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Synthesis and receptor properties of calix[4]pyrroles

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Published data about the synthesis and complexing properties of calix[4]pyrroles towards anions, ion pairs and neutral molecules of various nature are analyzed, summarized and classified. Synthetic approaches to the parent macrocycles and methods of their functionalization are presented. General principles, mechanisms and driving forces of the formation of calix[4]pyrrole-based supramolecular complexes are disscussed. Most attention is concentrated on the factors providing effective control of the formation of such structure.
The bibliography includes 79 references.

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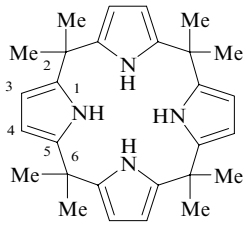
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I. Introduction

Calix[*n*]pyrroles form a special class of conformationally flexible nonaromatic tetrapyrrole macrocycles having high compexing ability towards ions and neutral molecules. The ease of functionalization enables wide use of these compounds as molecular platforms for the design of preorganized three-dimensional receptors for substrates of a particular type.[1 – 10]

Calix[*n*]pyrrole (**1**) was first synthesized by Baeyer in 1886 as a white crystalline powder by condensation of pyrrole and acetone and was given the name acetonepyrrole (taken from Ref. 1). Later, the structure of the compound was determined by Tronov and Chelintsev (see Ref. 1), who renamed it as α,β,γ,δ-octamethylporphyrinogen according to the Fischer Nomenclature for pyrrole compounds.[11 – 13]

Structure 1



1

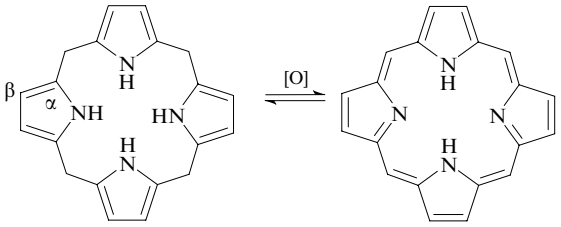
The simplest porphyrinogen is a natural colourless macrocyclic compound comprising four pyrrole moieties linked by sp^3 carbon bridges at the 2- and 5 positions of the ring.[14 – 16] Upon oxidation, it can be transformed into porphyrin (Scheme 1). The presence of two alkyl or aryl groups in the *meso*-position of octaalkylporphyrinogens makes such compounds resistant to oxidation. Until recently, they received far less attention than porphyrins but recently they caught the interest of researchers as anion receptors.[1 – 10]

The studies of these macrocycles have been started under the guidance of Professor Sessler, who proposed a new name for *meso*-octaalkylporphyrinogenes, namely, calix[*n*]pyrroles, similarly to calix[*n*]arenes.

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Scheme 1



Like calix[*n*]arenes, calix[*n*]pyrroles are named using trivial nomenclature.[1] According to this nomenclature, the number of pyrrole moieties in the macrocycle is indicated in the square brackets, and substituents can be located at positions 3 or 4 of the pyrrole rings (designated as β) or at the bridging carbon atoms (designated as *meso*). Like calix[*n*]arenes, calix[*n*]pyrroles are conformationally flexible molecules and can exist in four main conformations (Fig. 1). The X-ray diffraction studies and quantum chemical calculations performed by Sessler and co-workers [1, 17] have shown that the 1,3-alternate conformation is the most energetically favourable both in the solid state and in non-polar aprotic solvents.

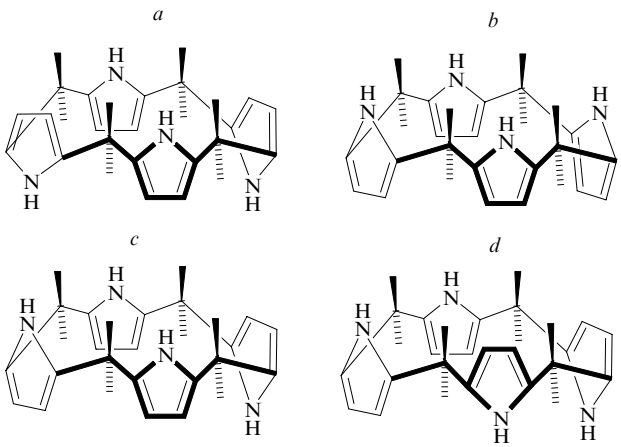


Figure 1. Conformations of calix[4]pyrrole (**1**): 1,3-alternate (*a*), cone (*b*), partial cone (*c*) and 1,2-alternate (*d*).[17]

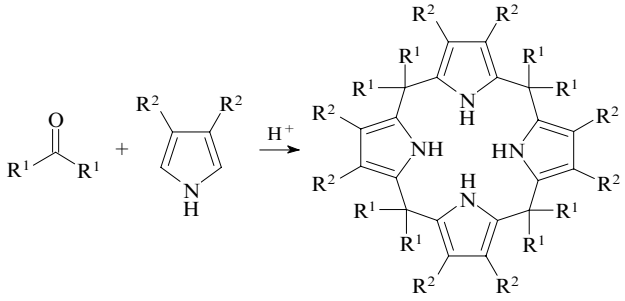
On anion binding, the 1,3-alternate conformation transforms into the cone conformation. The 1,2-alternate conformation is achieved in the presence of some polar ligands. However, the partial cone conformation, being the second most favourable conformation according to calculations,[18] has not yet been detected experimentally.

II. Key methods of synthesis of calix[4]pyrroles

Calix[*n*]pyrroles **1**–**4** symmetrically substituted at the *meso*- and/or β-positions are synhthesized by acid-catalyzed condensation of the corresponding symmetrical dialkyl ketones with 2,5-unsubstituted pyrroles, the product yields being ~60% (Scheme 2).[2–6, 19–21]

The condensation of cyclohexanone with unsubstituted or 3,4-dimethoxy-substituted pyrrole yields *meso*-cyclohexyl-substituted calix[*n*]pyrroles **5** and **6** (Scheme 3).[3–5]

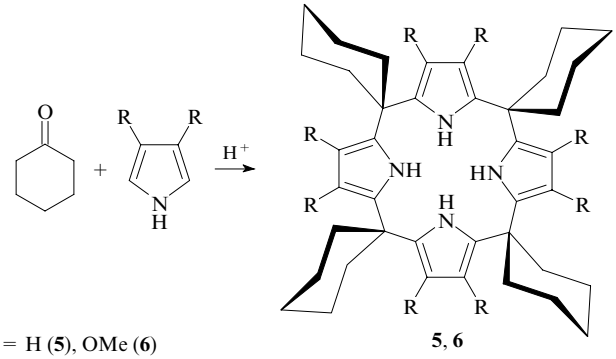
Scheme 2



1–**4**

R^2 = H: R^1 = Me (**1**), Et (**2**); R^2 = F: R^1 = Me (**3**), Et (**4**)

Scheme 3

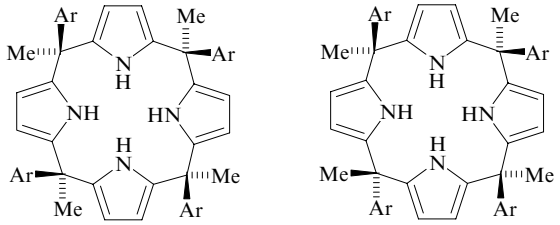


5, **6**

R = H (**5**), OMe (**6**)

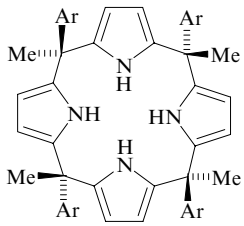
Calix[*n*]pyrroles **7** and **8** having both methyl and aryl substitutents in the *meso*-positions were synthesized by the reaction of the corresponding acetophenones with pyrrole.[22–25] These compounds exist as mixtures of configurational isomers (α,α,α,α; α,α,α,β; a,α,β,β and α,β,α,β), differing in the spatial arrangement of the substituents in

Structures 7, 8

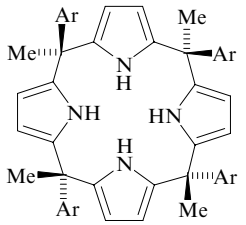


α,α,α,α-**7**, **8**

α,α,α,β-**7**, **8**



α,β,α,β-**7**, **8**



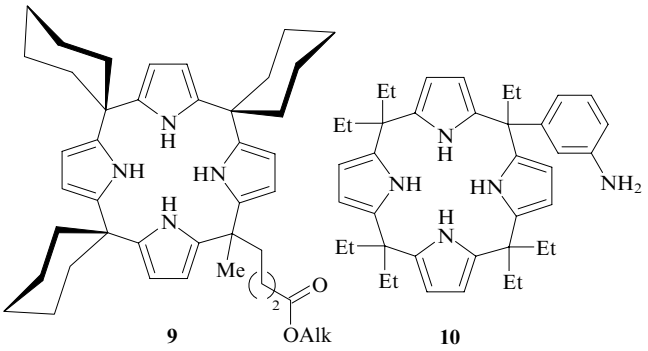
α,α,β,β-**7**, **8**

Ar = C_6H_4OH-4 (**7**), C_6H_4OMe-4 (**8**)

the macrocycle.† They are readily separated by SiO_2 column chromatography (elution with 6%–8% solution of MeOH in chloroform).

The reaction of pyrrole with a mixture of two different ketones gives rise to unsymmetrical calix[*n*]pyrroles bearing a different substituent, as compared with other ones, at one of the *meso*-carbon atoms of the macrocycle, *e.g.*, compounds **9** and **10**.[26,27]

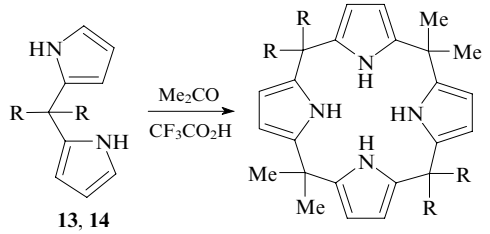
Structures 9, 10



9 **10**

To obtain calix[*n*]pyrroles **11** and **12** having two different *meso*-substitutents at the opposite sides of the macrocycle, bis(pyrrol-2-yl)methanes (dipyrrolylmethanes) are used as the starting compounds.[28] The reaction of *meso*-diaryl-substituted dipyrrolylmethanes **13**, **14** with acetone in the presence of boron trifluoride etherate afforded the corresponding macrocycles in 75% yield (Scheme 4).

Scheme 4

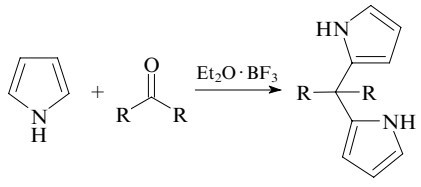


13, **14** **11**, **12**

R = Ph (**11**, **13**), 2-Py (**12**, **14**) (Py is pyridyl)

The starting dipyrrole compounds **13** and **14** are readily obtained by the reaction of pyrrole with benzophenone and its 2-pyridyl analogue under the same conditions (Scheme 5).

Scheme 5



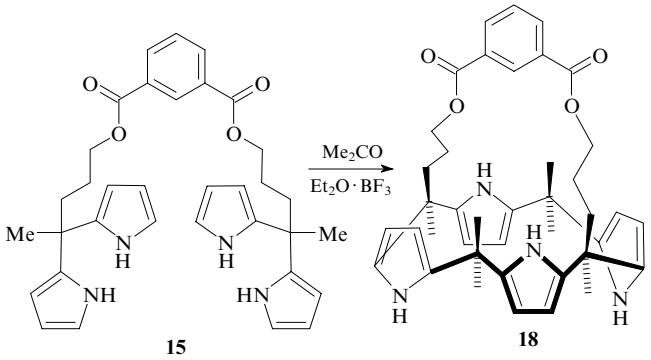
13, **14**

R = Ph (**13**), 2-Py (**14**)

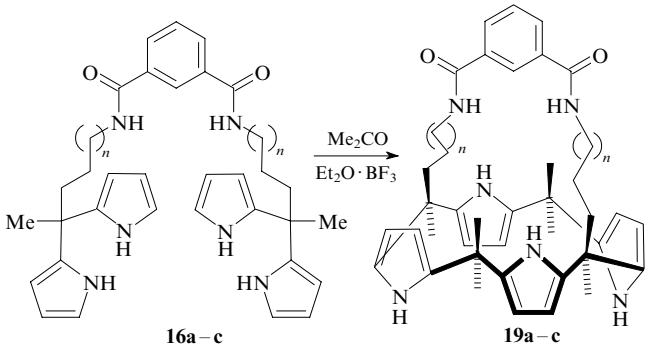
In regard to the design of spatially pre-organized macrocycles, great opportunities are offered by the synthetic approach to calix[*n*]pyrroles based on the use, as the key compounds, of bis(dipyrromethanes) in which the dipyrrole moieties are covalently bonded to each other by aryl-containing bridges bearing the necessary functional groups. These macrocycles are intended for the selective binding of substrates of various nature.

By the reaction of appropriate bis(dipyrrolylmethanes) **15**–**17** with acetone in the presence of catalytic amounts of boron trifluoride etherate, Sessler and co-workers[29–32] synthesized so-called strapped macrocycles **18**–**20** in moderate yields (~15%). In these compounds, calix[4]pyrrole moieties possess the 1,3-alternate conformation (Scheme 6).

Scheme 6

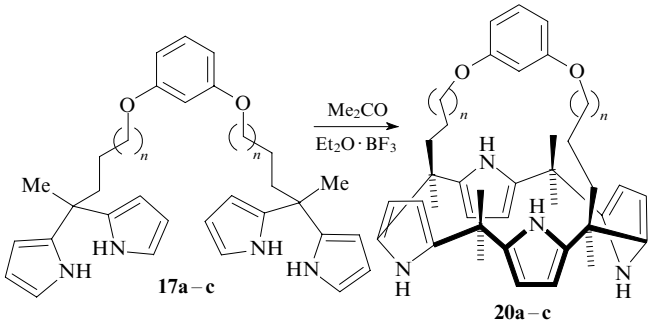


15 **18**



16a–c **19a–c**

n = 1 (**a**), 2 (**b**), 3 (**c**)



17a–c **20a–c**

n = 2 (**a**), 3 (**b**), 4 (**c**)

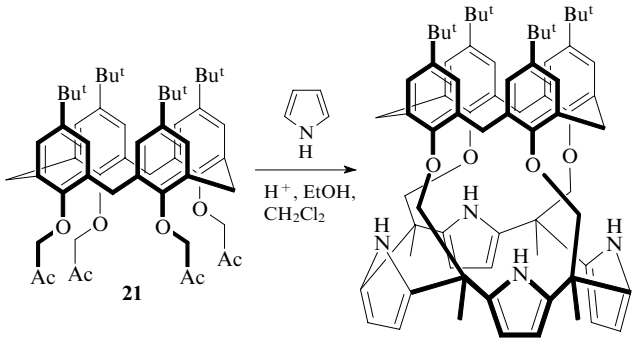
It was found experimentally that despite the significant complication of the molecular structure, calix[4]pyrrole macrocycles **18**–**20** retain the conformational flexibility: on binding halide anions, the 1,3-alternate conformation transforms into the cone or partial cone conformation.[9–32]

Using tetraacetyl-substituted calix[4]arene **21** as the template, covalently bonded calix[4]pyrrole–calix[4]arene conjugate **22** was obtained in 32% yield[33] (Scheme 7). X-Ray diffraction analysis showed that the calix[4]pyrrole moiety in the conjugate adopts the cone conformation. The

† The locants α (up) and β (down) as well as wedge–dash bonds are used in this review to designate methyl substituents on different sides of the macrocycle by analogy with sugars.

authors pointed out the additional stabilization of the crystal structure of **22** through hydrogen bonding between the NH hydrogen atoms of calix[4]pyrrole and the oxygen atoms in the lower rim of calix[4]arene.

Scheme 7



21 **22**

According to some publications,[34,35] the condensation of porphyrin-containing bis(dipyrromethane) **23** with acetone in the presense of boron trifluoride etherate under high dilution affords two conformational isomers **24** and **25** of the strapped calix[4]pyrroleporphyrin (Scheme 8). The isomers differ in the orientation of the *meso*-methyl groups relative to the porphyrin plane. The yields of calix[4]pyrroleporphirins **24** and **25** are 5% and 7%, respectively.

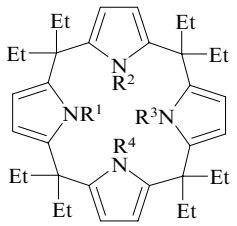
III. Chemical modification of calix[4]pyrroles

Typically, the purpose of calix[4]pyrrole modification is to introduce additional reaction centres (binding points) into the macrocycle. There are two principal types of these transformations: (i) substitution at the NH groups of the pyrrole moieties and (ii) introduction of substituents at the β-positions of the pyrrole rings.

N-Alkylation is an example of modification of the first type. The reaction of *meso*-octaethylcalix[4]pyrrole **2** with chloromethane in tetrahydrofuran in the presence of sodium hydride affords a mixture of N-substituted calix[4]pyrroles **26**–**29**. The yield of each of the products depends on the molar ratio of the reactants.[36]

The second type of transformation of calix[4]pyrroles may be exemplified by bromination of calix[4]pyrrole (**1**)

Structures 16–29

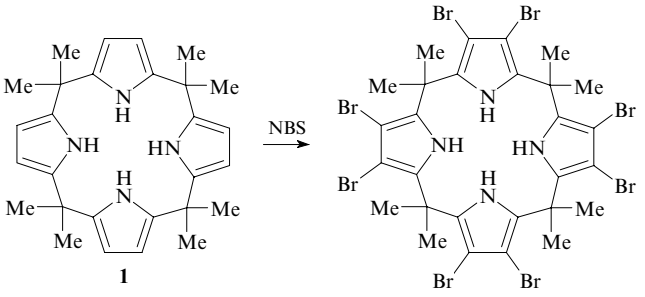


26–29

R^1 = Me, R^2 = R^3 = R^4 = H (**26**); R^1 = R^3 = Me, R^2 = R^4 = H (**27**); R^1 = R^2 = R^3 = Me, R^4 = H (**28**); R^1 = R^2 = R^3 = R^4 = Me (**29**)

with *N*-bromosuccineimide (NBS) in tetrahydrofuran giving β-octabromo-*meso*-octamethylcalix[4]pyrrole (**30**) in 73% yield (Scheme 9).[5]

Scheme 9

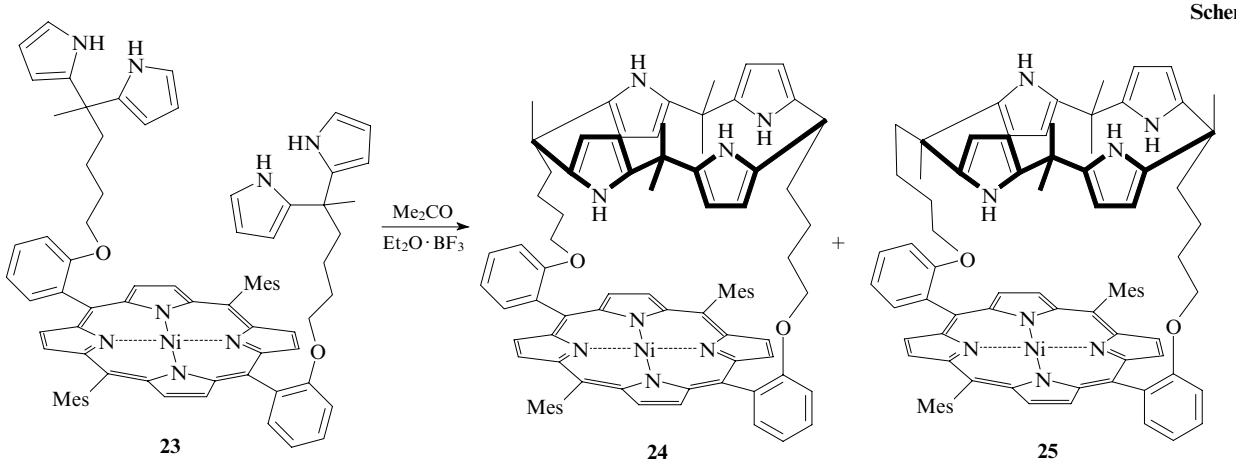


1 **30**

A two-step synthesis of iodo- (**31**), carboxy- (**32**), formyl- (**33**) and ethyxycarbonylmethyl-substituted (**34**) calix[4]pyrroles has been described[37] (Scheme 10). First, treatment of macrocycle **1** with n-butyllithium gives tetraanion **35**, which reacts with appropriate electrophiles to give calix[4]pyrroles **31**–**34** in the yields of 7% to 26%. The authors noted that conducting this reaction with cooling (−78 °C) under argon atmosphere furnishes mainly monosubstituted products.

The reactions of carboxy-derivative **32** with 1-aminoanthracene and ethoxycarbonylmethyl derivative **34** with 1-amino- and 9-aminomethylanthracenes afforded calix[4]pyrroles **36**–**38** bearing chromophore moieties.[38]

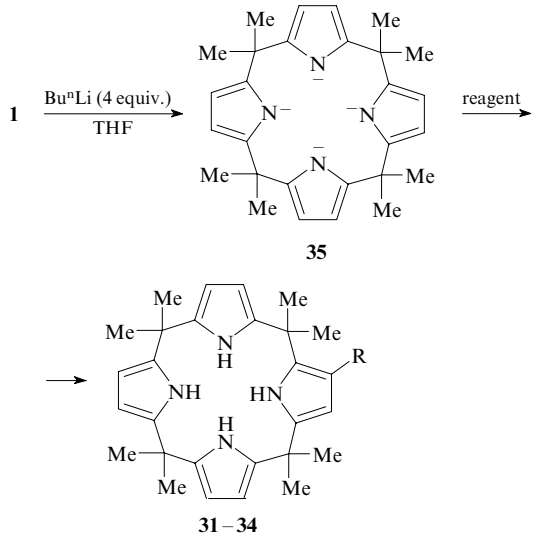
Scheme 8



23 **24** **25**

Mes = 2,4,6-$Me_3C_6H_2$

Scheme 10

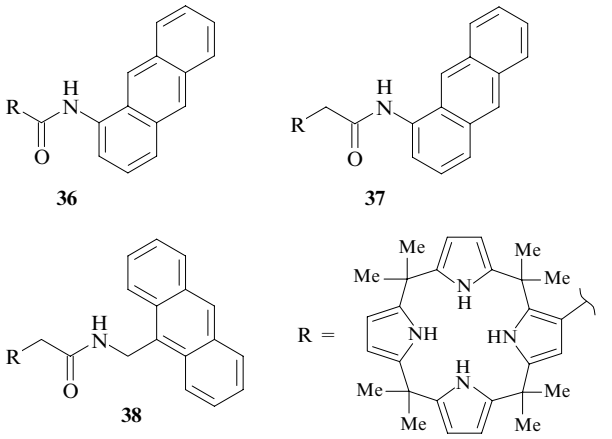


Compound	R	Reagent (amount)	Yield (%)
31	I	ICl (2 equiv.)	17
32	CO_2H	CO_2 (excess)	17
33	CHO	cyclo-[$(CH_2)_5$N]CHO (2 equiv.)	7
34	CH_2CO_2Et	$BrCH_2CO_2Et$ (3 equiv.)	35

Calix[4]pyrrole-containing acetylene **39** was obtained following a two-step procedure.[39] First, iodo-derivative **31** reacted with trimethylsilylacetylene in the presence of catalytic amounts of tetrakis(triphenylphosphino)palladium(0) to give 1-(calix[4]pyrrol-3-yl)-2-trimethylsilylacetylene **40**, which is converted to macrocycle **39** under the action of a weak base (tetra-n-butylammonium fluoride, TBAF) (Scheme 11). Bis(calix[4]pyrrolyl)buta-1,3-diyne (**41**) is a by-product of the reaction, resulting from self-condensation of ethynylcalix[4]pyrrole **39**.

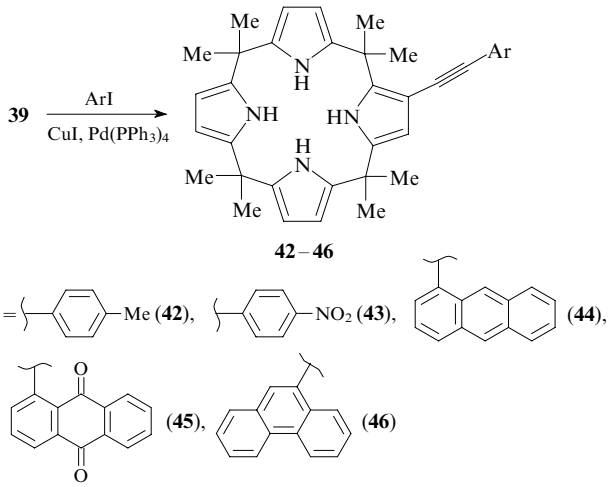
The Sonogashira cross-coupling of alkyne **39** with iodo derivatives of the corresponding aromatic hydrocarbons

Structures 36–38



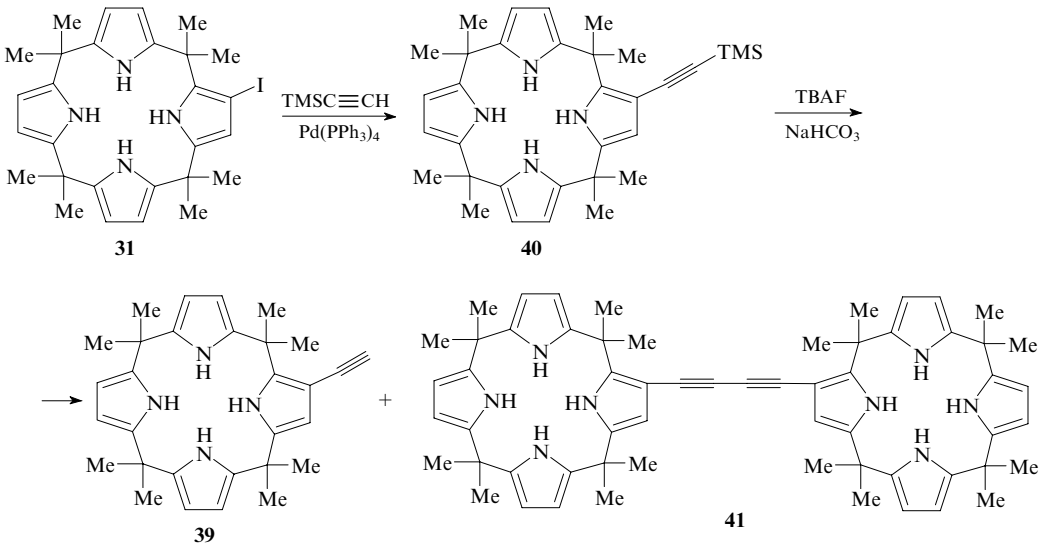
afforded aryl-substituted calix[4]pyrroles **42**–**46** (Scheme 12).[40]

Scheme 12



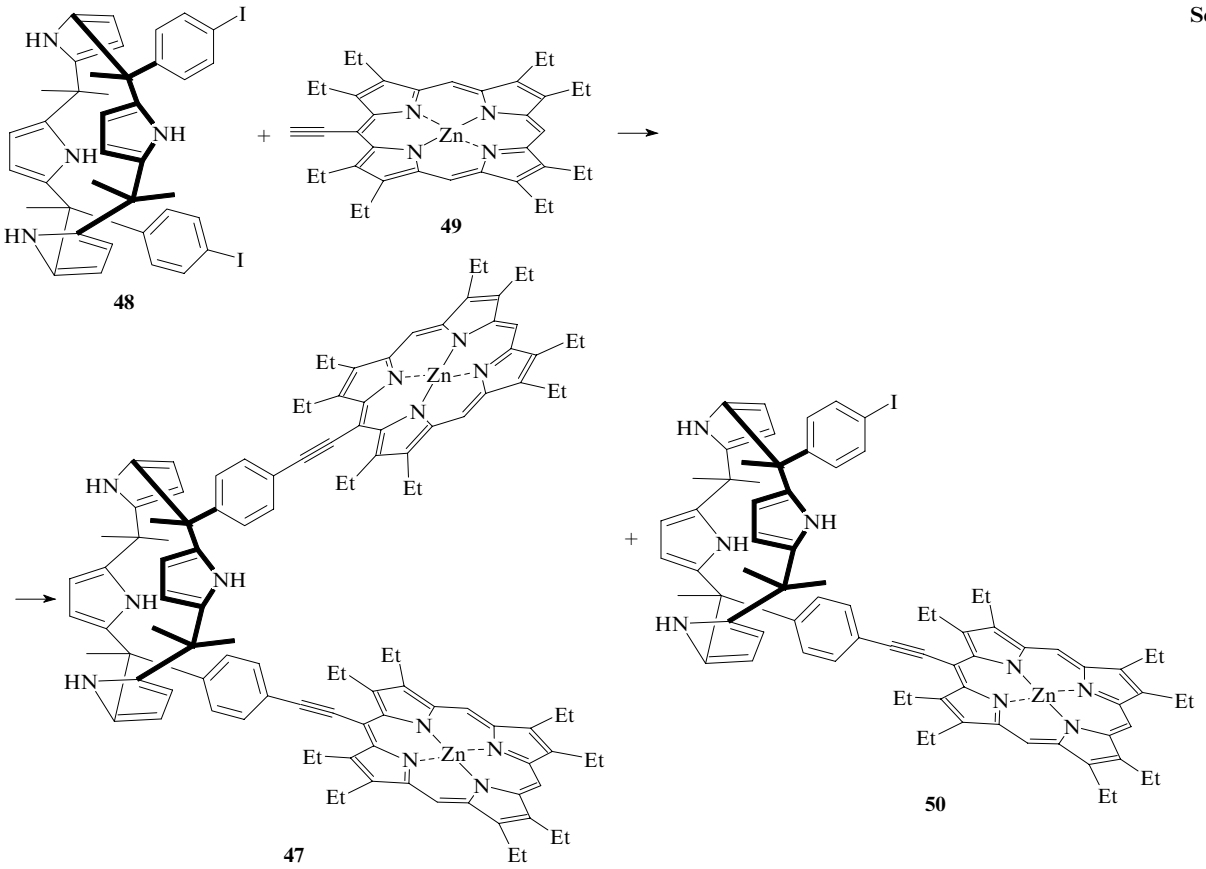
Bis-porphyrine **47** in which the face-to-face orientation of the tetrapyrrole moieties is provided by the presence of

Scheme 11



TMS is trimethylsilyl

Scheme 13



a calix[4]pyrrole bridge has been reported[41,42] (Scheme 13). This macrocycle was obtained by the reaction of *meso*-bis(4-iodophenyl)hexamethyl[4]pyrrole (**48**) with zinc 5-ethynyloctaethylporphyrin (**49**) under conditions similar to the synthesis of calix[4]arene–porphyrin conjugates.[43] In compound **47**, the calix[4]pyrrole macrocycle adopts the 1,3-alternate conformation. Chromatographic purification on alumina followed by crystallization from a dichloromethane–methanol mixture (1 : 1) gave the bis-porphyrin in 30% yield. As a by-product of the reaction, calix[4]pyrrole–porphyrin conjugate **50** is also formed.

IV. Selective binding of anions and neutral molecules to calix[4]pyrroles

Most often, the behaviour of macrocyclic hosts for anions obeys the same general features (pre-organization, complementarity and solvation) as the behaviour of cation hosts, including calix[*n*]arenes and crown ethers. However, there are also special features.[44] Since anions have rather large volume, they need significantly larger receptors compared to the cations (Table 1). Besides, even simple inorganic anions exibits a broader range of shapes and geometries. Finally, the free energies of solvation (*e.g.* hydration) of anions exceed those for cations of the same size (see Table 1).

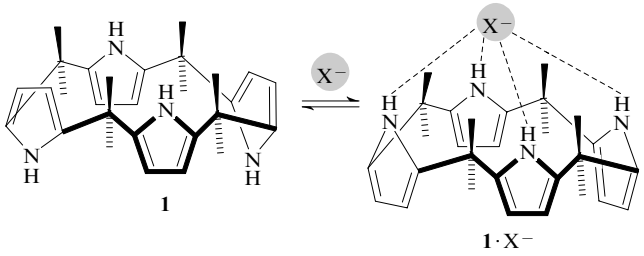
Extensive studies of the anion receptors began at the late 20th century. Since then, a wide range of various host molecules have been synthesized.[45–59] They include proteins, cryptands, cyclophanes with protonated amino groups in the aromatic rings, zwitter ions, calix[*n*]arenes and calix[*n*]pyrroles.[1–10,60–65]

Table 1. Radii and free energies of hydration for selected ions.[44]

Ion	Radius /Å	ΔG_{hydr} /kJ mol^{-1}
Cations		
Li^+	0.69	−475
Na^+	1.02	−365
K^+	1.38	−295
Zn^{2+}	0.75	−1955
Ca^{2+}	1.00	−505
NH_4^+	1.48	−285
Anions		
F^-	1.33	−465
I^-	2.16	−275
NO_3^-	1.79	−300
CO_3^{2-}	1.78	−1315
SO_4^{2-}	2.30	−1080
PO_4^{3-}	2.38	−2725

Calix[4]pyrroles belong to the family of neutral hosts. Despite the relatively small internal cavity, compound **1** effectively binds anions (X^-) of various nature, which occupy a roost type position at the site which can be regarded as the centre of the lower rim, according to the calix[4]arene terminology, due to the formation of four hydrogen bonds (Scheme 14).

Scheme 14



1 **1·X⁻**

As this takes place, the 1,3-alternate conformation of the free calix[4]pyrrole transforms into the cone conformation, *i.e.*, complex formation with an anion causes reorganization of the macrocycle. Analysis of published data shows that calix[4]pyrroles form the most stable complexes with fluoride ions, probably due to the best fit of the relatively small complexing cavity of the macrocycle to the small fluoride anion (Table 2).

Table 2. Stability constants (litre mol^{-1}) of calix[4]pyrrole complexes with anions in deuterated dichloromethane at 22 °C.[21]

Compound	Anion		
	F^-	Cl^-	$H_2PO_4^-$
1	1.7×10^4	3.5×10^2	97
2	2.7×10^3	4.3×10^3	6.5×10^2
5	3.6×10^3	1.2×10^2	<10
6	1.7×10^3	<20	–
30	2.7×10^4	4.3×10^3	6.5×10^2

Note. A dash means that the constant was not determined.

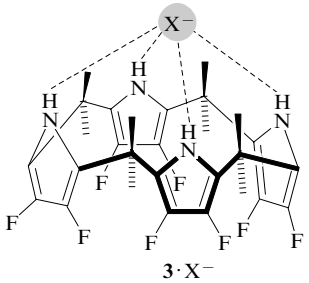
Calix[4]pyrrole (**1**) binds the fluoride ion in dichloromethane with the binding constant (stability constant, K) of 1.7×10^4 litre mol^{-1} and the selectivity with respect to the chloride ion of 50.[2,3,6] The complexing properties of calix[4]pyrroles towards anions may be considerably changed through the chemical modification of the tetrapyrrole macrocycle at *meso*- and β-positions.

For example, the presence of a cycloalkyl substitutent in the *meso*-position decreases the complexing ability of calix[4]pyrroles, whereas the introduction of halogen atoms (Br, F) into the pyrrole rings, conversely, increases the complexing ability. The most dramatic change of the complexing ability towards the Cl^-, Br^-, AcO^-, $H_2PO_4^-$ anions is obsered for the fluoro-substituted calix[4]pyrrole **3** in acetonitrile (Table 3).

Table 3. Stability constants (litre mol^{-1}) of calix[4]pyrrole complexes with anions in acetonitrile at 30 °C.[21]

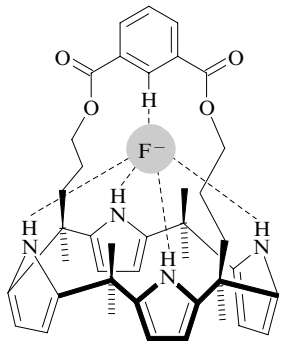
Anion	Compound	
	1	**3**
Cl^-	1.4×10^5	5.3×10^5
Br^-	3.4×10^3	8.5×10^3
AcO^-	2.9×10^5	1.9×10^6
$H_2PO_4^-$	5.0×10^3	1.7×10^4

Structures 3·X⁻, 18·F⁻



3·X⁻

X = Cl, Br, AcO, H_2PO_4



18·F⁻

The complexing properties of calix[4]pyrroles can also be improved by introducing various strapped bridges (compounds **18**, **19a–c**, **20a–c**) or chromophore groups (**36–38**) due to the appearance of the additional binding centres (Table 4). Thus it was shown [30] that on binding the chloride ions by calix[4]pyrrole **18**, the anion finds place in the macrocycle cavity, which occurs in the cone conformation and forms hydrogen bonds not only with four hydrogen atoms of the pyrrole NH groups but also with the CH groups of the aryl moiety. The distance between the CH groups and the chloride ion is 3.793 Å, corresponding to the hydrogen bond length of a moderate strength. The authors [30] studied binding of various anions to calix[4]pyrrole **18** using two methods, namely, ^{1}H NMR spectroscopy and calorimetric titration. Both methods showed that under these conditions, chloride ion binding is virtually irreversible. The stability constant of complex **18**·Cl^- is 1×10^5 litre mol^{-1}, whereas for complex **18**·F^- it is 3.9×10^6 litre mol^{-1}.

Table 4. Stability constants (litre mol^{-1}) of calix[4]pyrrole complexes bearing strapping bridges or chromophore groups with anions in acetonitrile.[29,38]

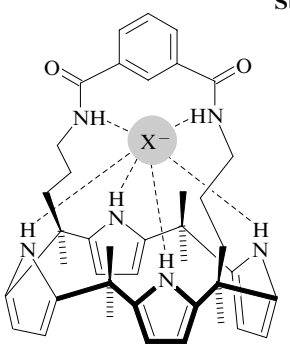
Compound	T/°C	Anion			
		F^-	Cl^-	Br^-	$H_2PO_4^-$
18	30	–	4.9×10^6	7.5×10^3	–
19a	30	–	3.6×10^6	3.0×10^4	–
19b	30	–	1.4×10^6	3.1×10^4	–
19c	30	–	1.4×10^6	1.2×10^5	–
20a	30	–	3.9×10^6	1.4×10^6	–
36	22	1.48×10^5	7.41×10^4	9.55×10^3	9.12×10^4
37	22	4.9×10^4	6.5×10^3	7.2×10^2	7.95×10^3
38	22	4.9×10^4	5.1×10^3	4.3×10^2	1.3×10^3

The influence of the nature of the strapping bridge and, correspondingly, of the internal cavity size on the anion binding has been studied for a number of calix[4]pyrroles **19a–c** and **20a–c** having bridges of various length.[30,32] As shown in Table 4, the strength of chloride ion binding by the strapped calix[4]pyrrole **18** is nearly 25 times greater than that for unsubstituted calix[4]pyrrole **1**. As the length of the strapping bridges increases, the binding ability of the calix[4]pyrrole macrocycle towards chloride anion decreases slightly, whereas the binding ability towards the bromide anion, on the contrary, increases.

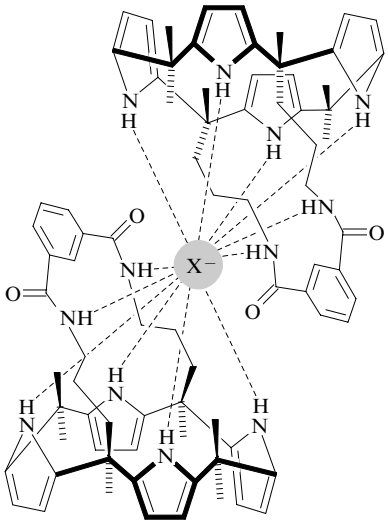
The highest binding constants were obtained for calix[4]pyrroles **19a–c**, which is due to increase in the number of hydrogen bonds due to the presence of two amide groups.[32] The additional hydrogen bonds have the most pronounced effect on the bromide ion binding. Indeed, the stability constants for the complexes **19a**·Cl^- and **19a**·Br^- differ by a factor of two.

On binding halide ions, calix[4]pyrroles **19b**,**c** having larger intramolecular cavity than compound **19a** form complexes of two types, namely, 1 : 1 and 1 : 2 complexes. With the smaller anion (fluoide), compound **19b** forms only 1 : 1 complexes, while with a larger anion (bromide), it forms 1 : 2 complexes. The reaction of the chloride ion with this compound gives an equilibrium mixture of both complexes.

Structures 19b·X^-, (19b)$_2$·X^-



19b·X^- (X = Cl, F)

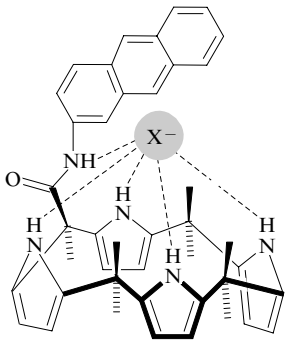


(**19b**)$_2$·X^- (X = Cl, Br)

For anthracene–calix[4]pyrrole conjugates such as compounds **36–38**, fluorescence quenching is observed upon anion binding.[38] The shorter is the linking bridge, the more pronounced is the energy transfer between the anthracene moiety and the calix[4]pyrrole. The stability constants of the corresponding complexes are given in Table 4.

Among the conformational isomers of the strapped calix[4]pyrrole–porphyrin conjugate **24** and **25** synthesized in Refs 34 and 35, only the first one show receptor behaviour towards the fluoride ions. The F^- ion is bound by the intramolecular cavity both through the four hydrogen bonds formed between the NH groups of the calix[4]pyrrole macrocycle and the anion and through the anion coordination with the cation of the porphyrin moiety having the

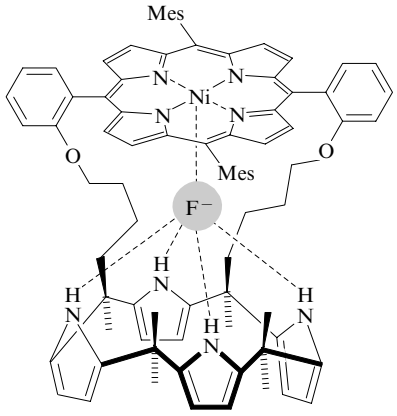
Structure 36·X^-



36·X^- X = Cl, F, Br, H_2PO_4

properties of a Lewis acid. The bound anion enters the intramolecular cavity and remains there, this process being independent of the nature of the central metal ion. There are no other examples of anion binding to calix[4]pyrroleporphyrins in the literature.

Structure 24·F^-



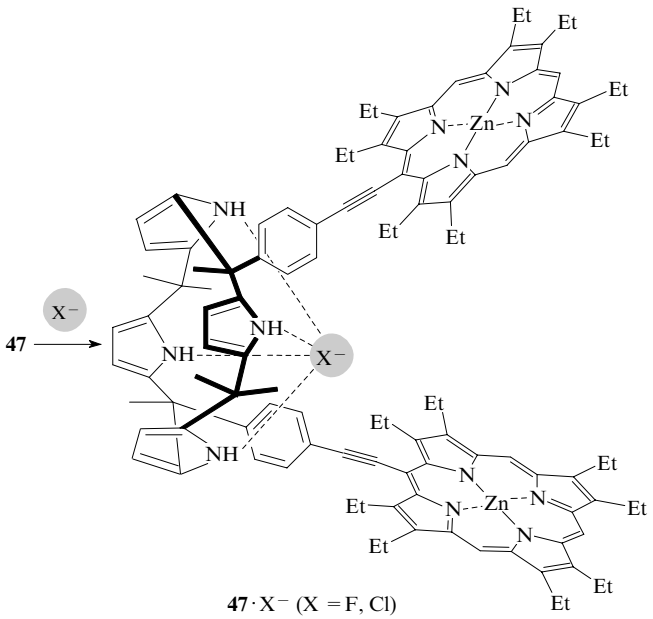
24·F^-

The calix[4]pyrrole moiety does not lose its ability to bind anions also when occurs in the conjugate with two porphyrin macrocycles. We have studied the complex formation of compound **47** with tetra-n-butyl- and tetraethylammonium halides in dichloromethane (Scheme 15).[41, 62, 63]

Among the anions investigated, the fluoride and chloride ions were found to bind to this conjugate most efficiently affording 1 : 1 complexes **47**·X^- (X = F, Cl). As in other calix[4]pyrroles, in this case, calix[4]pyrrole moiety changes its 1,3-alternate conformation for the cone conformation. In the ^{1}H NMR spectrum of complex **47**·F^-, such changes of the calix[4]pyrrole macrocycle are accompanied by a downfield shift of the proton at nitrogen (by 1.91 ppm) and an upfiend shift of β-pyrrole protons (by 0.40 ppm).

The upfield shifts of the porphyrin protons in the ^{1}H NMR spectra of the system during complex formation indicates that the mutual shielding action of the ring currents of the tetrapyrrole chromophores of the porphyrin dimer is enhanced. These changes may be explained by the decrease in the distance between the porphyrin moieties of conjugate **47** upon complex formation with the anions. Electronic spectroscopy data also attest to the decrease in the distance between the porphyrin moieties in compound **47** upon complex formation with the anions. On going from calix[4]pyrrole–zinc bis(porphyrin) **47** to its complex **47**·F^-, a hypochromic shift of the Soret band (~2.5 nm) and a decrease in its intensity are observed in the electronic absorption spectrum.

Scheme 15



According to literature data, these changes in the electronic and ^{1}H NMR spectra are indicative of enhancement of the mutual influence of the π-electron systems of the tetrapyrrole moieties as they approach each other. This may be considered as a result of conformational changes caused by the anion binding by the calix[4]pyrrole macrocycle.

The characteristic changes in the electronic spectra enabled the use of spectrophotometric titration to study the course of interaction between the calix[4]pyrrole moiety and anions.[62, 63] The stability constant of the complex **47**·F$^-$ in dichloromethane calculated from the spectrophotometric titration data is 1.5×10^3 litre mol^{-1}; the stability constant of the complex **47**·Cl$^-$ is much lower (670 litre mol^{-1}). The stability constant of **47**·Br$^-$ cannot be calculated by this method because of minor changes in the spectra upon the complex formation.

It was shown[64, 65] that in a water–organic solvent system, fluorinated calix[4]pyrrole is able exchange nitrate ions for more hydrophilic sulfate ions in the presence of quaternary ammonium salts (Fig. 2). Toluene and chloroform were chosen as organic media since they form no hydrogen bonds and minimize the influence of solvation effects on the anion exchange. Studies of this type are topical for the detection of selective binding/separation and removal of anions of various nature.

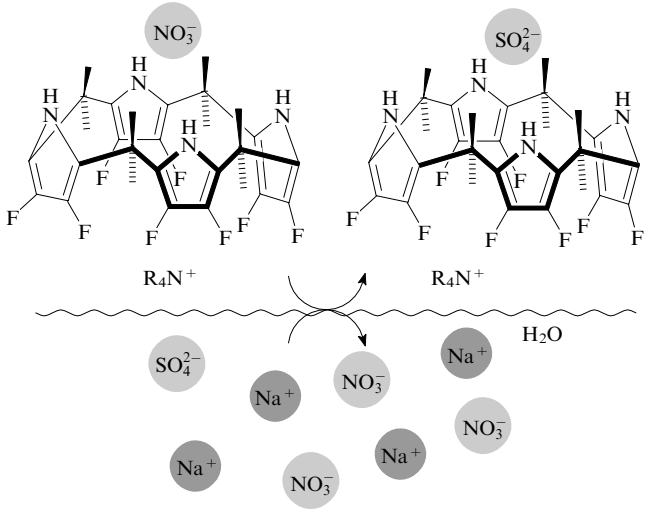


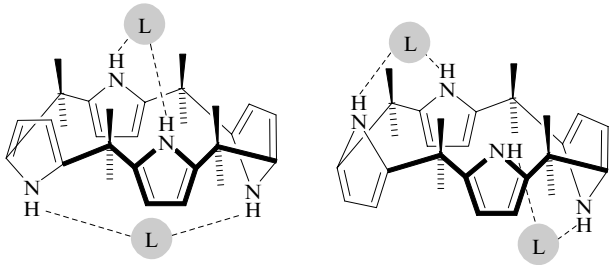
Figure 2. Extraction of sulfate anions by calix[4]pyrrole **3** from the aqueous phase.[64]

There are also a few studies in the literature concerning the receptor behaviour of calix[4]pyrroles towards neutral molecules. Thus the constants of binding of some organic solvents by calix[4]pyrrole (**1**) are as follows:[57]

Substrate	K/litre mmol^{-1}
Methanol	12.7
Ethanol	10.7
Propan-2-ol	7.0
DMSO	16.2
DMF	13.3
Acetone	2.2

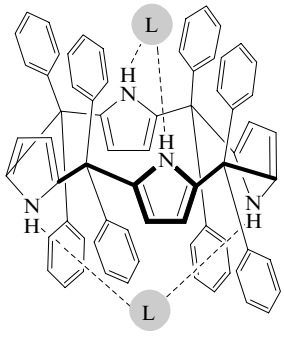
As mentioned above, in the free state, calix[4]pyrroles adopt mainly the 1,3-alternate conformation, while upon anion binding, they switch to the cone conformation. According to the X-ray diffraction data,[57] upon binding molecular substrates (L), the tetrapyrrole macrocycle may exist in various conformations. In the complex **1**·2 MeOH, calix[4]pyrrole macrocycle is in the 1,3-alternate conformation, whereas upon the formation of complex **1**·2 DMF, the macrocycle swiches to the 1,2-alternate conformation, which is scarcely found among calix[4]pyrroles.

Structures 1·2 L



Similar complexes with methanol are also formed by the octaphenylcalix[4]pyrrole **50** obtained by the condensation of 1,3-diphenylacetone with pyrrole.[57]

Structure 50·MeOH



It has been reported[23] that in the presence of DMF or AcOH, calix[4]pyrrole α,α,α,α-**7** forms dimeric and trimeric

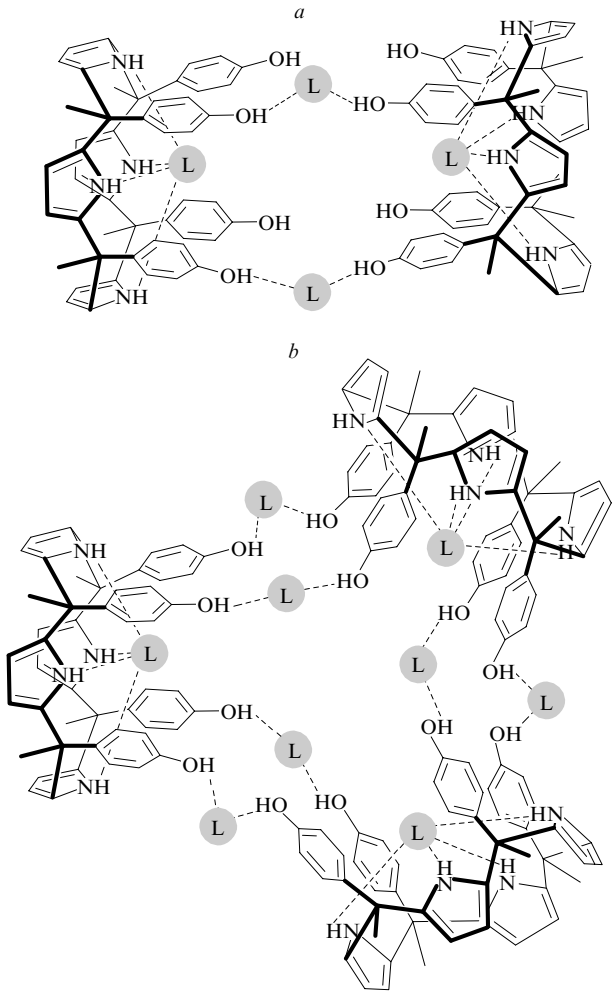


Figure 3. Molecular assemblies of calix[4]pyrrole α,α,α,α-**7** with DMF (*a*) and AcOH (*b*).[23]

assemblies, while retaining the cone conformation. In these structures, either four DMF molecules are bound by two calix[4]pyrrole macrocycles (Fig. 3 *a*) or nine AcOH molecules are bound by three molecules of calix[4]pyrrole (Fig. 3 *b*).

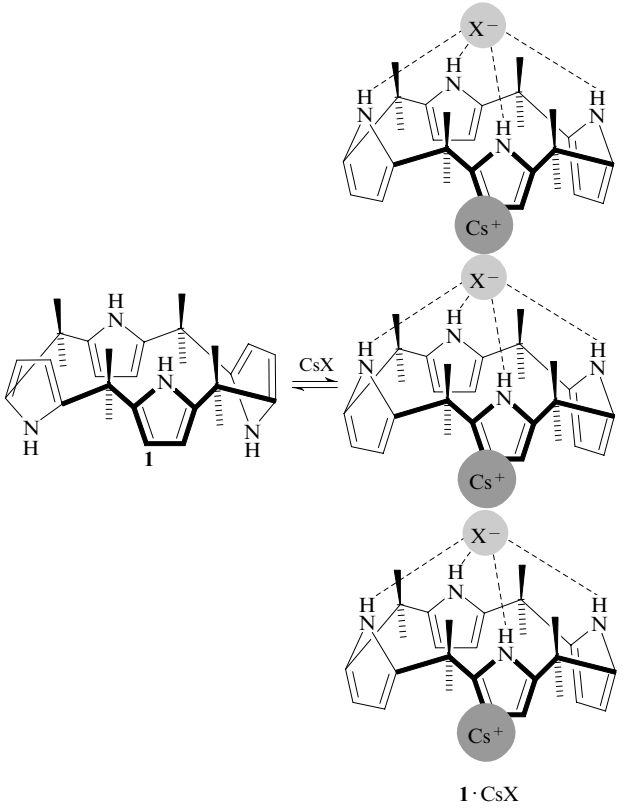
V. Calix[4]pyrroles and their derivatives as polyfunctional receptors

Aside from the monofunctional receptors to particular substrates (cations, anions and neutral molecules), polyfunctional receptors are known. Such compounds can bind simultaneously to the species of different nature due to the presence of different groups and moieties in their molecules.[66, 67] Of special interest are receptors for simultaneous or stepwise binding of anions and cations to form ion pairs, so called ion pair receptors.[9, 52, 68–76] On the one hand, cooperative effects are characteristic of such receptors, resulting in an increase in the complexing ability and selectivity in organic solvents, which can be used for directed substance transport across synthetic membranes. On the other hand, functioning of a polyfunctional receptor can simulate biochemical processes taking place in the living body.

In the receptor–ion pair complex, both ions of the pair may be either in direct contact or be separated by the solvent molecules or receptor peripheral groups.

It was shown[74] that calix[4]pyrrole (**1**) can serve as an ion pair receptor capable of simultaneous binding of caesium cations and halide anions. According to the X-ray diffraction data for crystalline samples, the fluoride ions in the complex **1**·CsF are coordinated by the hydrogen atoms of the NH groups of calix[4]pyrrole existing in cone conformation, while caesium atoms are held within the cone-shaped cavity (Scheme 16).

Scheme 16



The ability of calix[4]pyrrole (**1**) to selectively extract caesium chloride and fluoride from an aqueous solution into an organic phase (nitrobenzene) was studdied using liquid–liquid extraction.[75] A possible extraction scheme for caesium atoms comprising three steps was proposed. In the first step, the salt dissociates into ions. In the second step, the calix[4]pyrrole molecule switches from the 1,3-alternate conformation to the cone conformation upon halide anion binding. In the third step, the caesium cation enters the bowl-shaped cavity of the calix[4]pyrrole formed in the second step (Fig. 4). The stability constants of the complexes obtained were calculated.

A similar ion pair binding to compound **1** is observed for tetra-n-butylammonium halides (TBAX).[77, 78] Meanwhile, tetraacetoxy derivative **51** (having the α,α,α,α configuration) binds to the tetra-n-butylammonium cation through the intramolecular cavity formed by four acetoxy groups rather than through the bowl-shaped cavity of calix[4]pyrrole.[25]

Using calix[4]pyrrole (**1**) and a number of pyridinium and imidazolium dications, supramolecular assemblies **52** were obtained.[79] Their composition and structure were

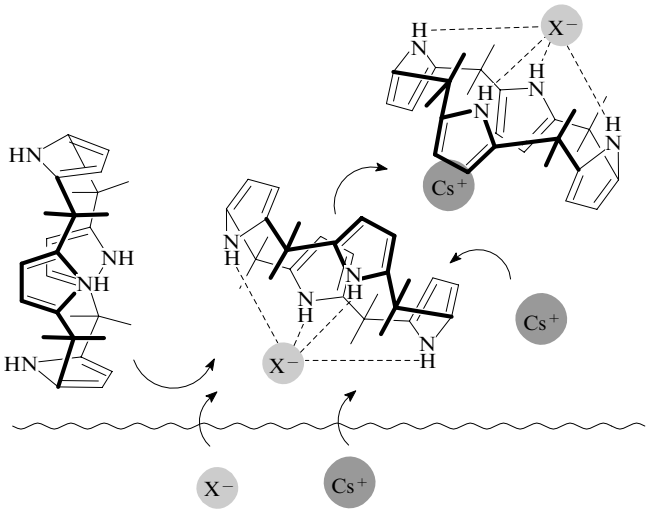
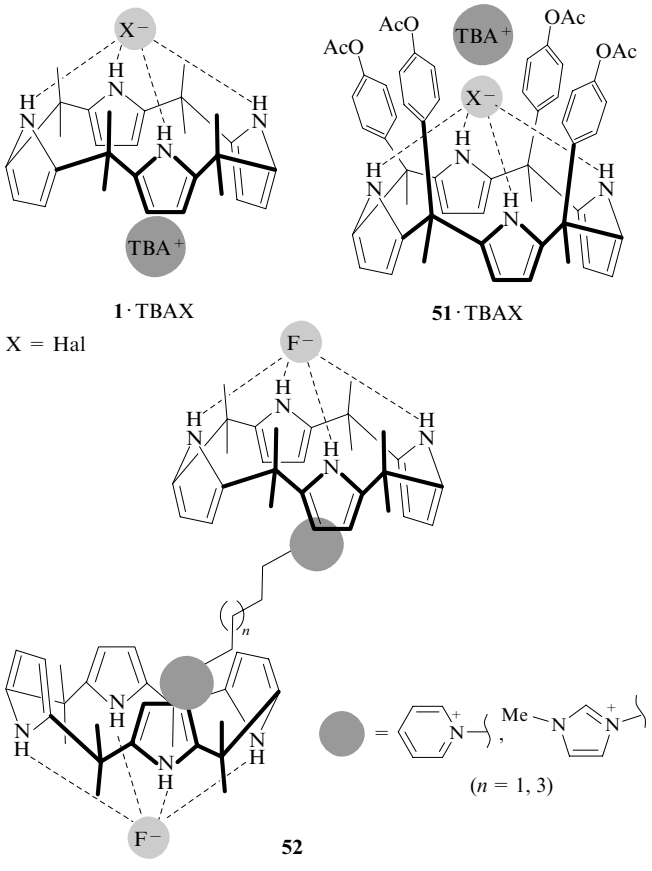


Figure 4. Stepwise extraction of caesium cations from the aqueous medium into an organic phase.[75]

confirmed by ^{1}H NMR spectroscopy and X-ray diffraction analysis. Similarly to the complex **1**·CsF, the anions in **52** are bound to the hydrogen atoms of the NH groups of calix[4]pyrrole exising in the cone conformation, while pyridinium and imidazolium cations are held by the bowl-shaped cavity of the macrocycle.

A conjugate of crown[6]ether witn calix[4]arene and calix[4]pyrrole representing an example of allosteric molecular switch has been described.[73] A study of the complex

Structures 1(51)·TBAX, 52



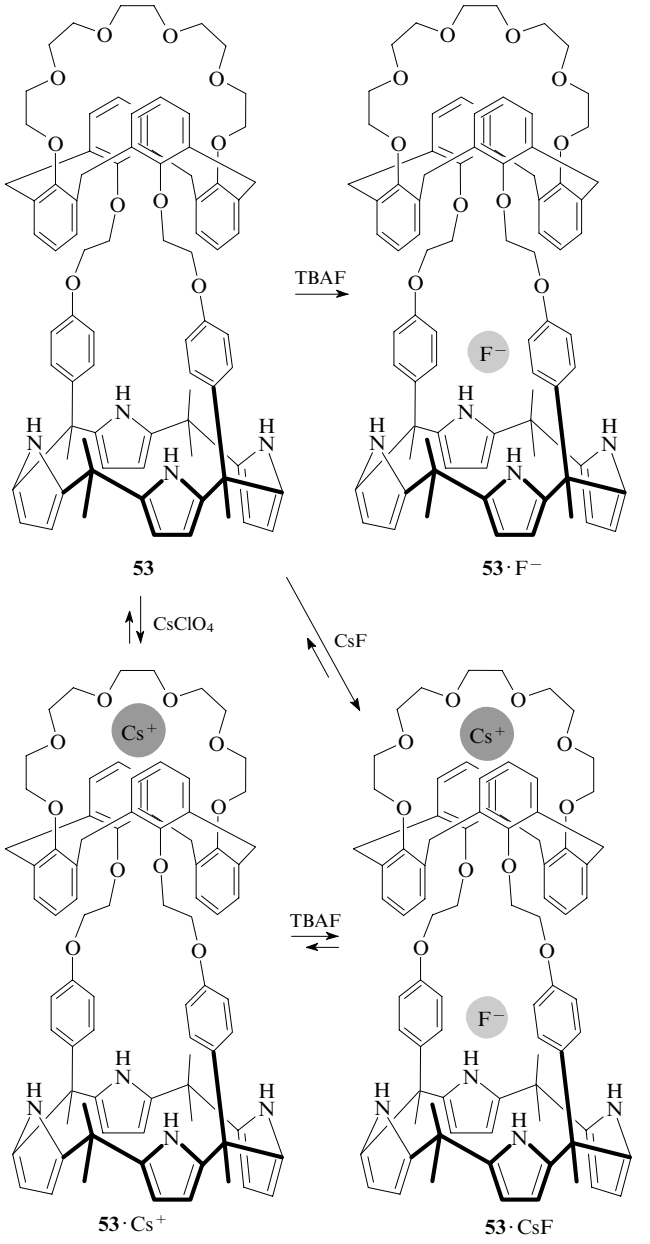
1·TBAX

51·TBAX

X = Hal

52

Scheme 17



53

53·F$^-$

53·Cs$^+$

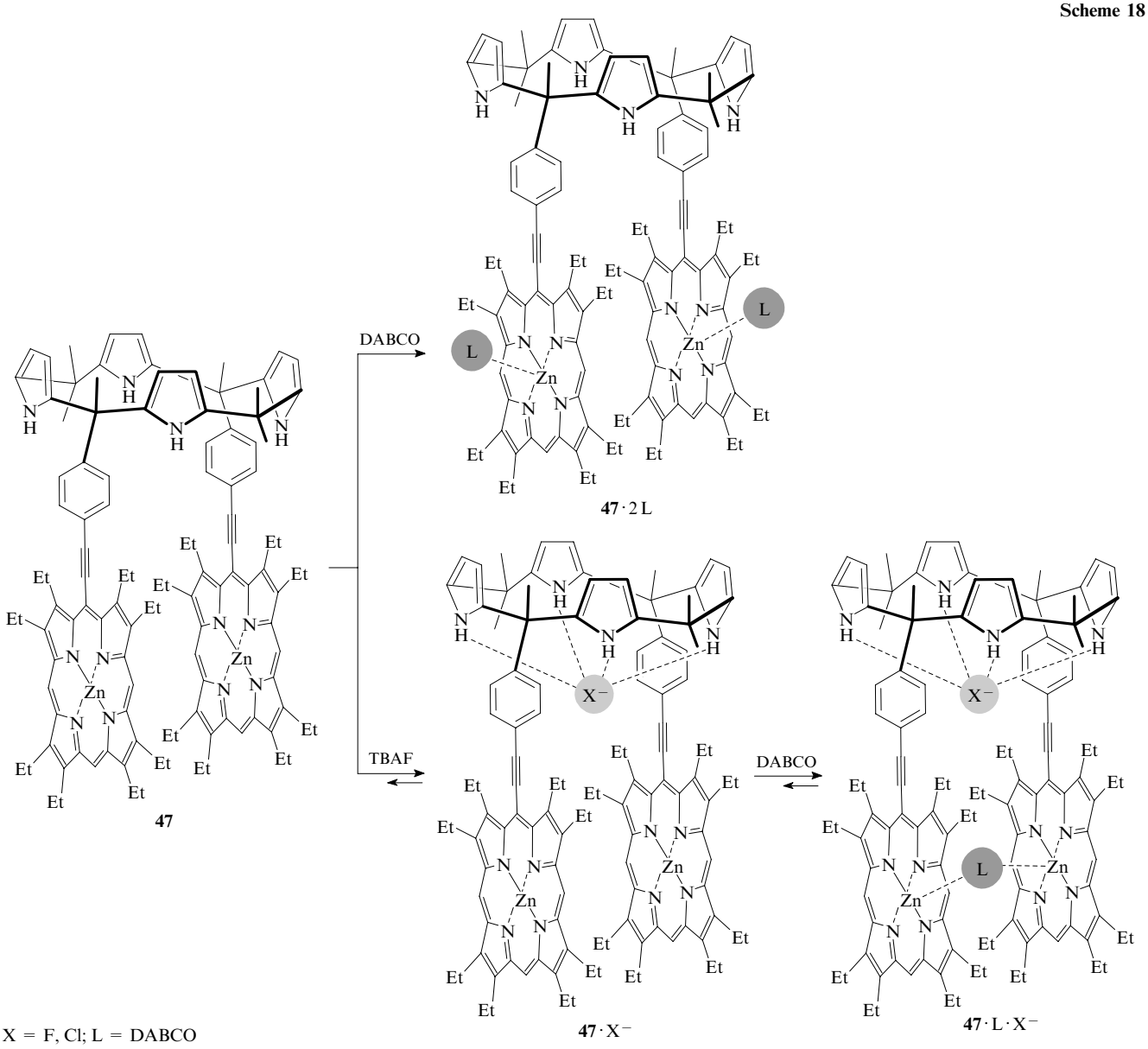
53·CsF

formation of conjugate **53** with CsF demonstrated that the ion pair binding occurs *via* a consecutive process, *i.e.* first, the caesium cation is bound to the crown[6]ether–calix[4]-arene moiety of the macrocycle. The allosteric changes that accompany this process create conditions for the effective fluoride ion binding to the calix[4]pyrrole moiety of receptor **53** (Scheme 17).

It was shown[62,63] that calix[4]pyrrole–bis(porphyrin) conjugate **47** behaves as a similar allosteric molecular switch (Scheme 18).

The reaction of conjugate **47** with a bidentate organic substrate such as 1,4-diazabicyclo[2.2.2]octane (DABCO) yields so-called outer 1 : 2 complex in which each porphyrin moiety of the receptor coordinates one molecule of the organic base through the donor-acceptor interaction. However, as a result of conformational changes caused by the complex formation between the calix[4]pyrrole moiety and the fluoride ion, the reaction with DABCO yields a stable inner 1 : 1 complex in which one DABCO molecule is

Scheme 18



located in the interporphyrin complex forming receptor cavity.

* * *

Thus, the material presented in the review demonstrates how diversified are the composition, architecture and binding modes (self-assembly) of supramolecular calix[4]pyrrole complexes. The research in this area is still at its infancy but the currently available results already provide clues for estimating the general principles, mechanisns and driving forces governing the selectivity of the complex formation processes. In some cases, factors allowing for the control over the the substrate–receptor interactions were elucidated with the aim of developing advanced functional materials and novel technologies.

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