

CALIXARENES BEARING AZAAROMATIC MOIETIES

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Abstract- The chemistry of calixarenes bearing azaaromatic moieties is reviewed. Calixarenes containing covalently and noncovalently bonded azaaromatic units are presented and their synthetic approaches along with complexing properties and catalytic activities are described.

1. Introduction
2. Calixarenes bearing covalently bonded azaaromatic moieties
3. Calixarenes bearing noncovalently bonded azaaromatic moieties
4. Conclusion

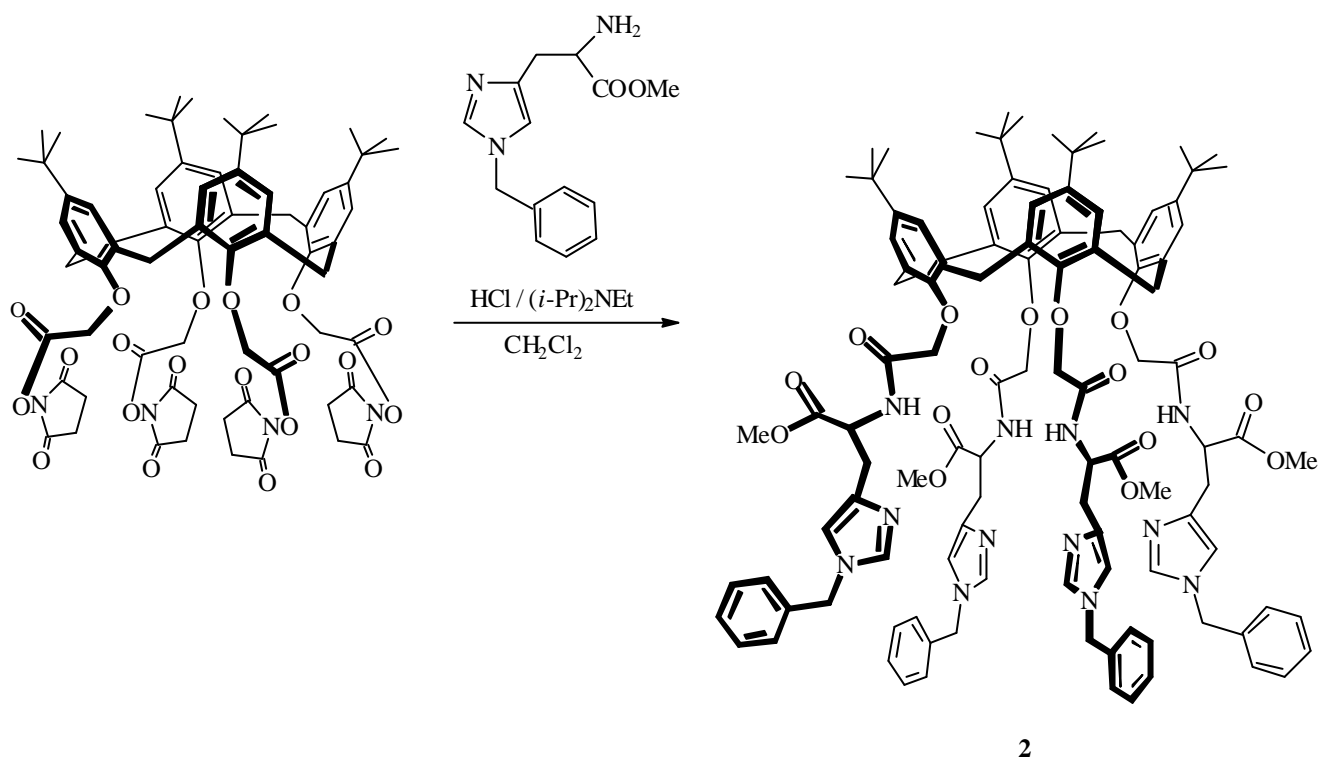
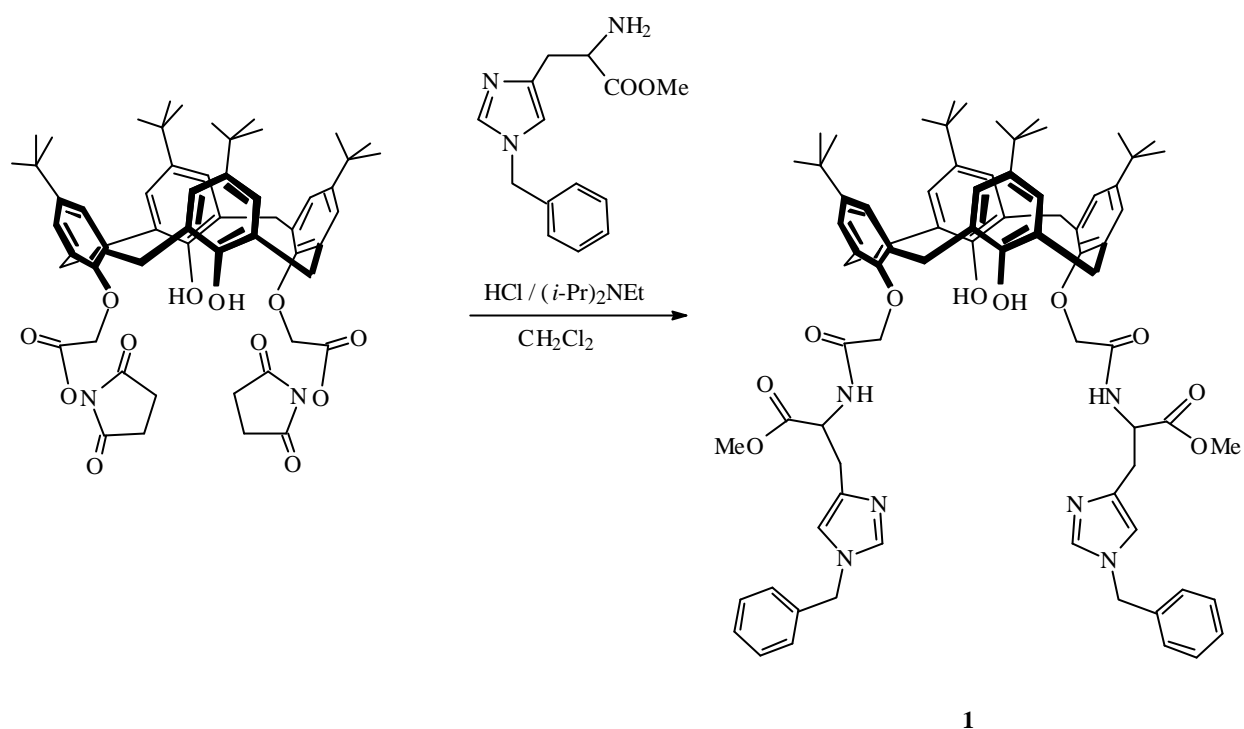
1. INTRODUCTION

Calixarenes, ¹⁻⁴ compounds of interesting shape, useful in supramolecular chemistry may be laterally substituted, ⁵ functionalized at lower ⁶ and upper ⁷ rims, or intramolecularly bridged, ⁸ these possibilities resulting in a great variety of their derivatives. ^{9,10} Due to the presence of oxygen atoms and in the case of their derivatives, of various introduced groups, calixarenes form many complexes with metal ions. ¹¹⁻¹³

In the present paper chosen examples of calixarenes containing azaaromatic moieties, covalently and noncovalently bonded with their molecules are described.

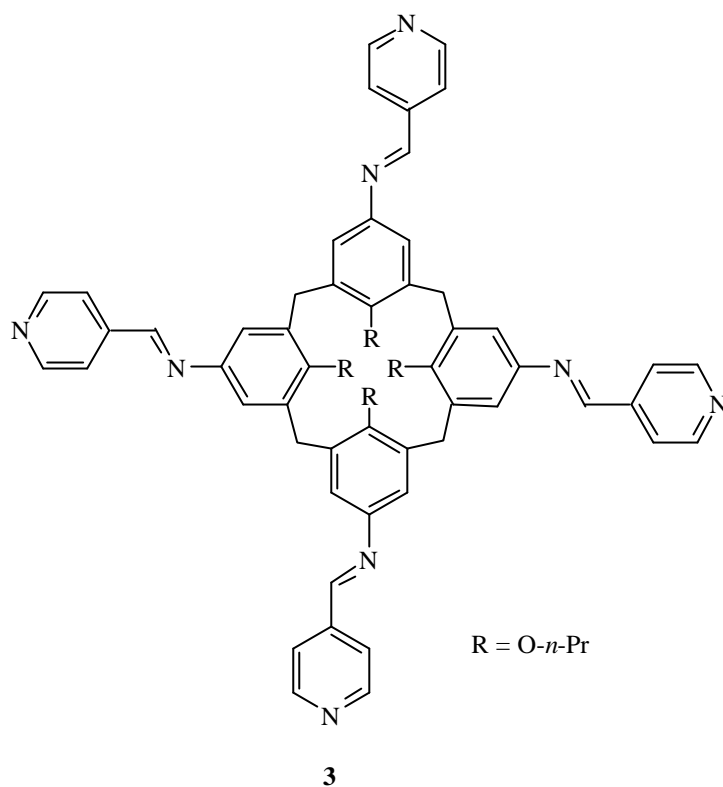
2. CALIXARENES BEARING COVALENTLY BONDED AZAAROMATIC MOIETIES

In the study of calixarenes containing amino acid groups, ¹⁴ calixarenes bearing two and four histidine moieties at the lower rim, **1** and **2**, respectively, have been synthesized in the following way. ¹⁵

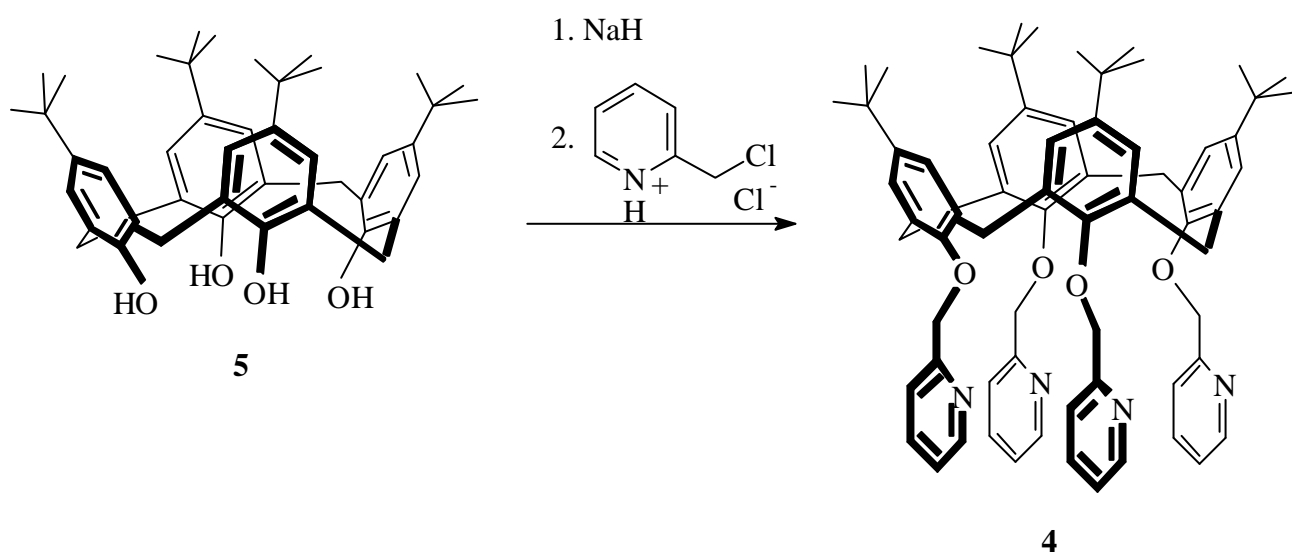


Compounds **(1)** and **(2)** form complexes with Co(II) ion of a 1:1 and 1:2 stoichiometry, respectively.

Calix[4]arene **(3)** existing in 1,3-alternate conformation contains four pyridine units acting as hydrogen bond acceptors.¹⁶

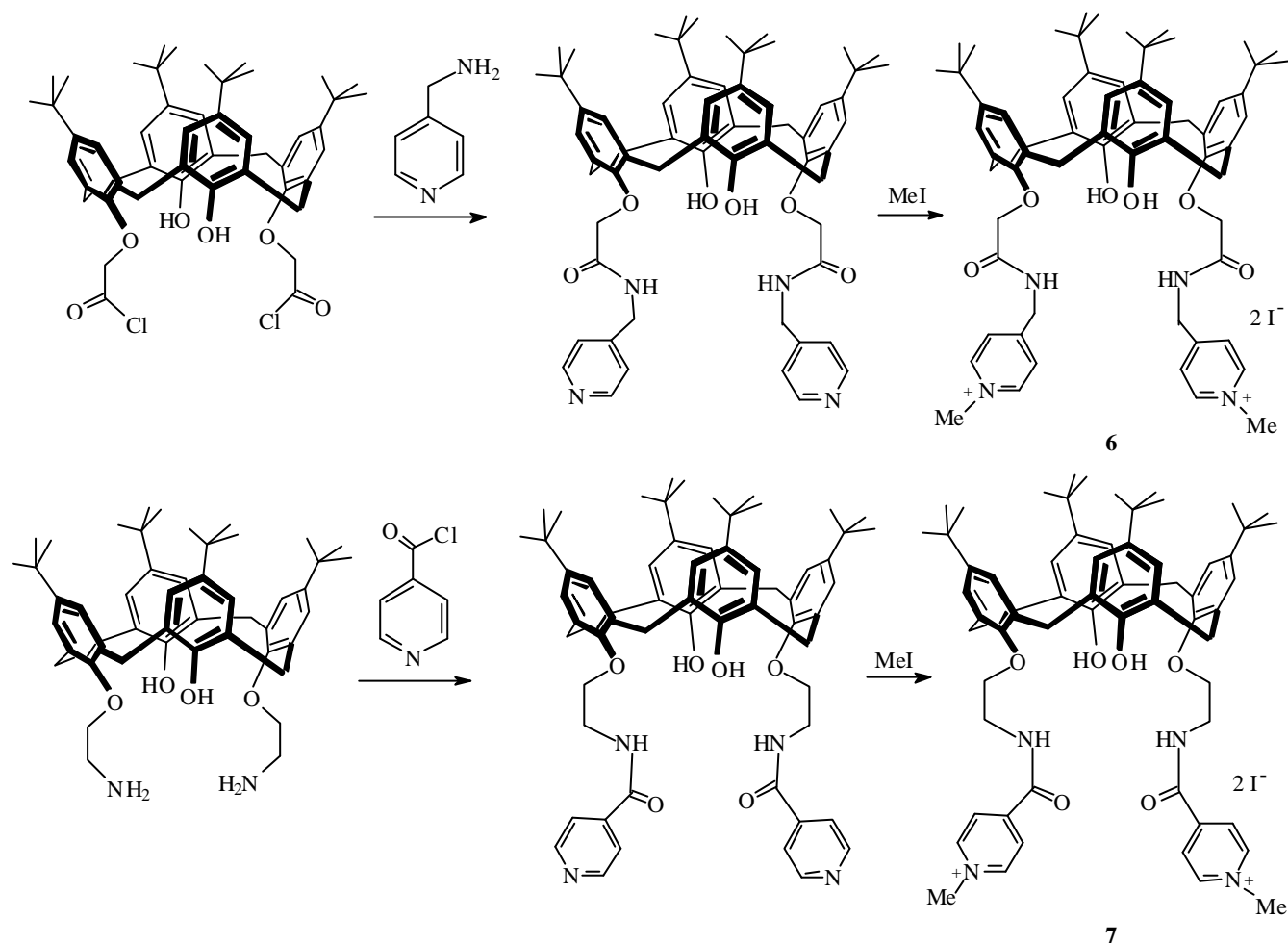


Calix[4]arene (**4**), of a cone conformation was synthesized from *p*-*tert*-butylcalix[4]arene (**5**) by treatment with sodium hydride followed by reaction with 2-chloromethylpyridinium chloride.¹⁷ Analogous derivatives of calix[6]arenes and calix[8]arenes are also known.^{18,19}



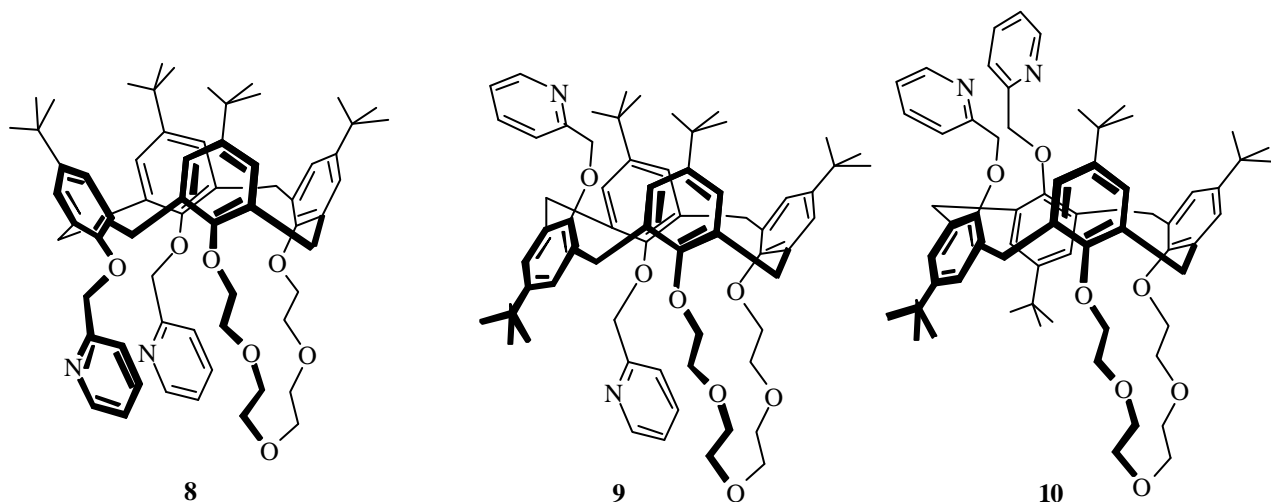
It was found that **4** forms 1:1 complexes with Li^+ , Na^+ and K^+ ions¹⁷ in acetonitrile and benzonitrile as well as with Ag^+ ion²⁰ in acetonitrile. Stability constants of complexes have been determined by titration microcalorimetry and by potentiometric method.¹⁷ The highest stability constant has been observed in the case of lithium complex.¹⁷

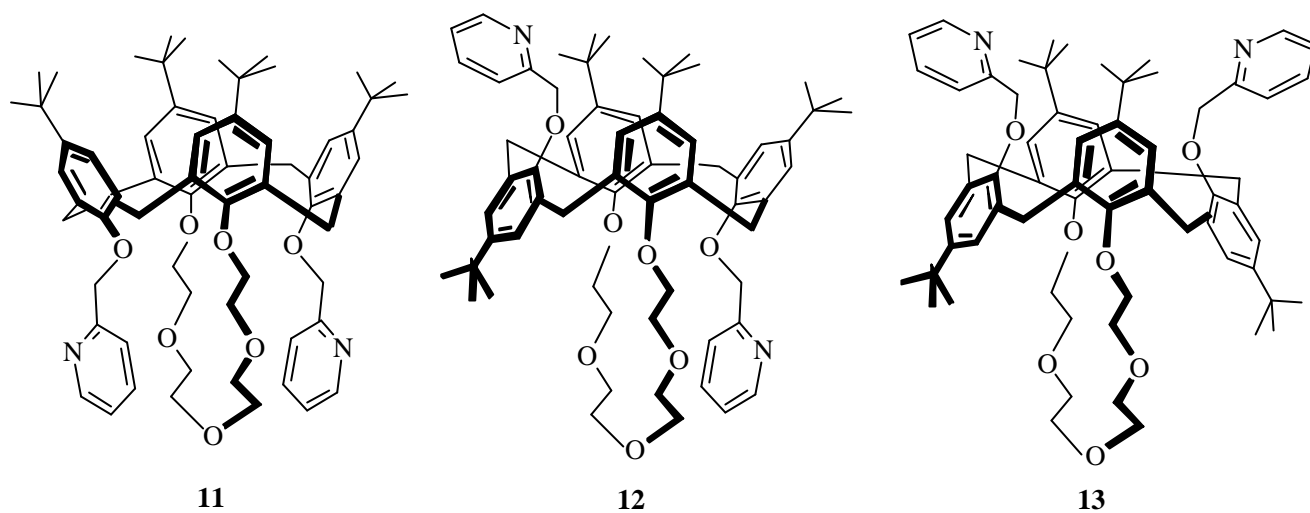
Calixarenes (**6**) and (**7**) bearing pyridine moieties have been obtained as follows.²¹



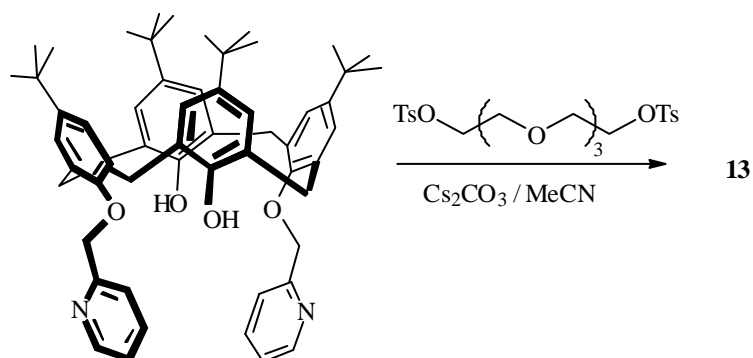
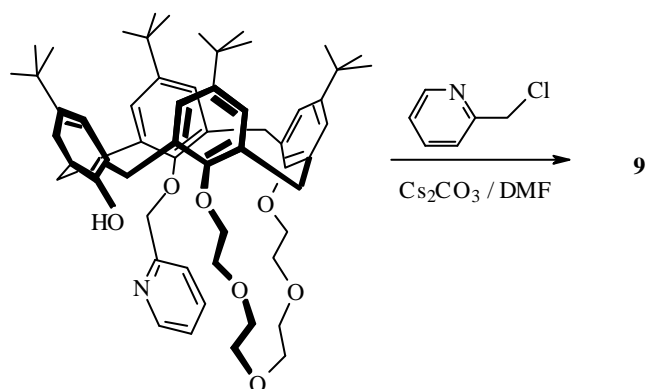
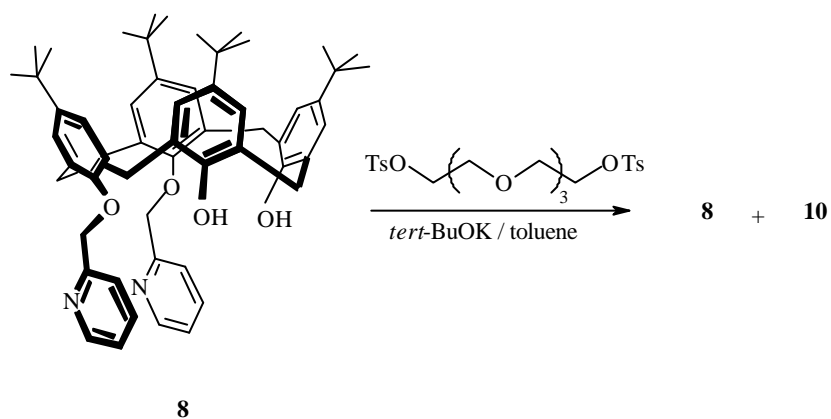
Calixarenes (**6**) and (**7**) form 1:2 complexes with H_2PO_4^- , HSO_4^- , Cl^- and Br^- anions. Stability constants determination has shown that **6** has a selectivity preference for H_2PO_4^- over Cl^- ; much weaker complexes are formed with Br^- and HSO_4^- anions. Compound (**7**) binds Cl^- in preference to Br^- and HSO_4^- ions.²¹

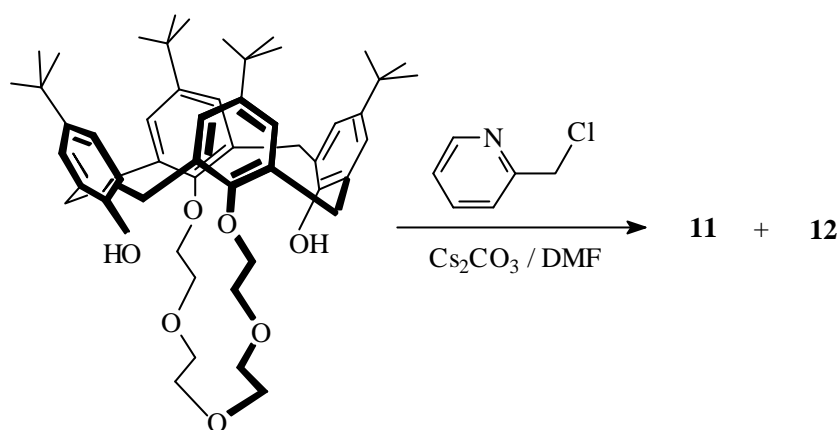
The 1,2- and 1,3-bridged calix[4]arenecrowns (**8-10** and **11-13**), bearing pyridine moieties, respectively, have been synthesized.²²





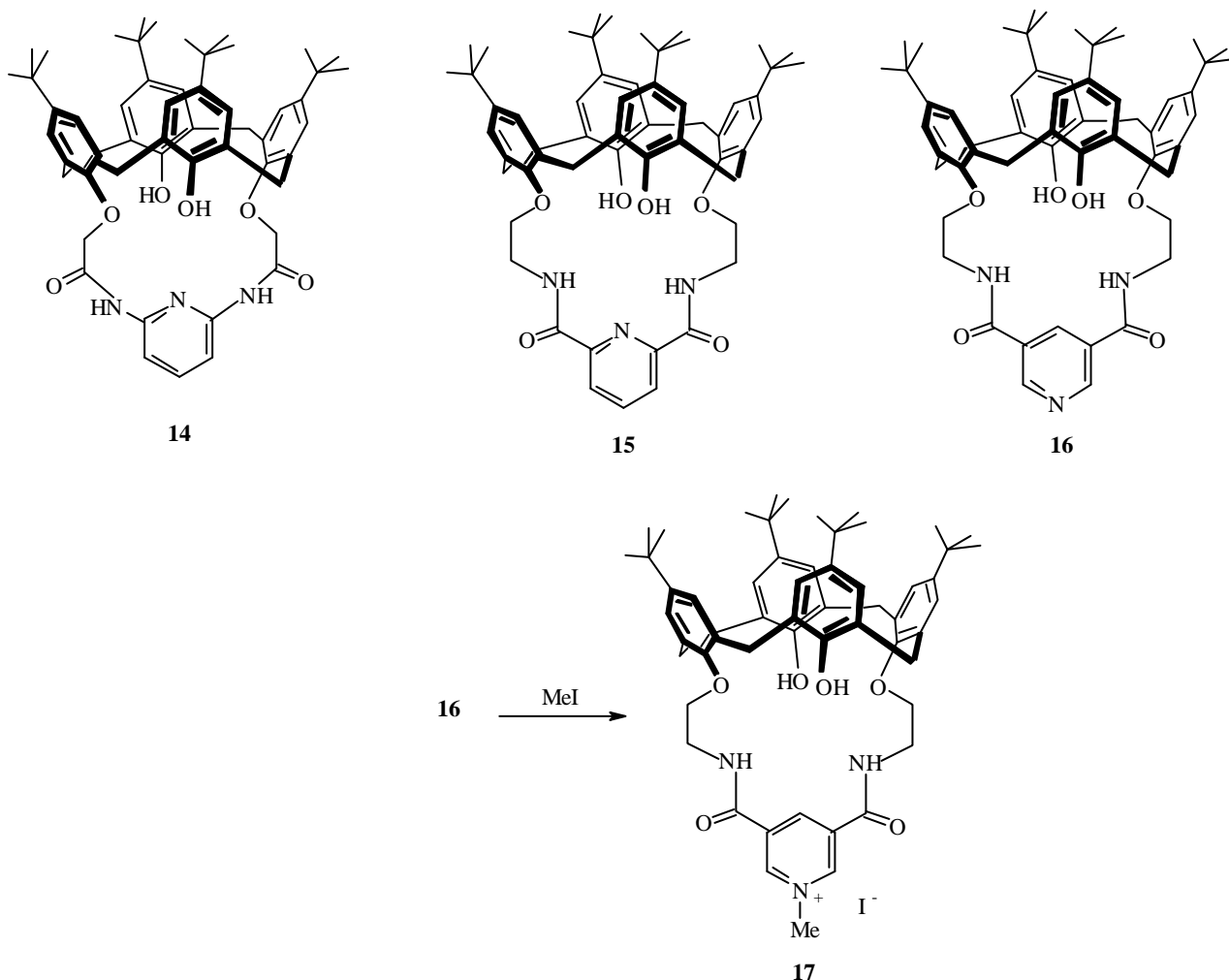
Synthetic procedures leading to **8-13** are shown below.²²



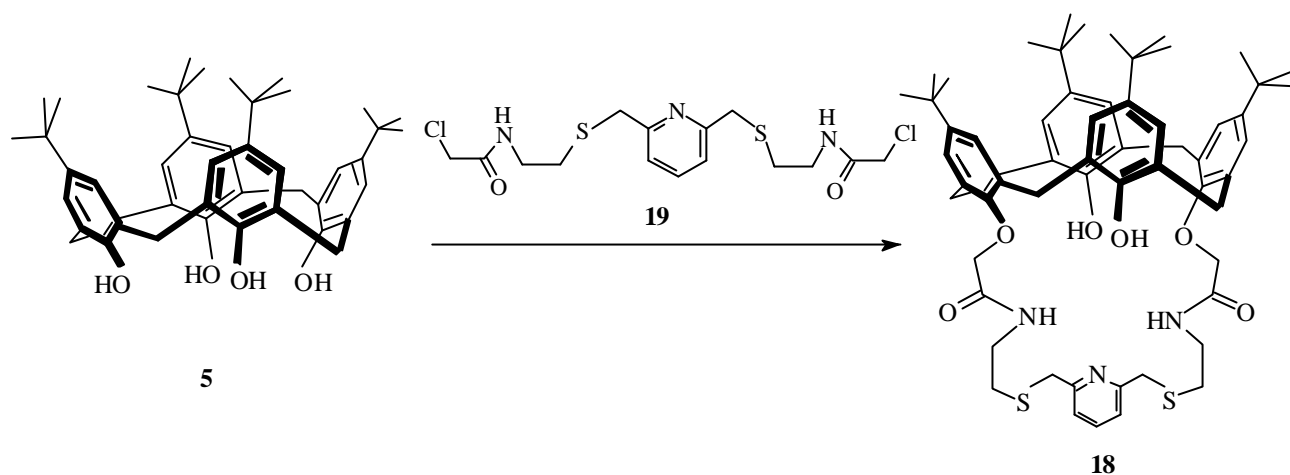


Calixarenecrowns (**8 – 13**) form 1:1 complexes with alkali metal cations. Complexes of 1,2-bridged calixarenecrowns are less stable than those of 1,3-bridged compounds.²² The 1,3-bridged calixarenecrowns have a strong affinity for K^+ , compounds (**12** and **13**) also for Rb^+ ion.²²

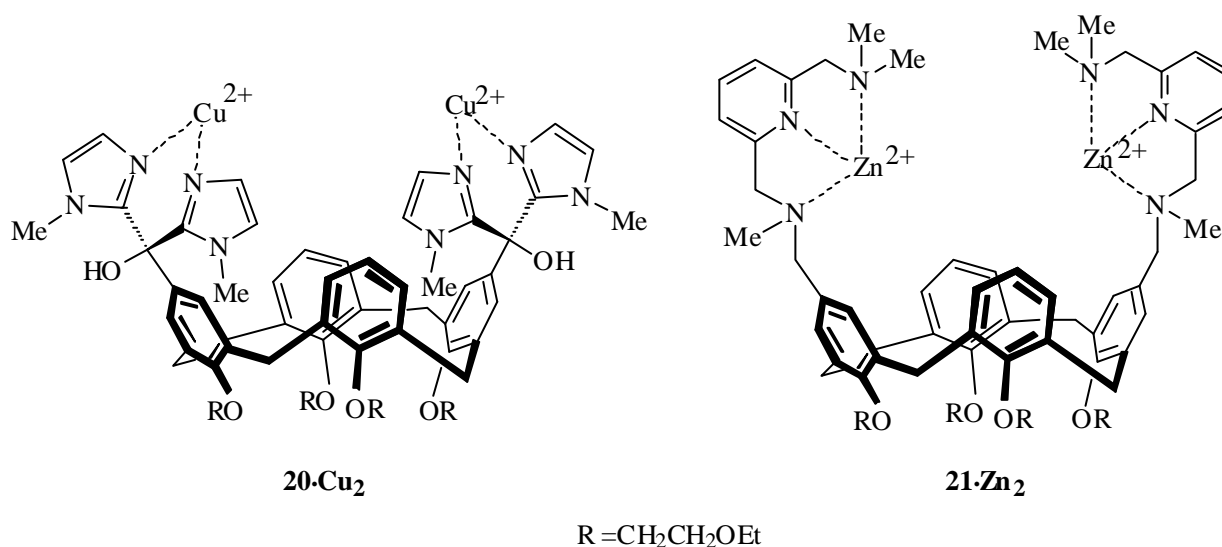
In the investigation of calixarenes (**14 – 16**) it was observed that **16** reacts with methyl iodide to give quaternary salt (**17**), while **14** and **15** do not undergo quaternization, presumably for steric reasons. Compound (**17**) forms 1:1 complexes with Cl^- and Br^- anions.²¹



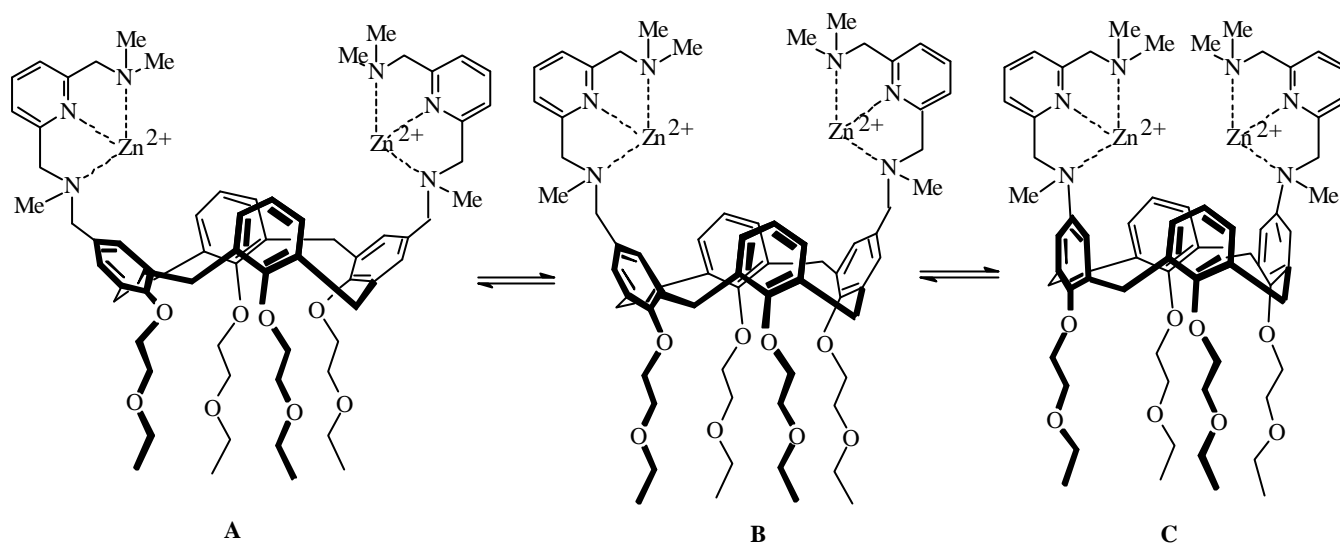
The one step synthesis of calixarene-crown (**18**) containing nitrogen and sulfur atoms, promising in the complexation of soft cations, involves the reaction of calixarene (**5**) with bischloroacetamide (**19**).²³ The ¹H and ¹³C NMR spectral analysis indicates for **18** the cone conformation.



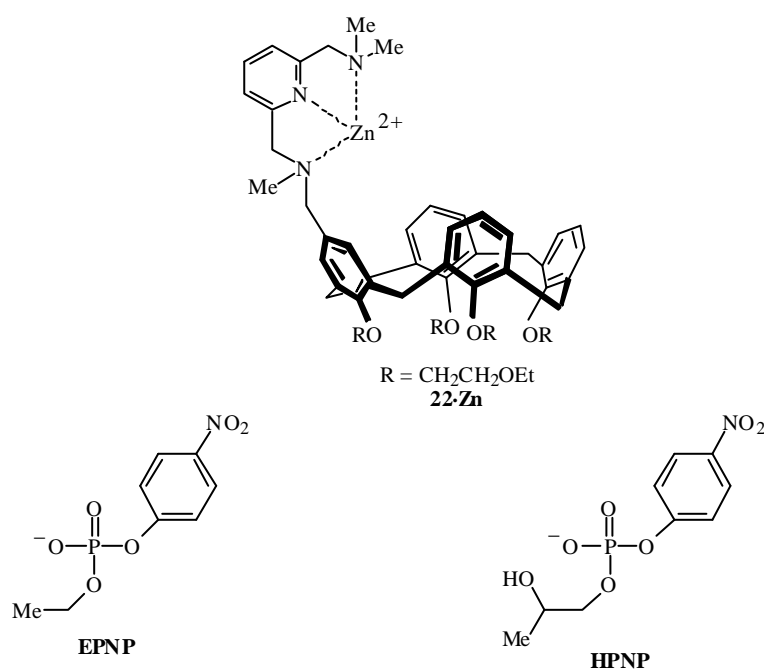
Calixarenes due to their flexibility and ease of functionalization are suitable building blocks for enzyme models. In this study dinuclear Cu(II) and Zn(II) complexes of calix[4]arenes (**20**) and (**21**), catalyzing phosphate diester cleavage have been investigated.^{24,25} These compounds are convenient models for natural hydrolases cleaving phosphate ester bonds, which often contain in their active site two metal ions such as Zn(II), Mg(II), Ni(II) or Fe(III) that cooperate as Lewis acid sites in the catalysis.^{26,27}



The ethoxyethyl groups increase the solubility in polar solvents and prevent inversion of the aromatic moieties through the annulus of the macrocycle.²⁴ The calixarene molecule exists in a rapid equilibrium (shown below for **21·Zn₂**) between conformations with two flattened or pinched opposing aromatic units **A** and **C**, respectively, formed *via* a symmetrical cone-intermediate **B**.²⁴

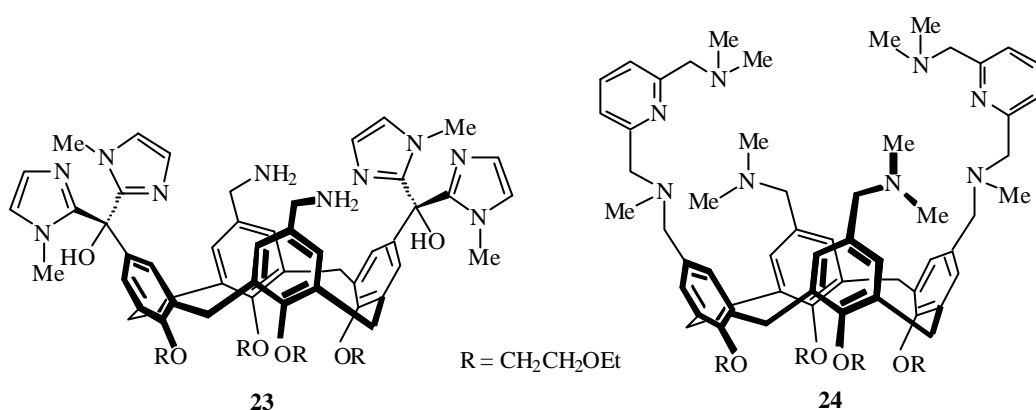


It was established that **21·Zn₂** shows a very high activity in the transesterification of the RNA model substrate 2-hydroxypropyl *p*-nitrophenyl phosphate (**HPNP**) and is not active in the hydrolysis of the ethyl *p*-nitrophenyl phosphate (**EPNP**). It should be pointed out that the catalytic efficiency of **21·Zn₂** is higher than that of mononuclear calix[4]arene Zn complex (**22·Zn**) due to the cooperation of two active centers.²⁸



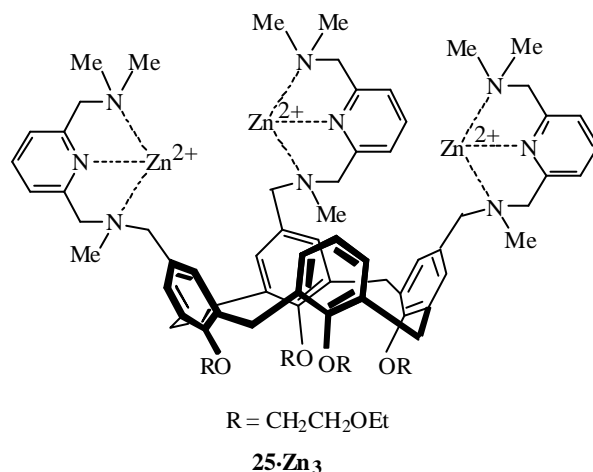
The complex (**21·Zn₂**) has a higher catalytic activity than its Cu(II) analogue **21·Cu₂**, while in the case of bisimidazolyl ligands the **20·Cu₂** complex is highly active, and **20·Zn₂** shows only weak catalytic properties.²⁴ Complex (**20·Cu₂**) is active in the transesterification of **HPNP**, and also in the hydrolysis of **EPNP**.²⁴

In order to increase the catalytic properties of **20** and **21** complexes, two amino groups which can provide general acid/base catalysis have been introduced into ligand molecules, giving rise to calixarenes (**23**)²⁹ and (**24**).³⁰



Compounds (**23**) and (**24**) form with $\text{Cu}(\text{ClO}_4)_2$ and $\text{Zn}(\text{ClO}_4)_2$ dinuclear complexes (**23·Cu₂**) and (**24·Zn₂**), both of them showing catalytic activity in the transesterification of **HPNP**.²⁴

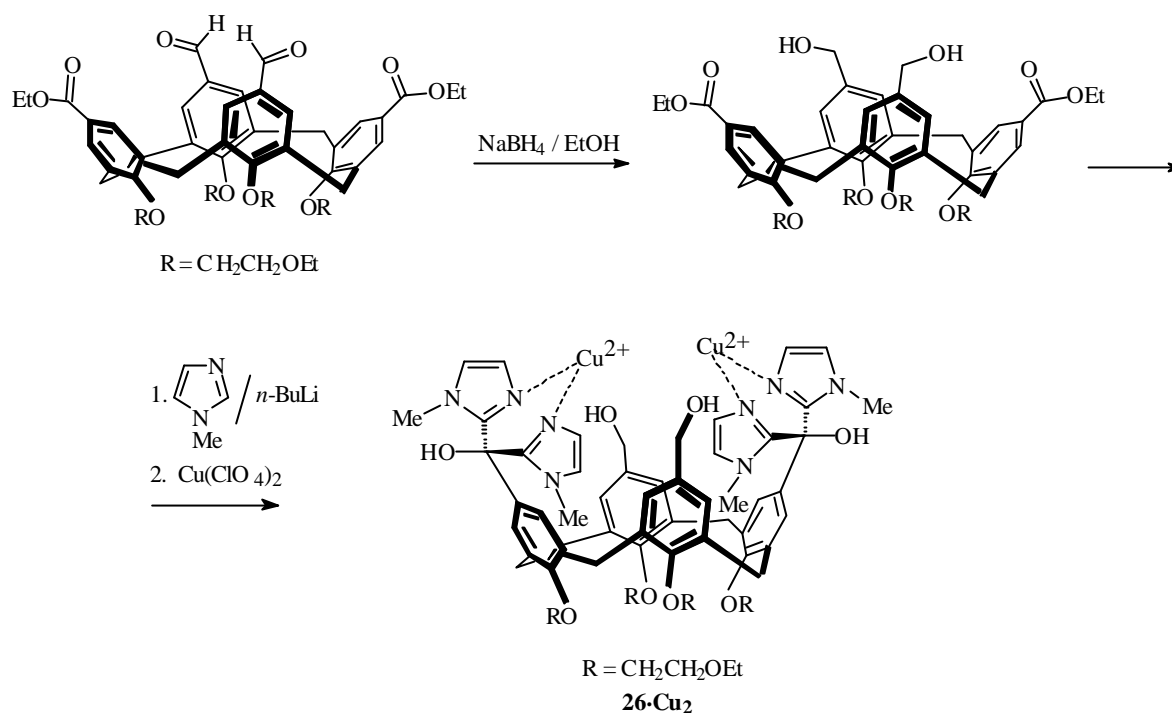
Dinuclear Zn(II) and Cu(II) complexes have higher catalytic activity in the cleavage of activated phosphate diesters like **HPNP** and **EPNP** than mononuclear species, this fact being due to the cooperative action of two Zn(II) or two Cu(II) ions. In the cleavage of natural substrates like RNA dinucleotides, however, these compounds are only weakly active. In order to improve the catalytic activity, the trinuclear complex (**25·Zn₃**) has been obtained.^{24,31,32}



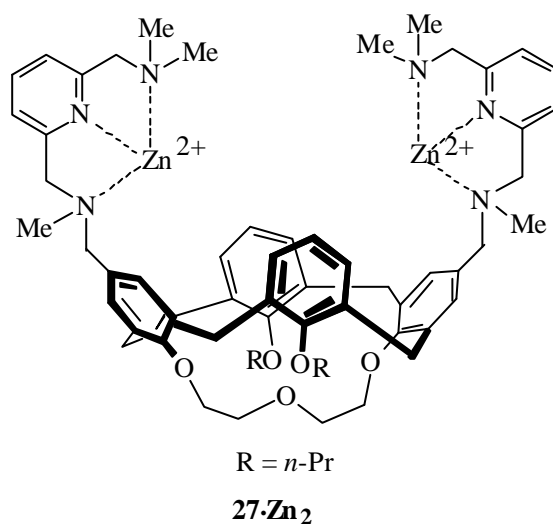
As expected, the cooperative action of three Zn(II) centers results in higher catalytic properties of **25·Zn₃** than in the case of dinuclear **21·Zn₂** complex in the cleavage of **HPNP**. However, the trinuclear Cu(II) analogue **25·Cu₃** is hardly active.²⁴

It was observed that a statistical mixture with the heterotrinuclear complex (**25·Zn₂Cu**) as the main species, shows higher activity than **25·Zn₃**, this fact being in accordance with the behavior of natural metallophosphoesterases containing two Zn(II) centers and one Mg(II) center.²⁶

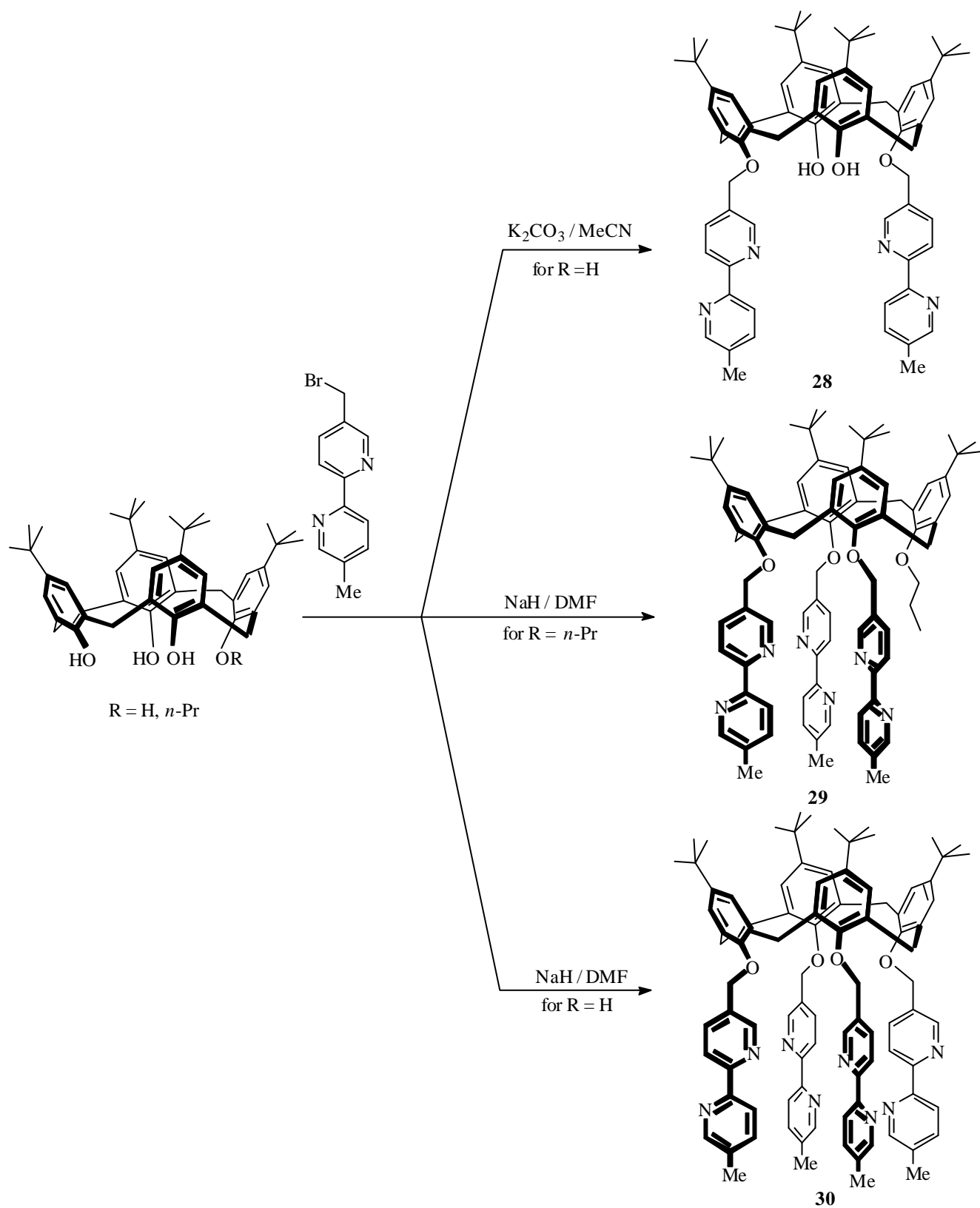
In the study of enzyme models, derivative of **20·Cu₂**, bearing two hydroxymethyl groups **26·Cu₂** has been synthesized.²⁹ It was observed that its catalytic activity in the cleavage of **HPNP** is higher than that of **20·Cu₂**.²⁹



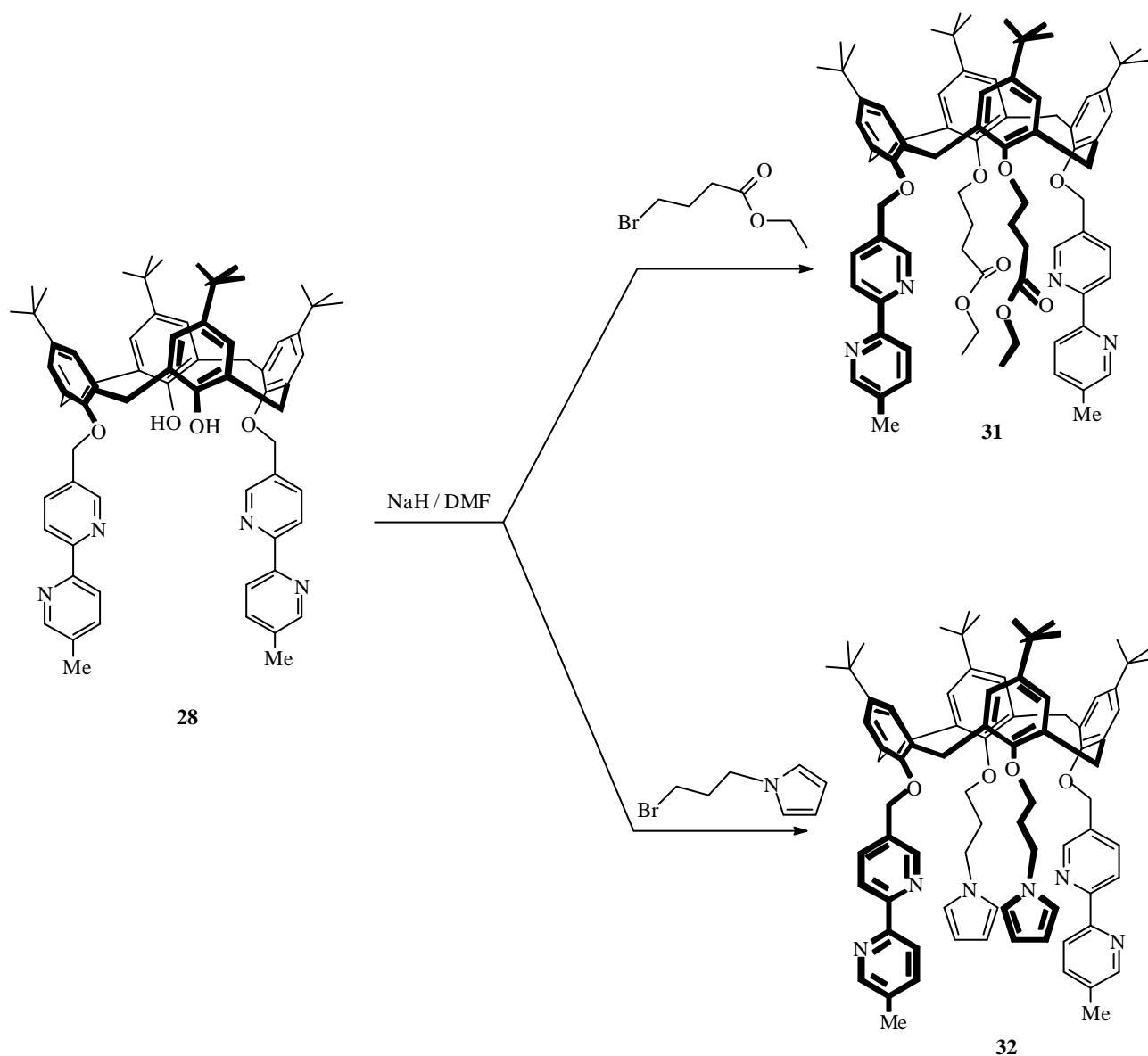
A certain flexibility between the cooperating catalytic centers in the calixarene complex is necessary for the catalytic action, this fact being indicated by the observation that **27·Zn₂** rigidified by a crown bridge shows a lower catalytic rate than **21·Zn₂**.³²



Calix[4]arenes (**28–30**) containing two, three or four 2,2'-bipyridine moieties, respectively, have been synthesized as follows.³³



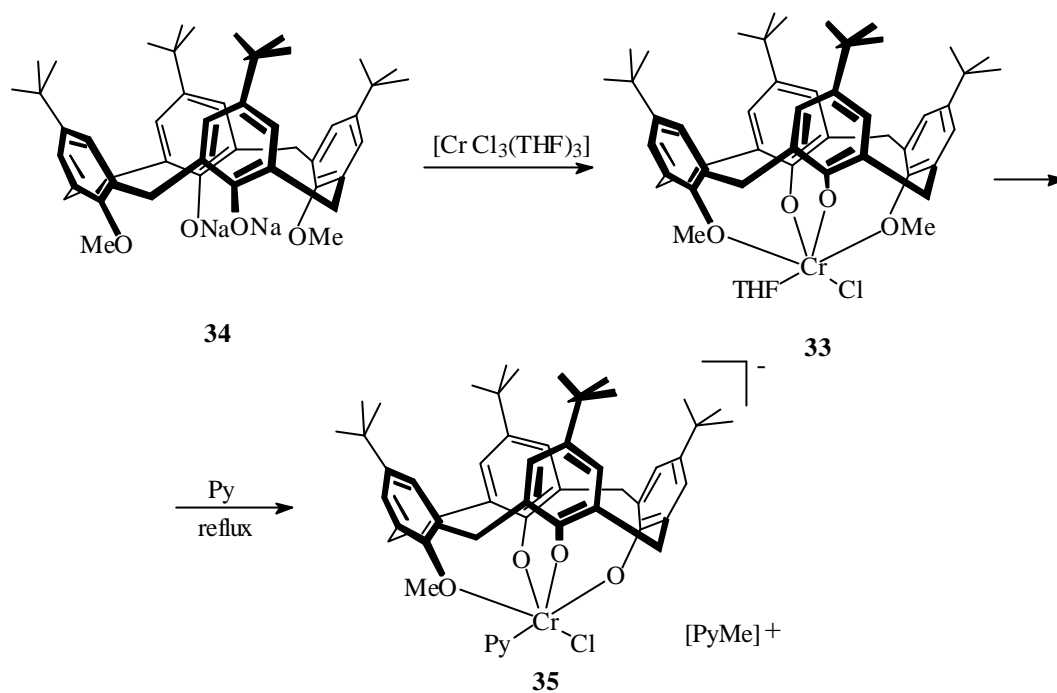
The reaction of **28** with sodium hydride in DMF, followed by ethyl 4-bromobutyrate or *N*-(3-bromopropyl)pyrrole treatment leads to compounds (**31**) and (**32**).³³



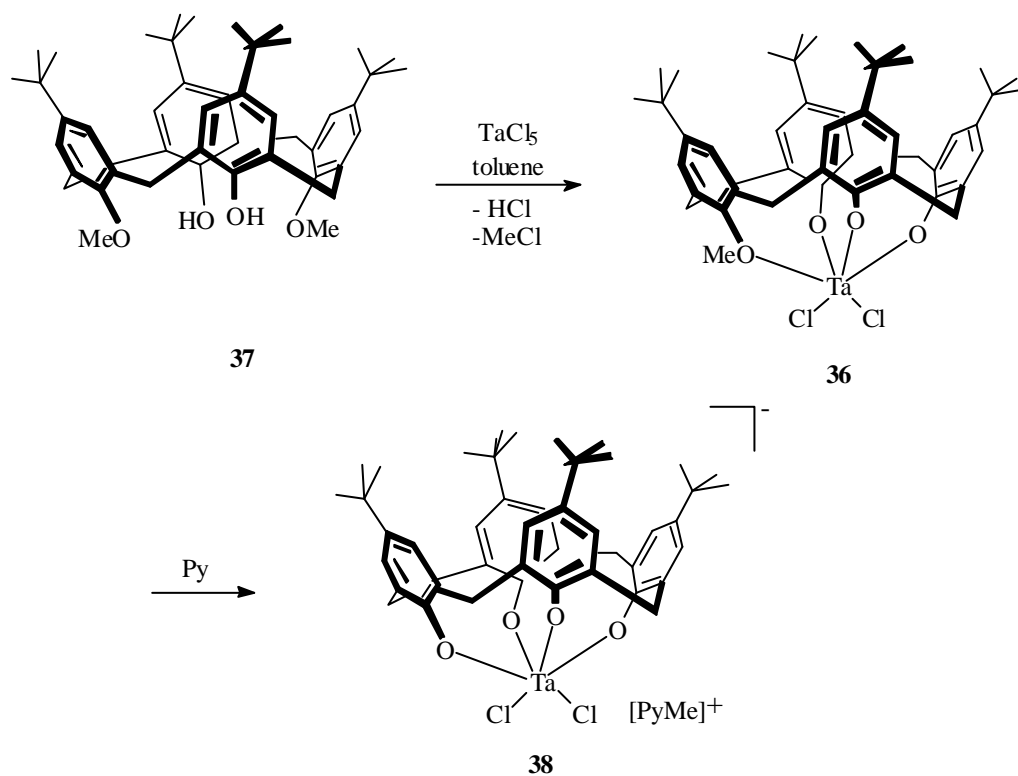
It was observed that calixarenes (**28** – **30**) form complexes with Eu(III) and Tb(III); europium complexes of **29** and **30** show high metal luminescence quantum yields. Compounds (**31**) and (**32**) do not form complexes with lanthanide ions.³³

2. CALIXARENES BEARING NONCOVALENTLY BONDED AZAAROMATIC MOIETIES

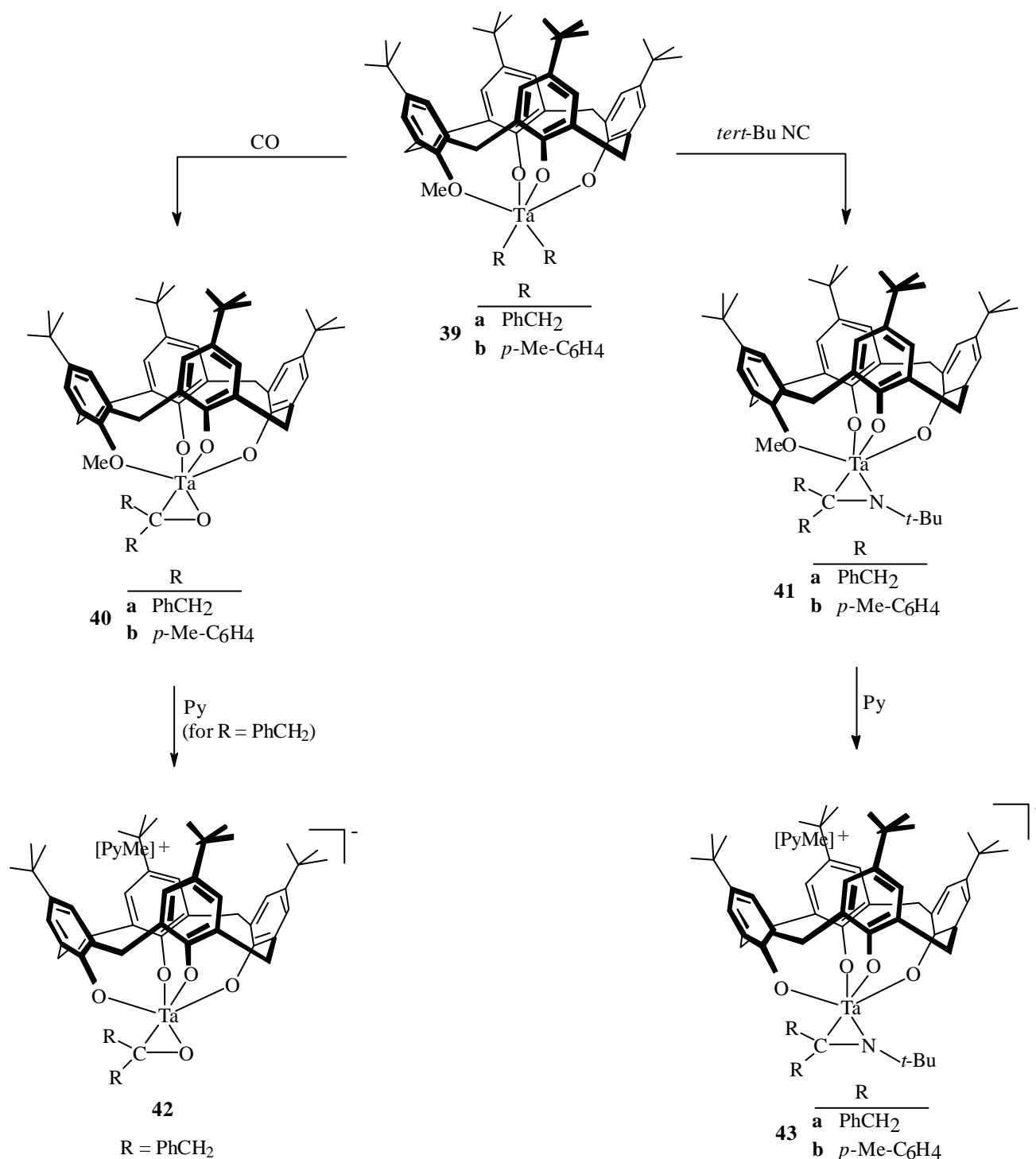
In the study of calixarene complexes with metal ions it was established that the reaction of $[\text{Cr}\{p\text{-tert-butylcalix}[4](\text{O})_2(\text{OMe})_2\}(\text{Cl})(\text{THF})]$ (**33**) (obtained from $[p\text{-tert-butylcalix}[4](\text{ONa})_2(\text{OMe})_2]$ (**34**) by treatment with $[\text{CrCl}_3(\text{THF})_3]$) with pyridine results in the demethylation of one methoxy group affording compound (**35**).³⁴⁻³⁶



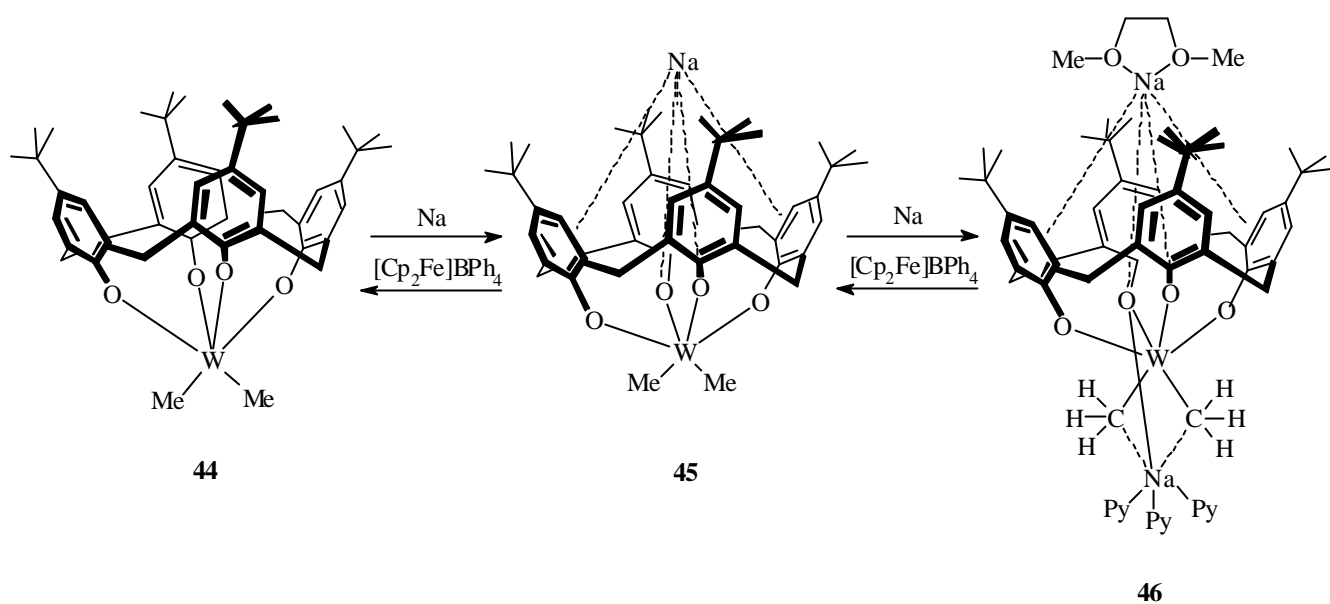
Complex (**36**) (prepared by demethylation of [*p*-*tert*-butylcalix[4](OH)₂(OMe)₂] (**37**) with TaCl₅) treated with pyridine undergoes a further demethylation to give compound (**38**), in which pyridine is an acceptor of the methyl carbocation.³⁷



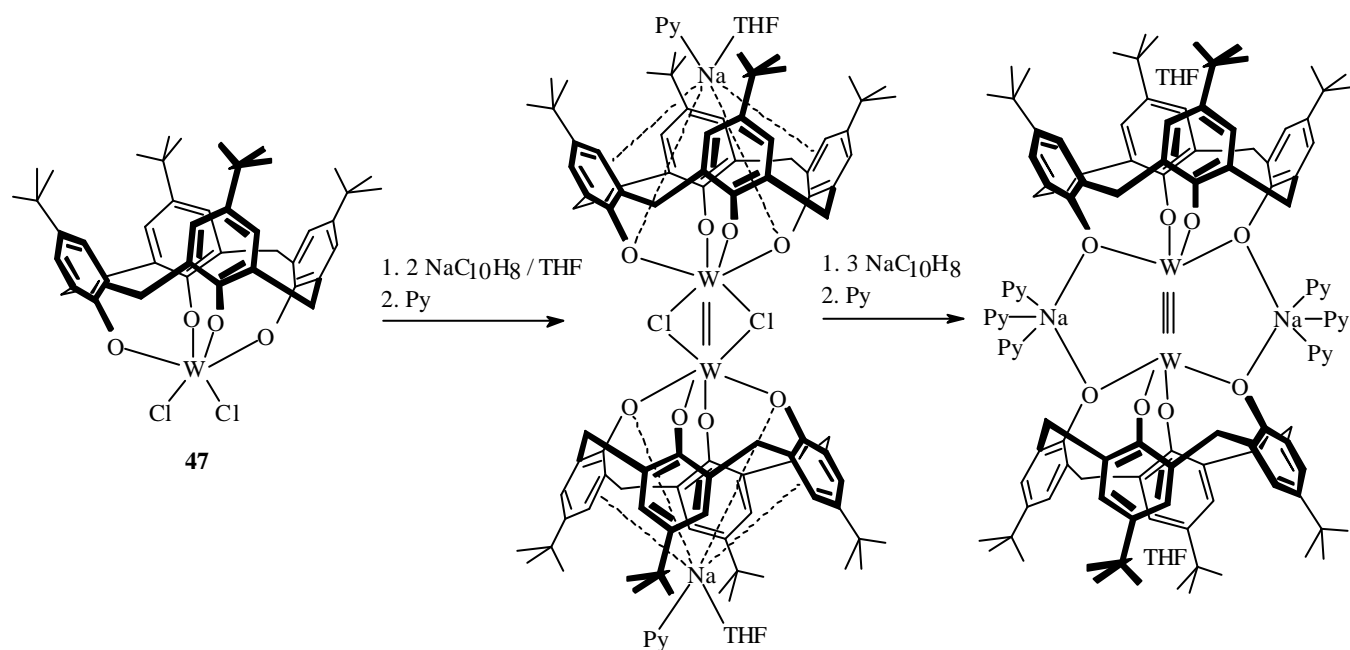
Complexes (**39a,b**) have been submitted to migratory insertion reactions with CO and *tert*-BuNC leading to η^2 -ketones (**40a,b**) and η^2 -imines (**41a,b**), respectively. Compounds (**40a**) and (**41a,b**) react with pyridine to give demethylated salts (**42**) and (**43a,b**). Pyridine removes the methyl carbocation forming the *N*-methylpyridinium ion situated inside the calixarene cavity.³⁷



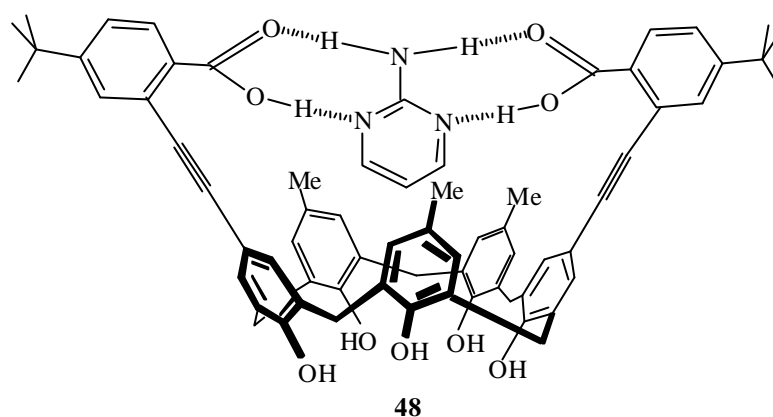
It should be mentioned here also the stepwise reduction of the tungsten complex (**44**) with sodium leading to *cis*-[(Me)₂W{*p*-*tert*-butylcalix[4](O)₄}Na] (**45**) and subsequently to the complex (**46**), crystallized from pyridine/1,2-dimethoxyethane. The back oxidation of **45** and **46** with [Cp₂Fe]BPh₄ results in **44** and **45**, respectively.³⁸



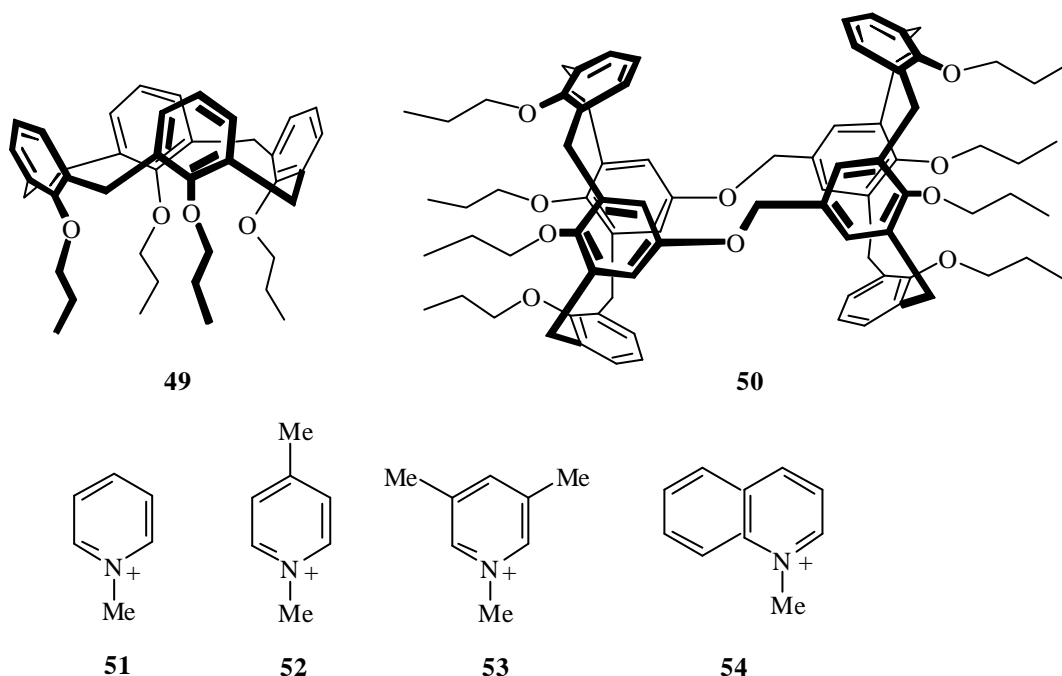
In the study of the metal-metal bonded calix[4]arenes, following reactions of $[\text{cis-Cl}_2\text{W}(\text{calix[4]arene})]$ (**47**) have been performed.³⁹⁻⁴¹



The 1:1 inclusion system (**48**) contains as a host the calix[5]arene bearing benzoic acid molecules, and 2-aminopyrimidine as a guest.⁴² The two benzoic acid moieties form hydrogen bonds with polar guests and the aromatic cavity helps to bind the guests by van der Waals interaction.⁴²



Calix[4]arene (**49**) and biscalix[4]arene (**50**) have been investigated as receptors for cationic species (**51** – **54**).⁴³



Comparison of found K_a values shows that K_a is the largest in the case of the host (**50**) and the guest (**51**); the observed K_a value is 500-fold greater than in the case of calixarene (**49**) used as a host. This fact results from the cooperative action of the two π -basic cavities in **50**.^{43,44} The inclusion of the quaternary salt (**52**) into calixarene (**49**) is more difficult due to steric hindrance, and for bigger **53** and **54** molecules no complexation with **49** was observed.⁴³

4. CONCLUSION

The development of research concerning calixarenes bearing azaaromatic units has its reflection in a great number of reports.⁴⁵⁻⁵⁰ In the present review chosen examples of these compounds, interesting from theoretical and practical viewpoint have been described. As calixarenes form a number of complexes, an attention was paid to complexation abilities of presented species.

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