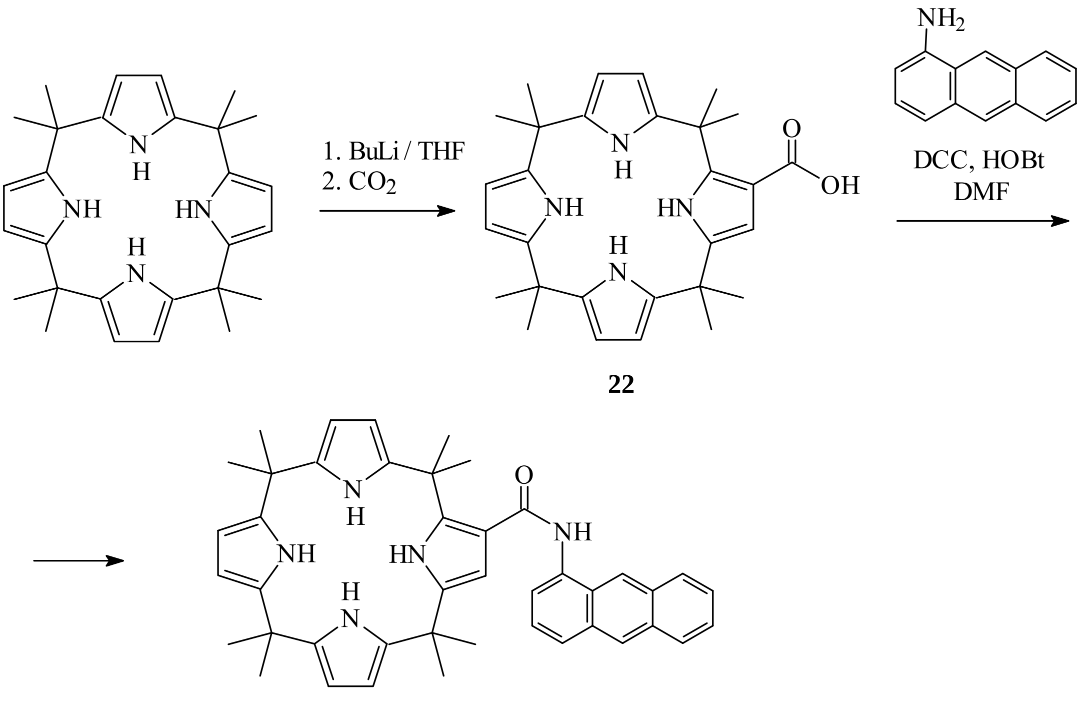
18



The analysis of UV spectra of **18b** and **18c** upon addition of anions such as F^-, Cl^- and $H_2PO_4^-$ in CH_2Cl_2 shows considerable red shifts in the λ_{max} values, resulting from the charge transfer from the bound anion to the electron deficient nitro- and dinitrobenzene groups mediated by the conjugating alkynyl bond serving as an electron wire. This observation suggests the possibility of application of **18b** and **18c** as anion sensors.[31]

In a search for optical sensors for anions,[32-34] fluorescent, anthracene-linked calix[4]pyrroles (**19**, **20** and **21**) have been synthesized. These compounds can detect the presence of anions (e.g. F^-, Cl^-, $H_2PO_4^-$) by quenching their fluorescence.[23] Calix[4]pyrroles are effective anion receptors in solution and in the solid state; when linked with a fluorescent reporter group they act as optical sensors for anions.

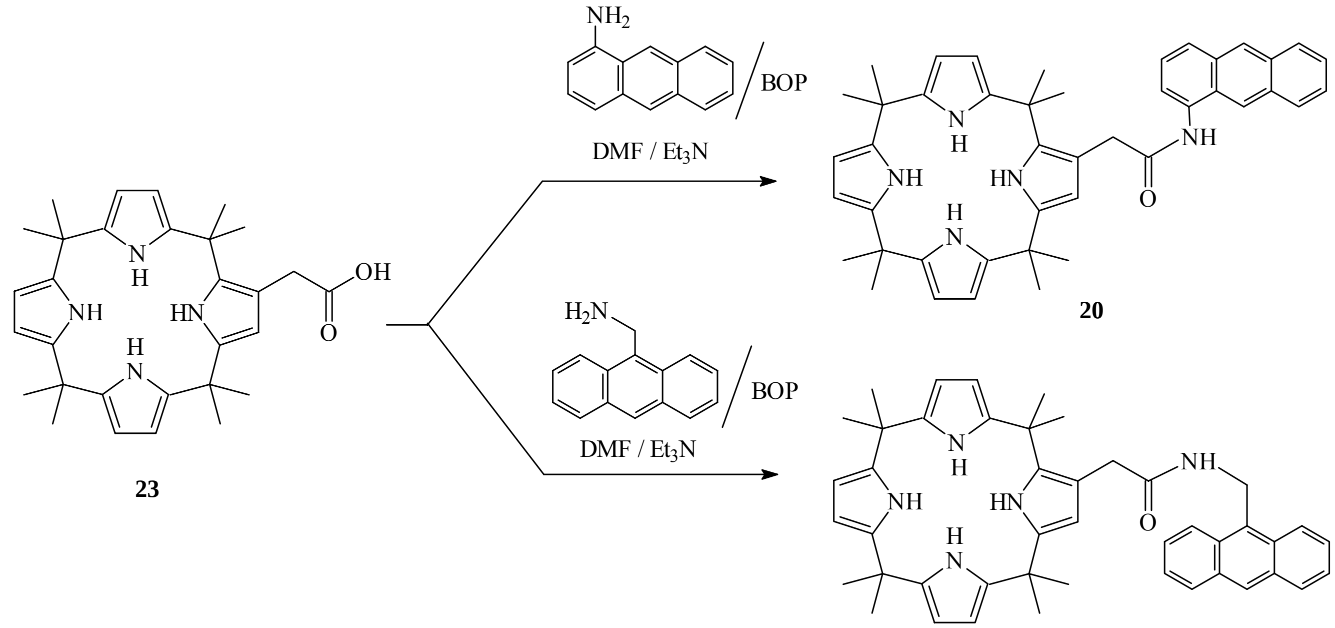
The synthesis of **19** begins with the reaction of **1** with n-butyllithium, followed by CO_2. The subsequent acidification with perchloric acid gave **22** .The activation of **22** with DCC and hydroxybenzotriazole hydrate (HOBt) in DMF, followed by treatment with 1-aminoanthracene afforded **19**.[23]



22

19

The reaction of calixpyrrole monoacid (**23**) [15] with 1-aminoanthracene using the benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP) amide coupling agent in DMF in the presence of Et_3N leads to **20**; in an analogous way **21** has been obtained upon treatment of **23** with 9-aminomethylanthracene.



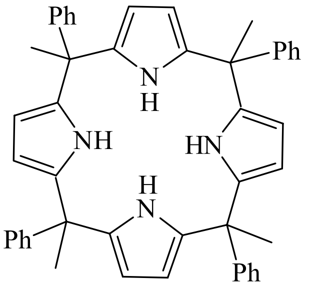
23

20

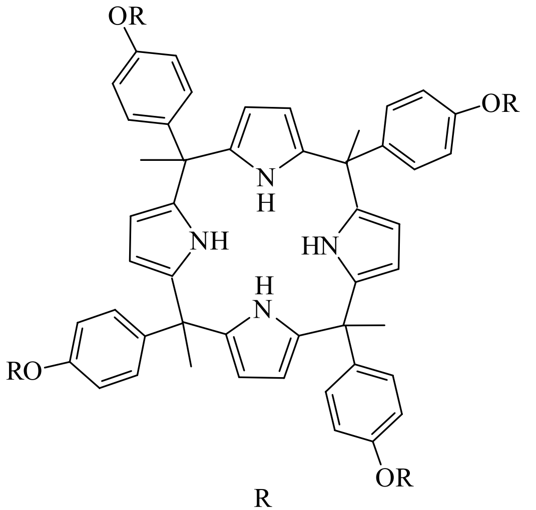
21

In order to perform quenching experiments, solutions of **19**, **20** and **21** in CH_2Cl_2 or MeCN were treated with solutions of anions (F^-, Cl^- or $H_2PO_4^-$). As a result a significant fluorescence quenching took place, the most efficient in the case of **19** and the least efficient in the case of **21**.[23]

In the study of anion binding receptors [22,23] many derivatives of octamethylcalix[4]pyrrole (**1**) have been investigated, e.g. **24** [35] and **25a,b**. [36,37]

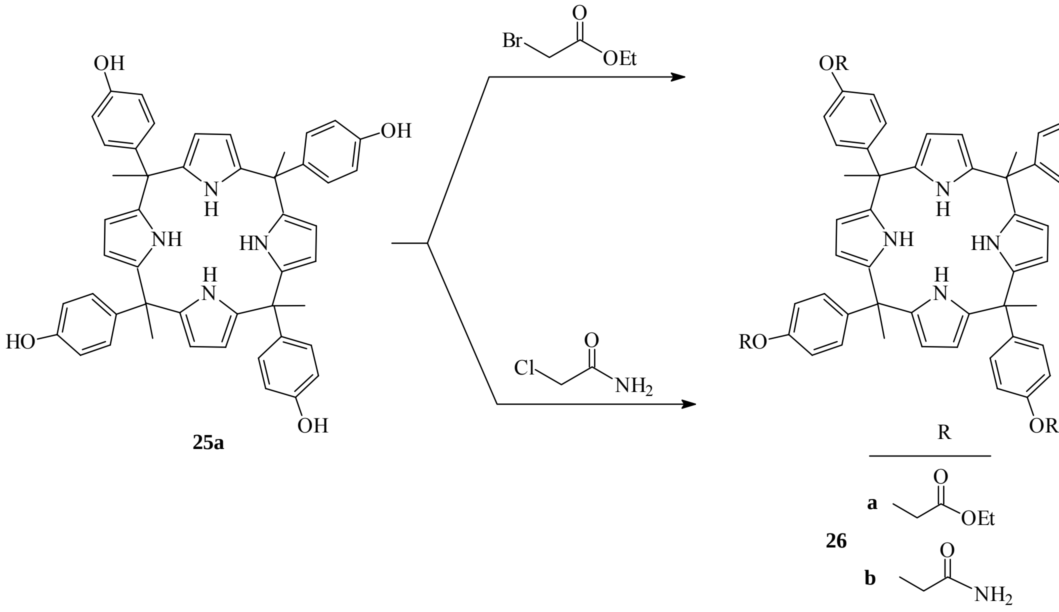


24



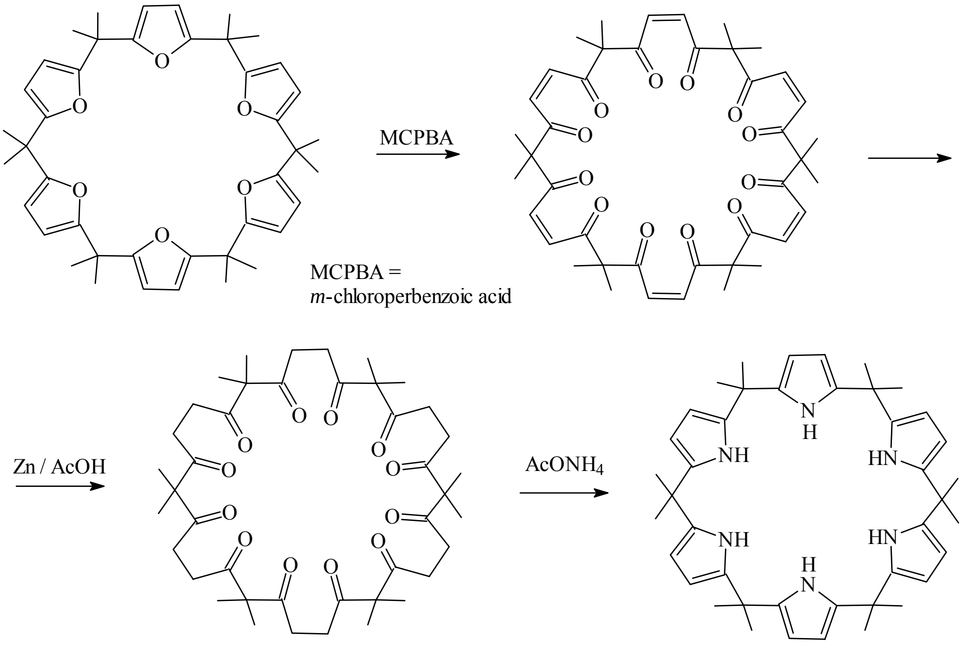
		R
25	**a**	H
	b	Me

In order to achieve a deeper cavity of these species, **25a** has been submitted to reactions with ethyl bromoacetate and with 2-chloro-*N*,*N*-diethylacetamide leading to compounds (**26a,b**), respectively. [38]



Binding properties of **26a,b** have been investigated using ^{1}H NMR spectral titration in DMSO-d_6. It was found that **26a,b** selectively bind F^- ion in DMSO-d_6 and do not interact with Cl^-, Br^-, I^-, HSO_4^- nor $H_2PO_4^-$ anions. [38]

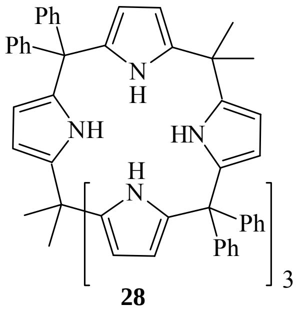
As an example of expanded calixpyrrole may serve calix[6]pyrrole (**27**) obtained as follows. [39]



27

The X-Ray crystal structures of 1:1 complexes of **27** with Bu_4NCl and Bu_4NBr have been investigated. It was observed that **27** adopts D_{3d} symmetry and encapsulates the halide ions within its cavity *via* six N-H hydrogen bonds. [20] It is worth noting that **27** binds Cl^- ion considerably stronger than does **1**, the cavity of the latter being too small for this purpose. Calixpyrrole (**1**) does not form complexes with F^- and Cl^- by the inclusion of these anions within its cavity which is too small; complexation occurs by facial arrangement involving hydrogen bonding interactions of anion with four pyrrole NH groups. [20]

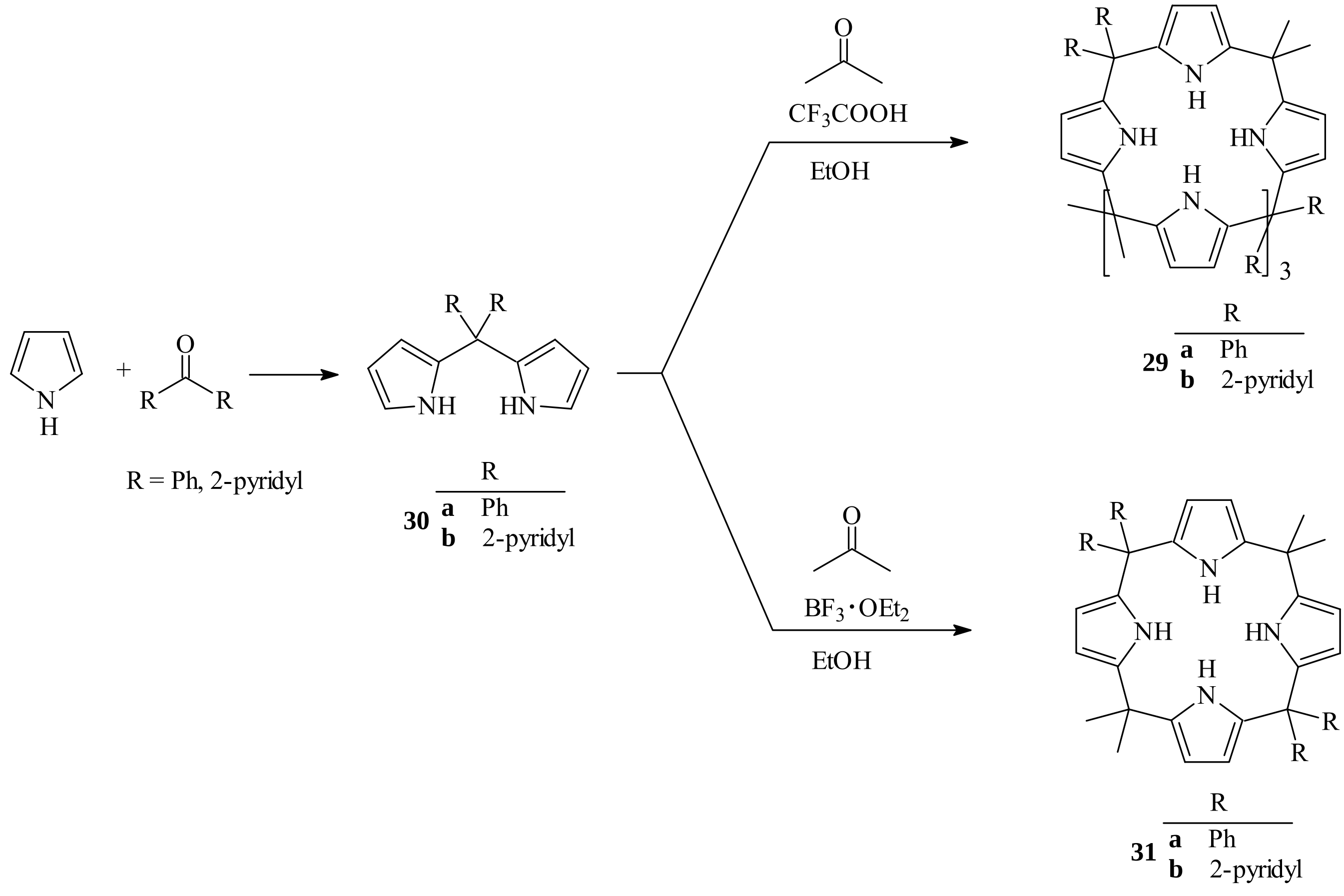
Calix[6]pyrrole (**28**) [39,40,41] strongly binds large anions such as I$^-$ as well as electron deficient aromatic guests due to the more extended cavity than in the case of **24** [35] which is not able to complex the above species. [20,22]



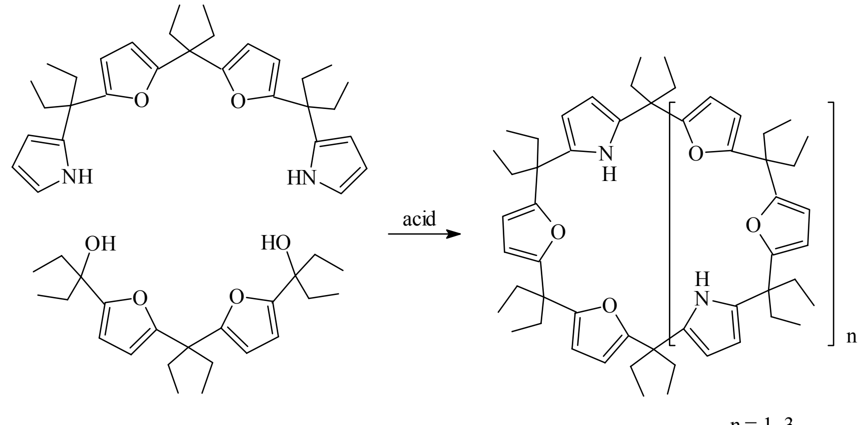
28

The complexation properties of **28** have been investigated with the use of ^{1}H NMR spectrometry. [12,23] It was established that **28** adopts cone-like conformation able to incorporate guests. [20] The binding order of **28** is I$^-$ > F$^-$ >> Cl$^-$ > Br$^-$ in contrast to complexing properties of octamethylcalix[4]pyrrole (**1)** for which the binding order is F$^-$ >> Cl$^-$ > Br$^-$ > I$^-$. Calix[6]pyrrole (**28**) binds also trihalogenated species such as trifluoroacetate, trifluoroethanol, trichloroethanol and tosylate anion, [41] which form only weak complexes with smaller calix[4]pyrroles.

Expanded calix[6]pyrroles (**29a,b**) have been investigated.[40] Their synthesis begins with the condensation of pyrrole with benzophenone or di-(2-pyridyl) ketone, leading to compounds (**30a,b**). The reaction of **30a,b** with acetone in the presence of CF_3COOH affords expanded *meso*-substituted calix[6]pyrroles (**29a,b**), while in the presence of $BF_3{\cdot}OEt_2$ calix[4]pyrroles (**31a,b**) are formed.[40]

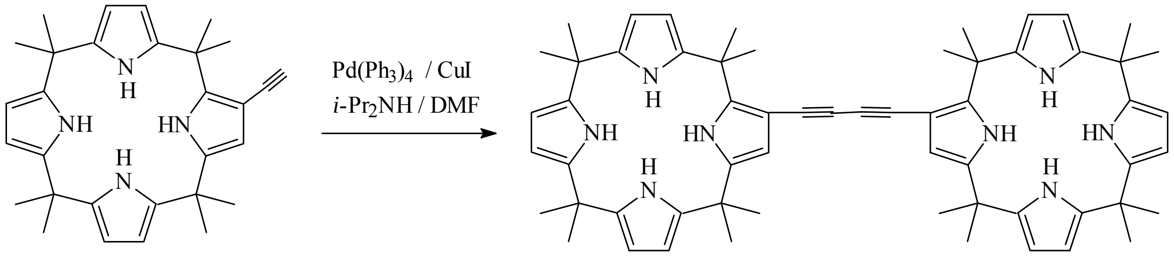


One should mention here also super-expanded calixfuranopyrroles (**32**), obtained as follows: [42]

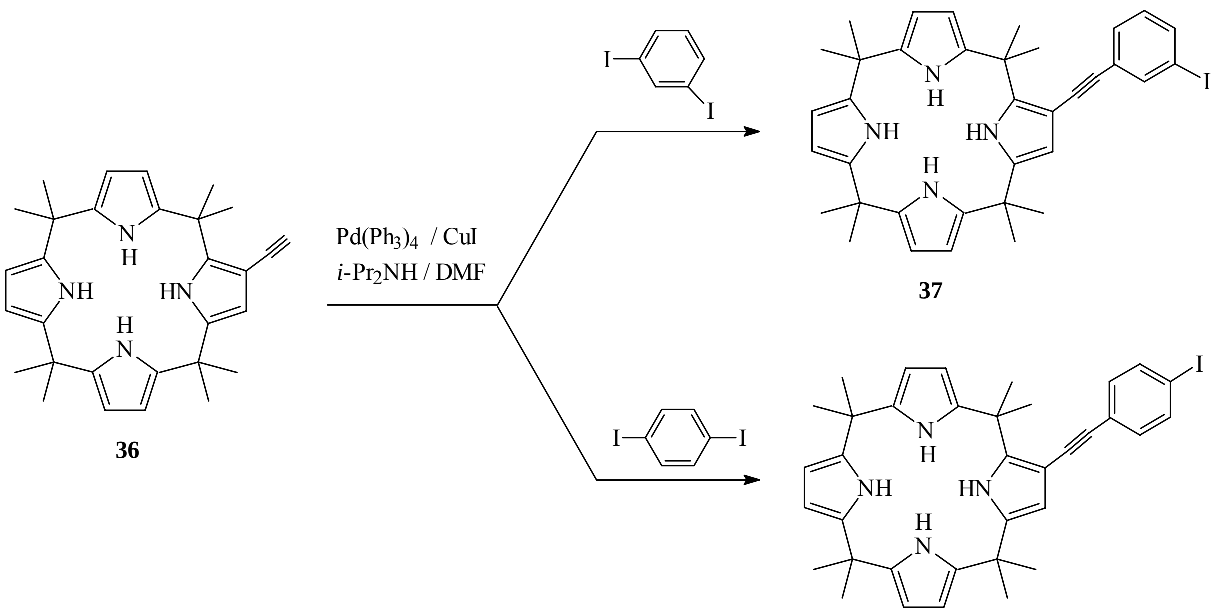


32

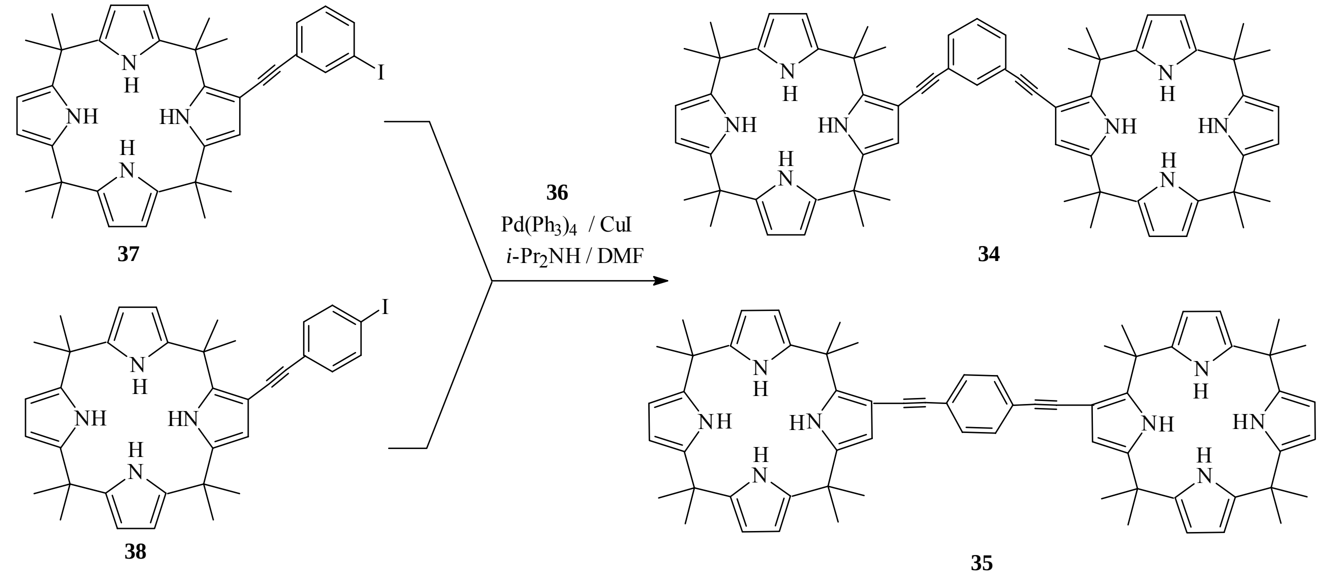
In the search for receptors of anionic species, acetylene-linked calixpyrrole dimers (**33**, **34** and **35)** have been obtained. Their synthesis involves a palladium(0) catalyzed C-C bond formation.[31,43-45] The dimerization of ethynylcalix[4]pyrrole (**36)** leads to **33** while its treatment with diiodobenzenes affords derivatives (**37)** and (**38)**, reacting with **36** to give **34** and **35**.



36 **33**



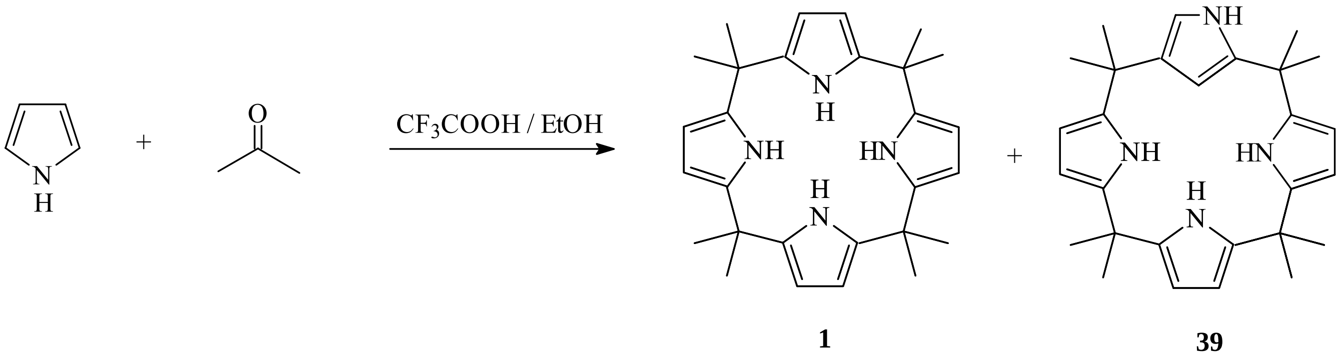
36 **37** **38**



37 **38** **34** **35**

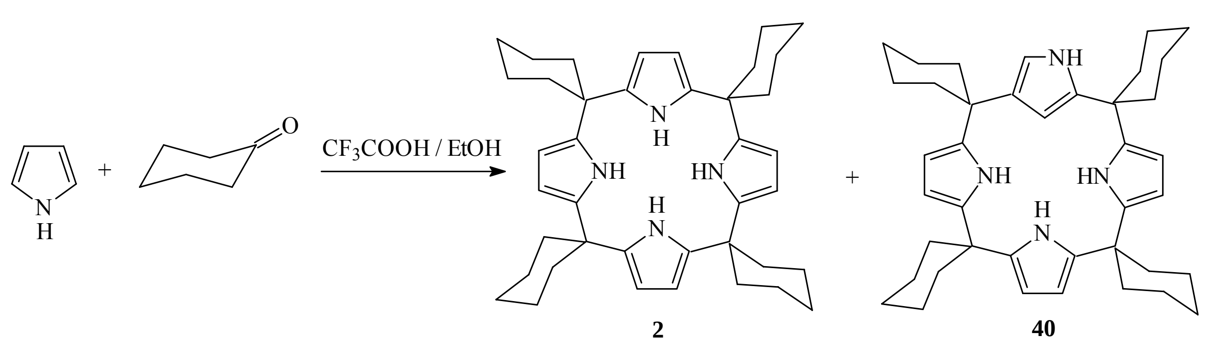
Investigation of binding properties of obtained compounds towards anions has shown that **33** forms with benzoate and phthalate ions 1:2 complexes, while with isophthalate anion the 1:1 stoichiometry and a higher association constant have been observed.[43]

Confused calixpyrroles are known; for example the reaction of pyrrole with acetone in ethanol carried out in the presence of CF_3COOH as catalyst afforded the mixture of calix[4]pyrrole (**1**) and confused calix[4]pyrrole (**39**), the former being the major product.[46]



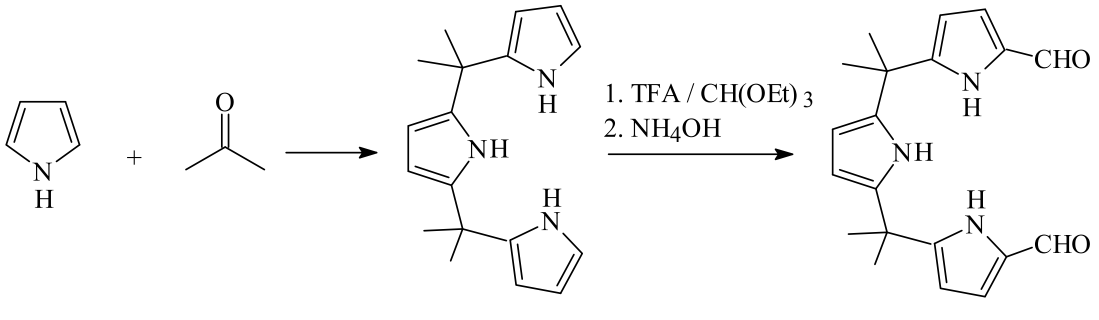
1 **39**

The cyclocondensation of pyrrole with cyclohexanone under these conditions leads in an analogous way to the mixture of calixpyrroles (**2**) (major product) and (**40**).[46]

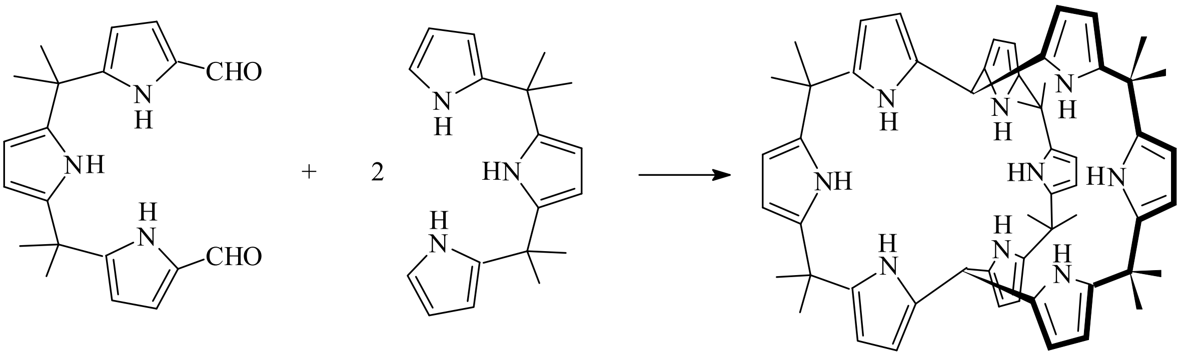


2 **40**

The bicyclic[3.3.3]nonapyrrole (**41**) is the first example of cryptand-like calixpyrroles. [47] The synthesis of **41** begins with the reaction of pyrrole with acetone leading to tripyrrane (**42**) [48] which was formylated to give the tripyrrane aldehyde (**43**). The acid-catalyzed condensation between **43** and **42** affords cryptand-like calixpyrrole (**41**). [47]



42 **43**

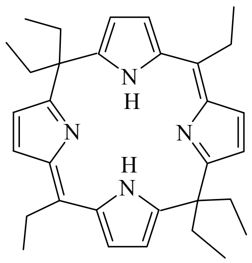


43 **42** **41**

It was found that **41** binds fluoride, chloride, bromide, nitrate and dihydrogenphosphate anions, the binding mode, however, is different from that of simple calixpyrroles. [47]

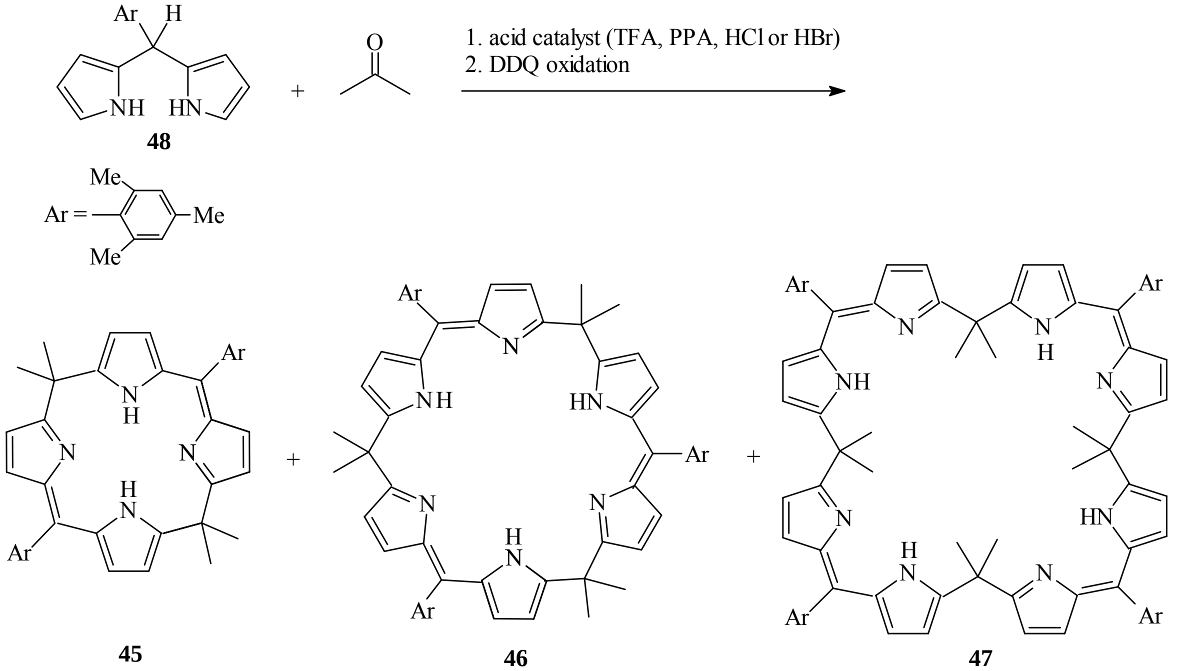
3. CALIXPHYRINS

Calix[4]phyrins, i.e. porphodimethenes lie at the intersection between calixpyrroles and porphyrins. [49-51] Calix[4]phyrin (**44**) belongs to compounds having nonconjugated character of calixpyrroles and conjugated character of porphyrins. [52]



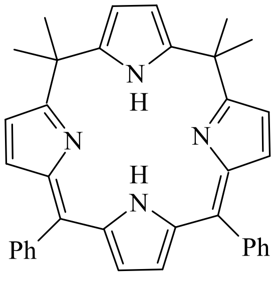
41

A simple synthesis of calix[4]phyrin (**45**) and its two homologs calix[6]- and calix[8]phyrins (**46**) and (**47**), respectively, has been reported.[53] These compounds are obtained by the acid-catalyzed coupling of mesityldipyrrolylmethane (**45**) with acetone, followed by DDQ oxidation.[54]



Compounds (**45-47**) are promising as receptors. It was found that they bind anions, **45** forms complexes with Cu^{II} and Zn^{II}, and **46** with Co^{III} and Ru^{III} ions.[53]

Other examples of calixphyrins are **49**,[55] **50**[56] and the confused compound (**51**).[56]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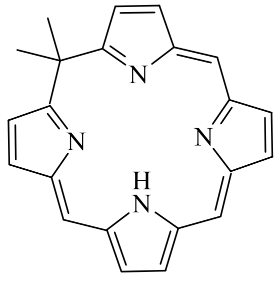
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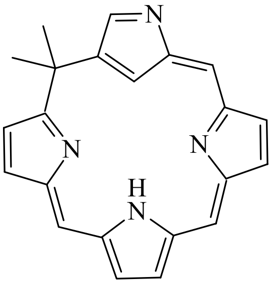
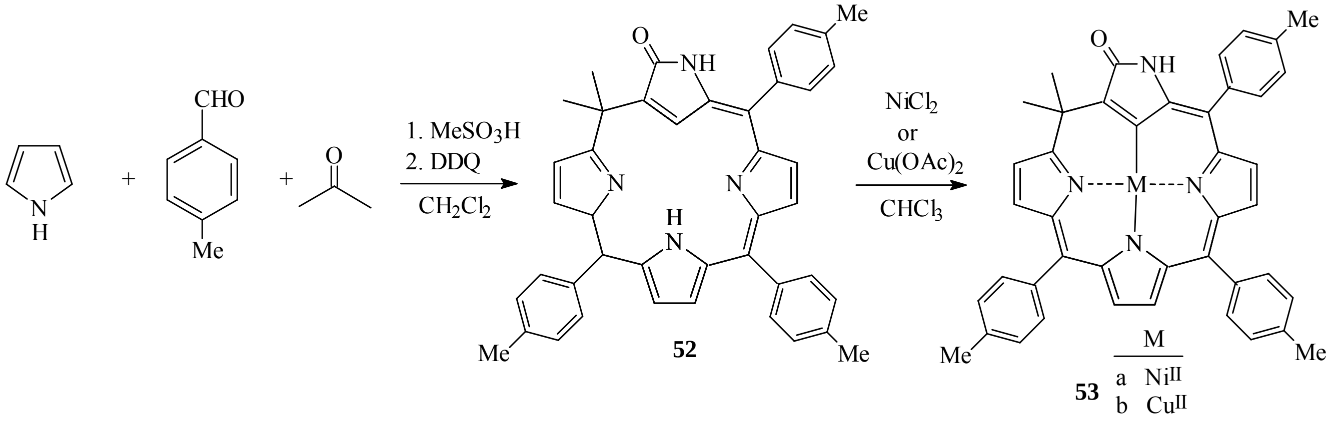

51

It is of interest that the confused species (**51**) may bind metal ions *via* formation of a metal-carbon bond leading to organometallic compounds.

N-Confused calixphyrin (**52**) containing an amide group in the confused pyrrole ring has been obtained in the reaction of pyrrole with *p*-tolualdehyde and acetone followed by oxidation with DDQ.[56,57] The obtained (**52**) forms Ni^{II} and Cu^{II} complexes (**53a,b**) by treatment with $NiCl_2$ or $Cu(OAc)_2$, respectively.



4. CONCLUSION

Numerous works deal with calixpyrroles, so expanded and confused species, as well as with calixphyrins; for example ruthenium complexes of calixpyrroles have been reported. [58,59] However, a special attention is paid to anionic receptors [60] of this kind, due to the significant role of anion recognition in chemical and biological processes. [61-63] From this viewpoint the design of new calixpyrroles, which are able to bind anions is of a great importance. [64,65]

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