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AZACALIXARENES

Abstract: In the paper azacalixarenes as members of a new heteracalixarene class are presented. The reactivity and synthetic approaches of these species are described, pointing out their complexation properties.

Azacalixarenes, more precisely referred to as homoazacalixarenes are analogues of calixarenes containing CH_2-NR-CH_2 linkages instead of methylene groups. Calixarenes are receiving now a growing attention due to their particular shape allowing formation of host-guest complexes and serving as supramolecular building blocks [1-12], azacalixarenes however are less investigated than their parent compounds.

Azacalixarenes belong to heteracalixarenes containing in their macrocycle linkages nitrogen, oxygen or sulfur atoms. In a continuation of our papers concerning heteracalixarenes [13,14], here azacalixarenes are described, showing their reactivity and synthetic approaches.

Azacalixarenes are bifunctional species containing nitrogen and oxygen atoms, this fact being promising in their wide applications as host molecules.

Azacalixarenes have longer spacers CH_2-NH-CH_2 between benzene rings than single methylene groups in calixarenes, therefore they are more flexible than these parent compounds. Imino linkages may be substituted by various groups, in this way allowing a number of modifications of the molecule [15].

In the investigation of hexahomotriazacalixarenes it was observed in **1** a strong intramolecular hydrogen bonding between the nitrogen atoms and phenol hydroxyl groups, therefore the formation of complexes with alkali metal ions is impossible.

The *O*-functionalization of **1** eliminates the intramolecular hydrogen bonding, locks the macrocycle into either cone or partial cone conformation and

enhances the coordination ability of phenolic oxygen atoms [16]. As *O*-functiona-
lization of **1** the silylation has been chosen. Azacalixarene **1** reacts with
1-(trimethylsilyl)imidazole and with 1,1,1,3,3,3-hexamethyldisilazane to give
the cone isomer **2a**, while with bis(trimethylsilyl)-trifluoroacetamide
the mixture of cone isomer **2a** and partial cone isomer **2b** is formed [16].
The structure of **2a** was confirmed by X-ray analysis. No equilibration of **2a**
and **2b** isomers was observed.

	R
1	H
2	SiMe$_3$
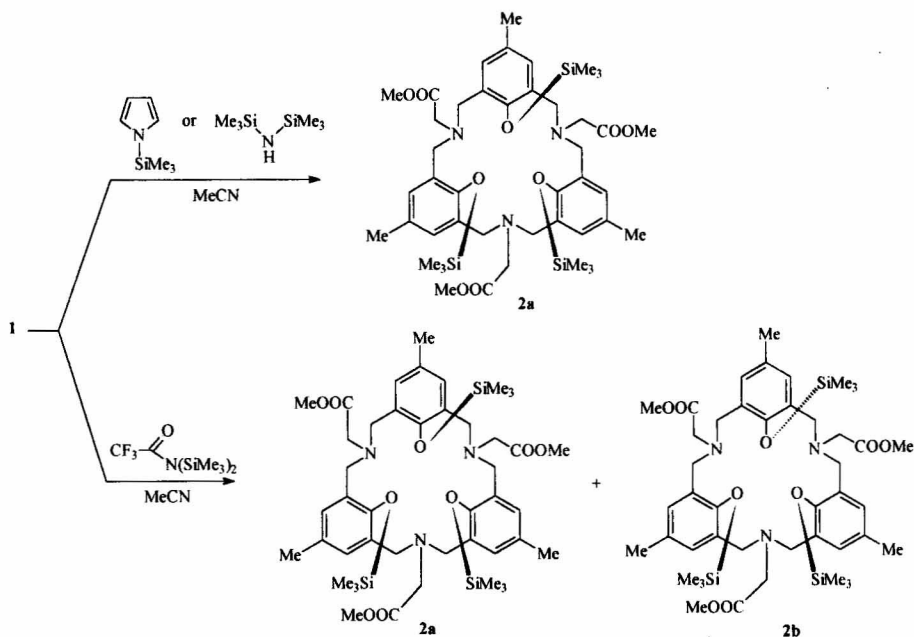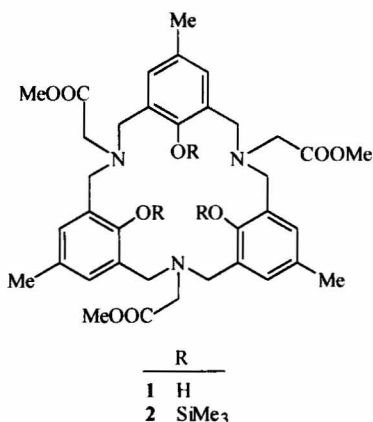
Compound **3a** in spite of its cone conformation does not include guest molecules due to its not large enough cavity, this fact resulting from the considerable distortion of the macrocycle by three bulky trimethylsilyl groups [16].

In the study of lanthanide complexes of calixarenes [17-20], important in view of the lanthanide/actinide separation during nuclear fuel reprocessing and design of luminescent probes, the neodymium complex **3** of azacalixarene **4** has been obtained. The reaction of 2,6-bis(hydroxymethyl)-4-chlorophenol with benzylamine leads to **4**. The treatment of **4** with neodymium (III) nitrate followed by recrystallization from pyridine gives neodymium complex $(Nd^{3+})4(NO_3^-)_3 \cdot C_5H_5N$ **3** [21].
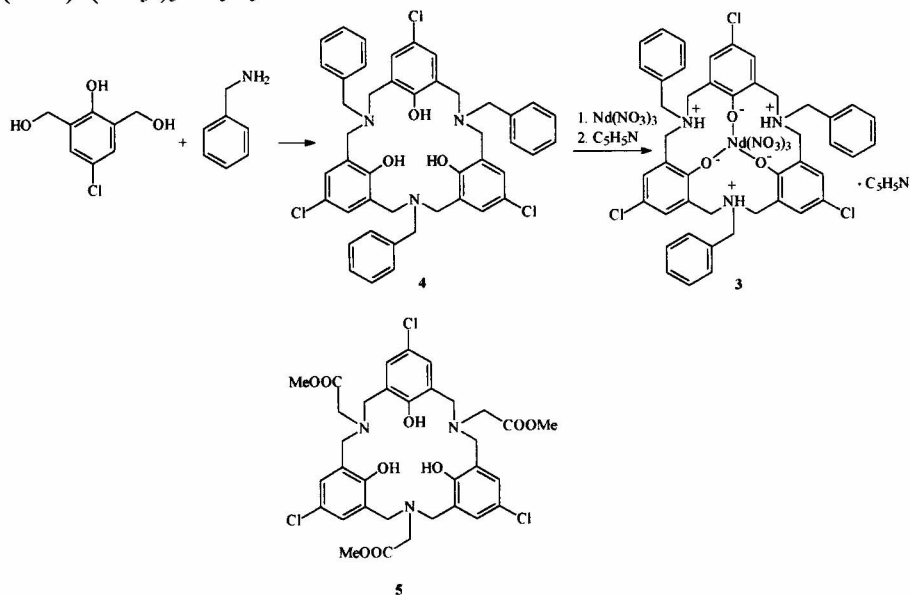

The coordination number of Nd^{3+} in **3** is nine, as it is usual for early lanthanoids. In **3** the cation is bound to the three phenoxide oxygen atoms and to three bidendate nitrate ions. Azacalixarene **4** exists in a form of shallow cup, therefore it cannot include any solvent molecules.

Azacalixarene **4** has proton-donating hydroxyl groups and proton-accepting tertiary amino groups. The investigation of crystal structure of **4** and **5** serving as a model compound has shown that the phenolic protons are situated on the oxygen atoms, in **3** however the protons are localized on the nitrogen atoms. As **4**, along with other azacalixarenes has in its molecule the basic agent, the complexation proceeds without addition of an extra base, in contrast to parent calixarenes unsubstituted at their lower rim, requiring for complexation of lanthanide cations an additional basic agent (e.g. NEt₃, imidazole or K₂CO₃) which is also necessary to solubilize calixarene in organic solvents.

It was observed that **4** and other azacalixarenes form uranyl complexes; here also the addition of a base is unnecessary [21].

In order to obtain azacalix[4]arenes, i.e. species containing four phenolic units, the reaction of the diphenol **6** with methylamine was performed. This process affords two products, tetrahomodiazacalix[4]arene **7** and tetra-homoazaoxacalix[4]arene **8**. It should be pointed out that **8** contains OH, O and N donor groups [22].
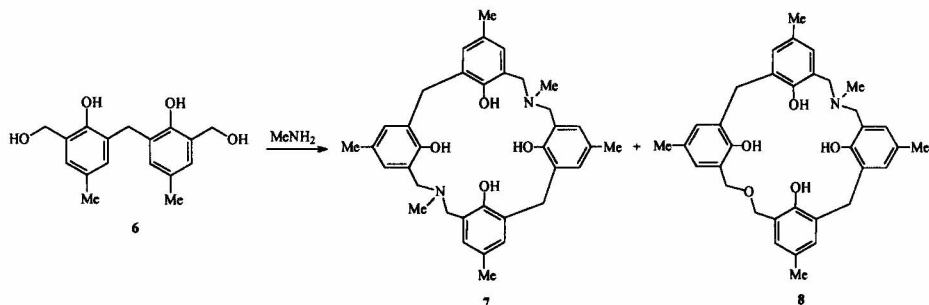
The direct methylation of **7** could not be achieved, therefore hydroxyl groups have been protected by their acetylation. Quaternization required the use of a strong methylating agent, CF_3SO_3Me. The subsequent deprotection by HCl in methanol gave the diammonium compound **9**. The treatment of **9** with $NaHCO_3$ leads to azacalix[4]arene betaine **10** [22].
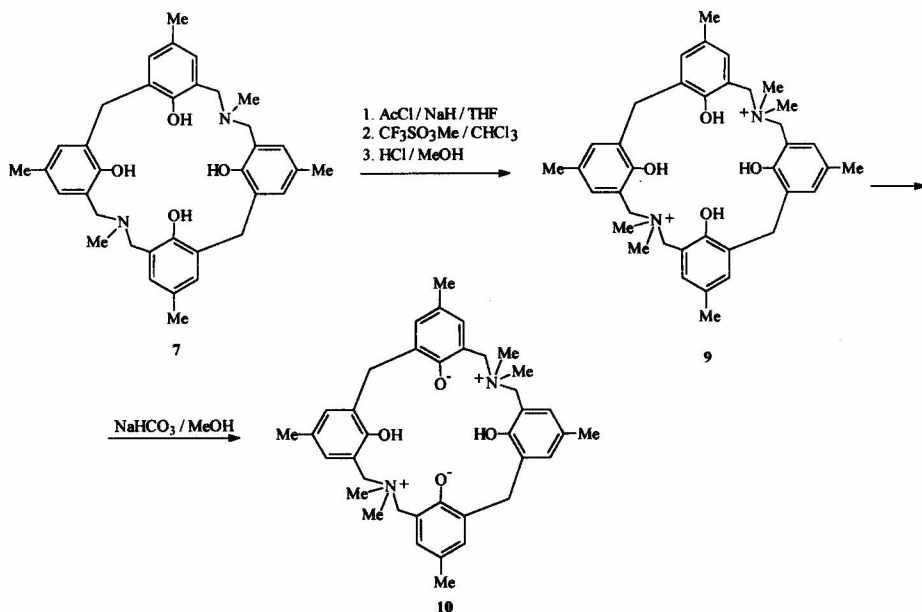
Chiral dihomodiazacalixarenes containing amino acid ester residues **11** have been obtained by coupling diphenol **12** with hydrochlorides of amino acid esters.
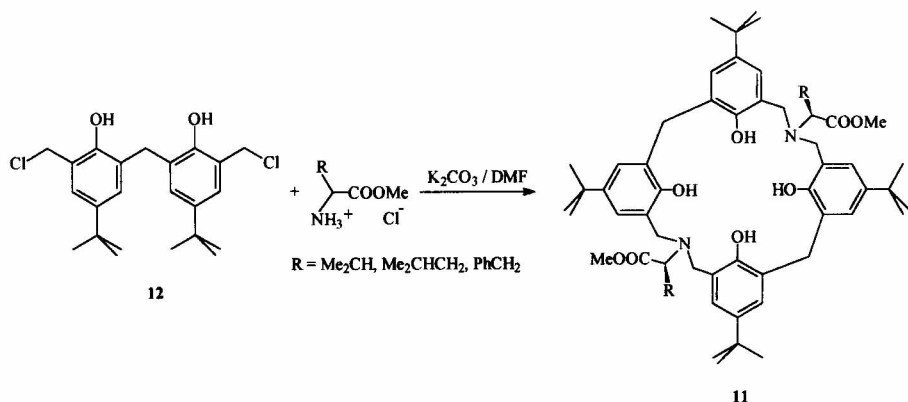
Compounds **11** exist in a cone conformation and their cavities are suitable for inclusion of ammonium ion [23].

In the search for water soluble receptors of anionic guests [24-26], the azacalixarene **13** has been synthesized. The conformational analysis of **13** was made and its recognition toward anionic guests has been investigated [15].


13
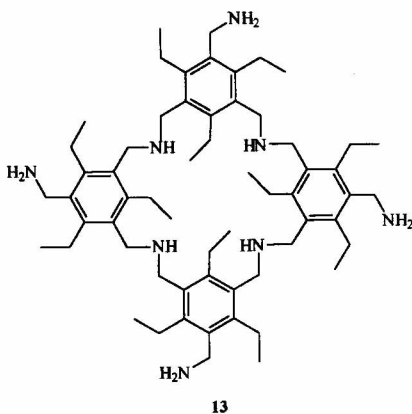
Azacalixarene **13** has a larger cavity than the parent calix[4]arene containing methylene groups, this fact allowing the binding of bulky anionic carbohydrates. . Three ethyl groups have been introduced into the benzene ring in order to cause the orientation of the amino groups towards the interior of the cavity .

Synthesis of **13** begins with the reaction of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene **14** with sodium azide leading to mono-azido compound **15** along with bis- and trisazido derivatives. The trisazido compound was reduced with triphenylphosphine to give trisamine **16**. The reaction of **15**

and **16** afforded the bis-azidoazacalixarene **17** which was reduced with triphe-nylphosphine to **13**. Azacalixarene **13** exists at -70 °C in a cone conformation.
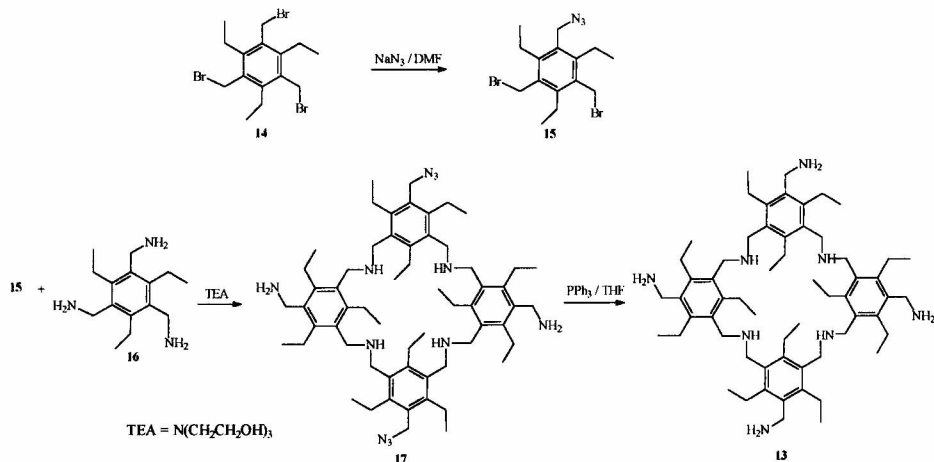

Investigating recognition behaviour of **13** towards indicators, the fluorescent indicator was replaced by an anionic guest [27,28]. Replacement of the indicator can be detected by changes of UV-VIS and fluorescence spectra. In these experiments 5-carboxyfluorescein **18** and 1-hydroxypyrene-3,6,8-trisulfonate **19** have been used; both of them are pH indicators very sensitive to their surrounding microenvironment .
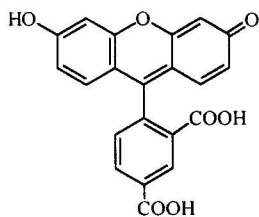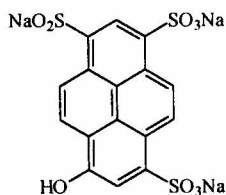
In the study of binding properties of **13** toward anionic guests, as those phosphorylated carbohydrates, exemplified by inositol triphosphate IP_3 **20** and fructose 1,6-diphosphate **21** have been used, along with gluconic acid anion **22** and adamantane-1,3-dicarboxylate **23**. It was observed that **13** strongly associates with the above anionic guests in aqueous solution [15].

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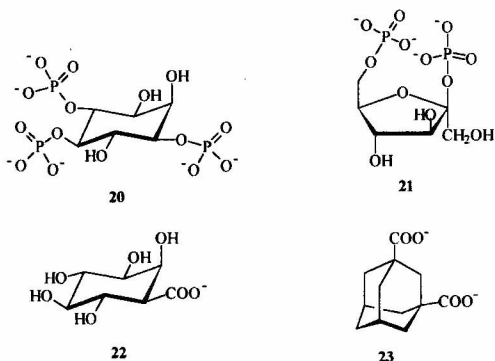
Examples of *para*- and *meta*-xylylene-bridged azacalixarenes are **24**, rigidly fixed in shallow cone conformations [29].

|	R	Y	n
a	Me	*p*-C6H4	1
b	Me	*m*-C6H4	2
c	*t*-Bu	*m*-C6H4	3
d	*t*-Bu	*m*-C6H4	4
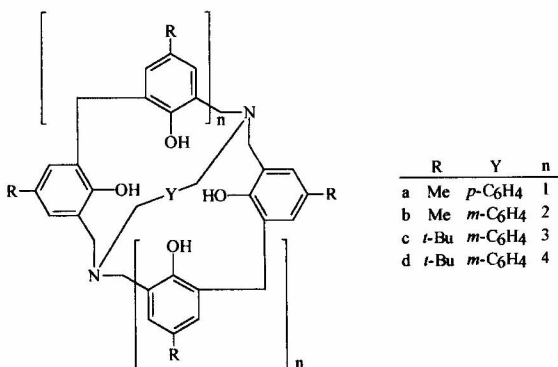
One should mention here also fluorine-containing macrocycles **25-28** and cage compounds **29** and **30** which may be considered as species related to azacalixarenes [30,31]. These compounds have been investigated in order to elucidate their complexation abilities towards metal ions. It was observed a strong influence of the spatial arrangement of the fluorine atoms on the donor ability of the host molecules.

Compound **25** in which six fluorine atoms are arranged in a quasi planar fashion has only weak affinity towards NH_4^+ and Ag^+ ions and does not show any affinity towards alkali metal ions. Compound **28** also does not form complexes with alkali metal ions. In the study of the complexation of cage compounds **29** and **30** it was found that the hexafluoro cage compound **25**, with six fluorine atoms in an octahedral geometry shows a strong coordination ability towards K^+, NH_4^+ and Ag^+ ions. On the other hand, the cage compound **30** with four fluorine atoms shows only very weak affinity towards these cations.

It was established that fluorine acts as an effective donor atom towards cations. Investigating the structure of the complex of **29** with K^+ ion it was found that in **29** the bridgehead nitrogen atoms do not act as donors, but six

fluorine atoms coordinate to the potassium ion in an octahedral fashion. The compound **29** can surround the spherical ions with six fluorine atoms forming a three-dimensional coordination site, while in **25, 28** and **30** the geometries of C-F units are almost planar .

The synthesis of the compound **25** begins with the reaction of 2-fluoro-1,3-bis(bromomethyl)benzene **31** with p-toluenesulfonamide under phase-transfer conditions affording the cyclophane **32** along with the trimer **33**. The detosylation of **32** leads to the mixture of *syn* and *anti* isomers **34a** and **34b**, which was used directly to the reaction with **31** giving rise to **25** accompanied by the trimer **35** and tetramer **36**.
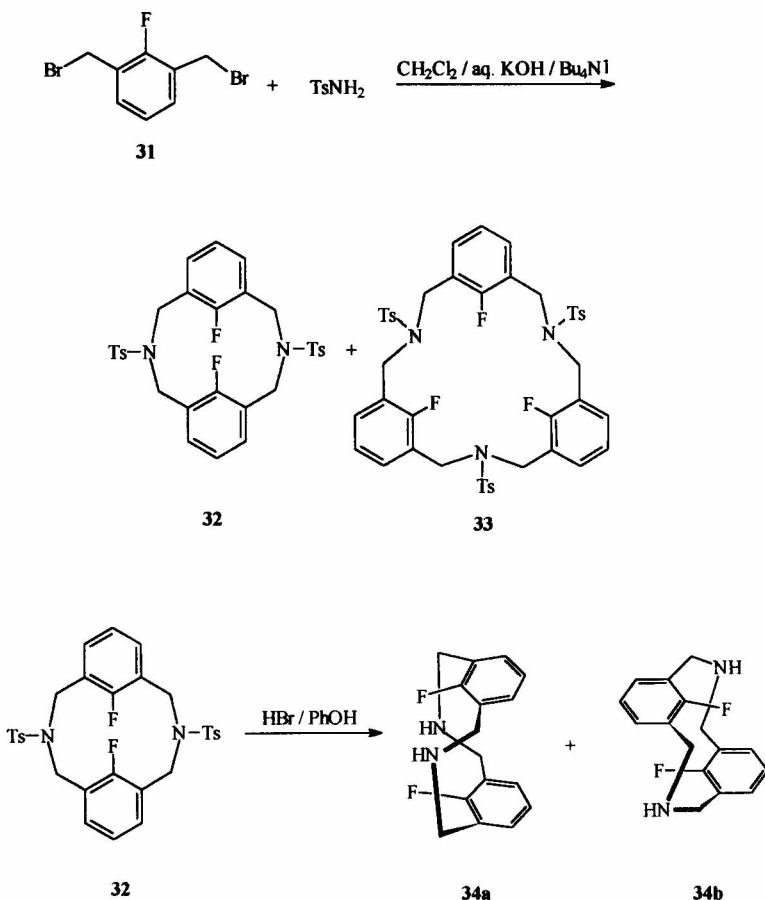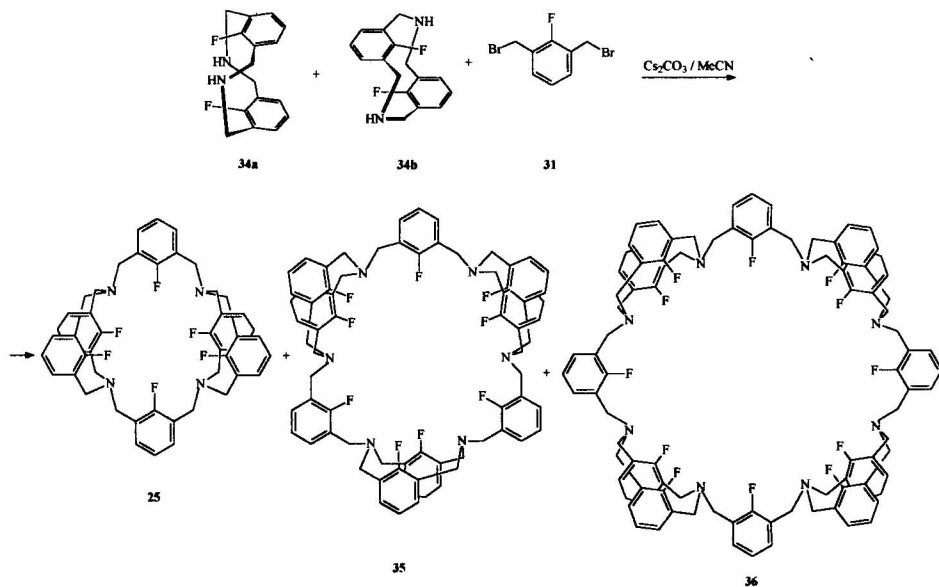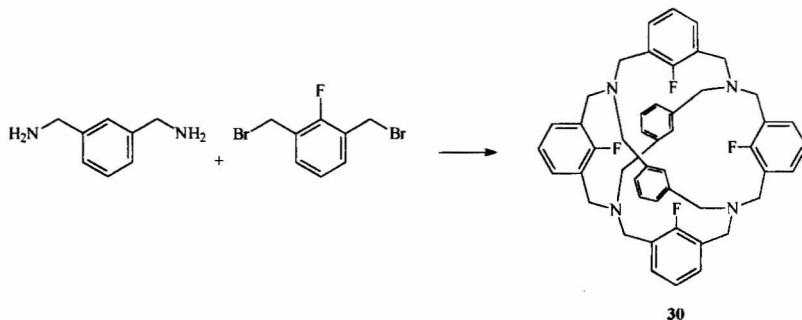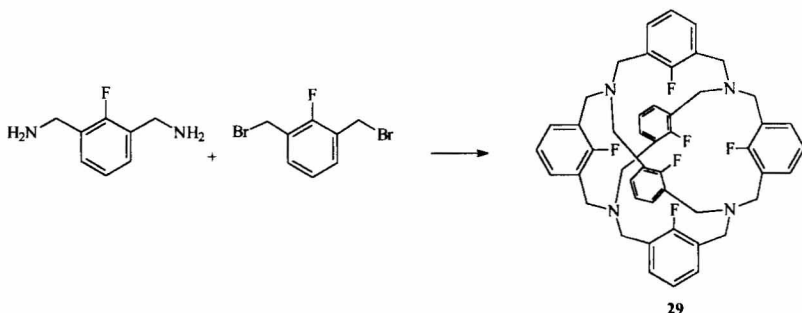
Compound **28** has been obtained by the same procedure, except for the reaction of the mixture of **34a** and **34b** in which 1,3-bis(bromomethyl)benzene **37** instead of **31** has been used; the process leads to **28** along with the trimer **38**.
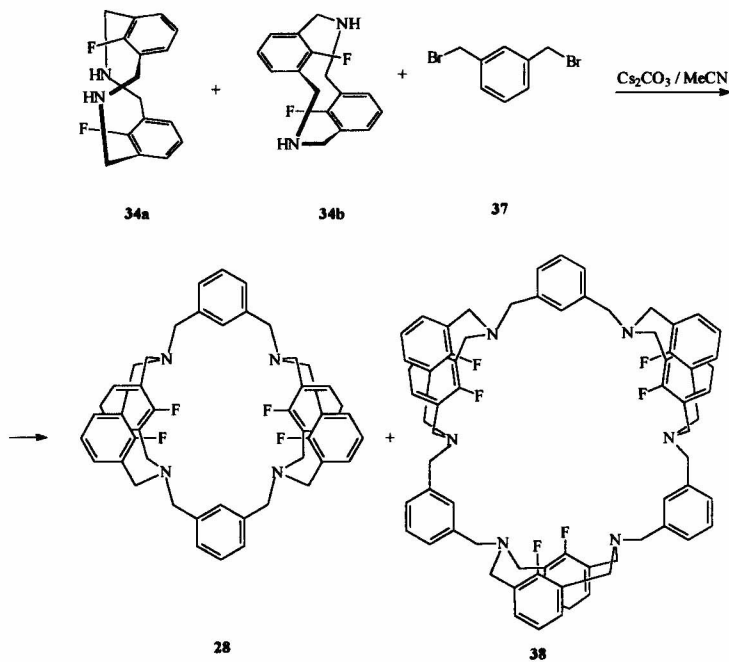
The synthesis of cage compounds **29** and **30** proceeds as follows: [30,31]

29

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An azacalixarene–like structure may be found in C$_3$-symmetric metacyclophanes **39** of anion-binding properties [32] and in chiral „calixsalenes" **40**, i.e. salen dimers forming Mn^{3+} complexes, which are of interest as catalysts for enantioselective epoxidation of alkenes [33].

R = H, Et

39

R = H, Me, *i*-Pr, *t*-Bu

40
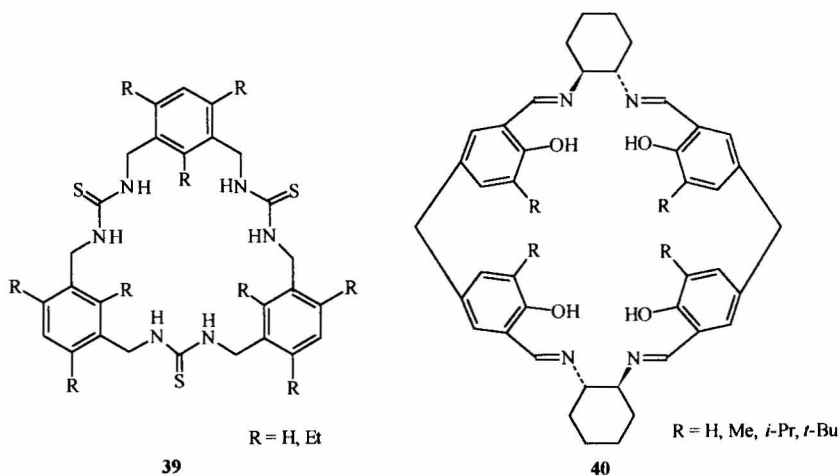
Concluding remarks

Investigation of azacalixarenes is a new research field, these species being not so widely studied as parent calixarenes. The interesting properties of azacalixarenes, especially those allowing their use as receptor molecules are promising for the future development of this new class of heterocycles.

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Streszczenie: W artykule przedstawiono azakaliksareny jako układy należące do nowej klasy heterakaliksarenów. Opisano reaktywność i syntezy tych związków ze szczególnym uwzględnieniem ich właściwości kompleksujących.