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REVIEW

Homooxacalixarenes: I. Structure, Synthesis, and Chemical Reactions

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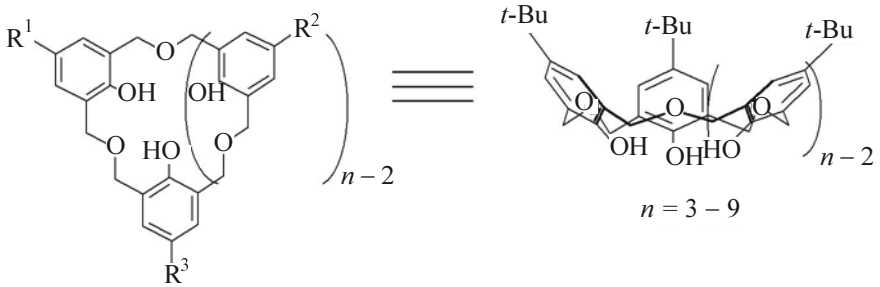
Abstract—Data published on the structure, preparation, and chemical reactions of homooxacalixarenes with various number of aromatic fragments and dihomooxabridges in macrocycles were analysed and summarized.

1. INTRODUCTION

Homooxacalixarenes represent a new class of macrocyclic receptors analogous to calixarenes [1–4] where some or all methylene bridges between the aromatic rings are replaced by CH_2OCH_2 moieties. Nowadays the following homooxacalixarene systems are known which are distinguished by a number of phenol fragments and ether bridges in the macroring.

Oxacalix[*n*]arenes with CH_2OCH_2 bridges



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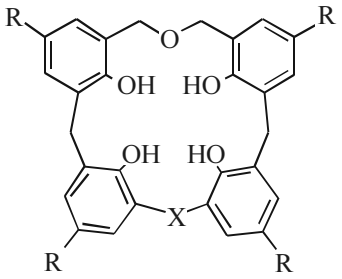
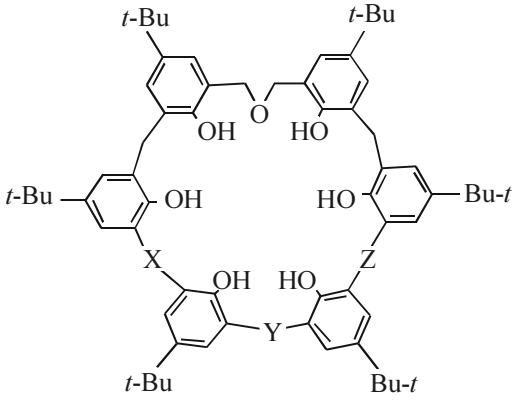
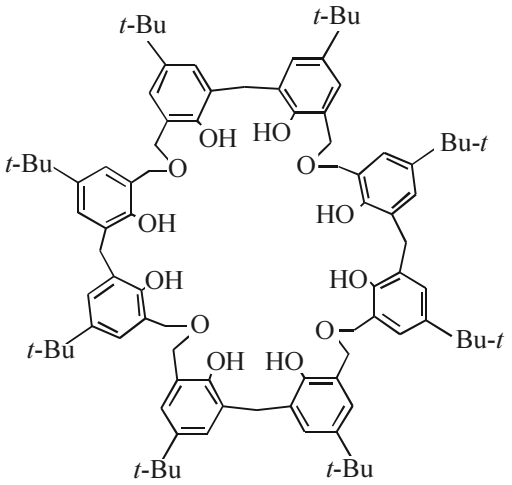
Oxacalix[*n*]arenes with CH_2OCH_2 and CH_2 bridges



Oxacalix[4]arenes, X = CH_2, CH_2OCH_2.*

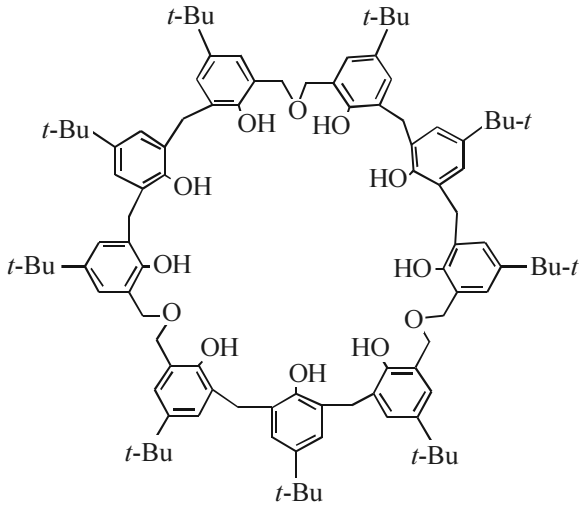


Oxacalix[6]arenes, X = Y = Z = CH_2; X = CH_2OCH_2, Y = Z = CH_2; X = Z = CH_2, Y = CH_2OCH_2; X = Z = CH_2OCH_2, Y = CH_2.



Oxacalix[8]arene

The most studied are now the derivatives of hexahomotrioxacalix[3]arene **1** that attract special interest not only because of their accessibility but also for other reasons [5, 6].



Oxacalix[9]arene

(1) The inner cavity of compound **1** is formed by a 18-membered ring (whereas in the "classic" 4-*tetr*-butylcalix[4]arene **2** the ring is 16-membered, and in calyx[6]arene **3** 24-membered ring is present). Thus the inner cavity of compound **1** is imtermediate between those of calixarenes **2** and **3** [7].

(2) The inversion rate in calix[3]arene **1** possessing flexible ether bridges should be higher than in the "classic" calyx[4]arene [8, 9]. In contrast to calyx[4]arene **2** existing in 4 conformations: *cone, paco,* 1,2-, and 1,3-*alt* (crown, partial crown, 1,2- and 1,3-alternating) only two conformations, *cone* and *paco*, are possible for oxacalixarene **1**.

(3) The ether oxygen atoms can cooperate with phenol oxygens in binding metal ions.

(4) The prevailing conformation of compound **1** possesses C_3 symmetry that frequently is favorable for receptors sensitive to ammonium ions RNH_3^+.

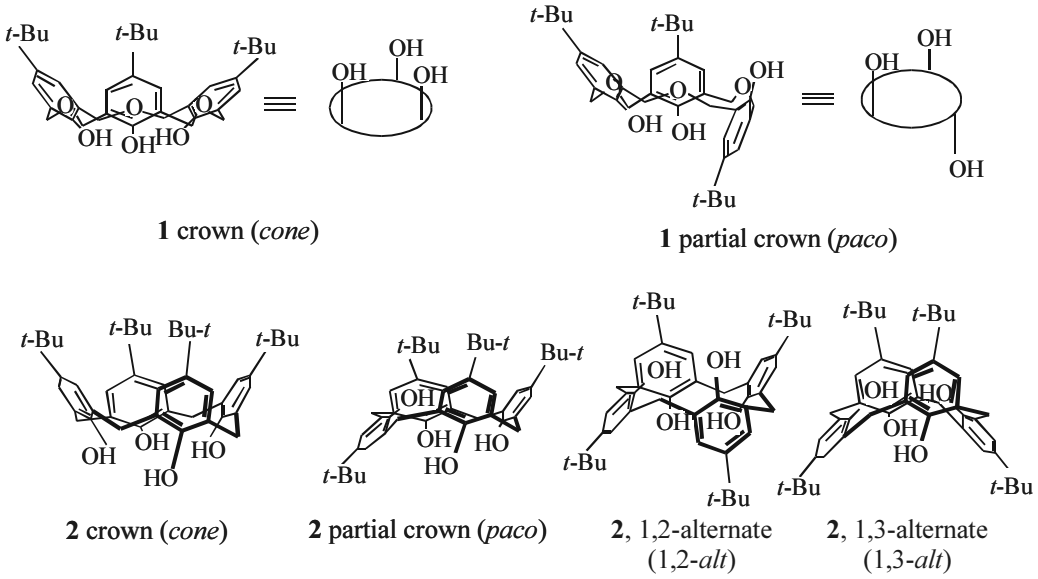
The above qualities make oxacalixarene **1** a promising basis for creating a new class of synthetic receptors. This review is aimed at collecting, systematizing, and analyzing published data on the structure, synthesis, and possible modification of homooxacalixarenes. The subsequent review will deal totally with the receptor characteristics of these compounds.

2. SYNTHESIS OF HOMOOXACALIXARENES

2.1. Formation of homooxacalix[4]arenes a by 4-alkylphenoles condensation with formaldehyde

In 1979–1981 Gutsche et al. [8, 10] in developing a one-pot procedure for preparation of calyx[*n*]arenas by

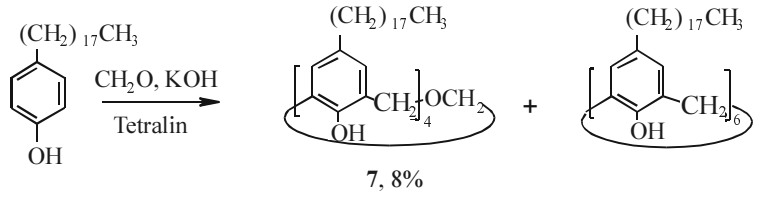
* Tetrahomodioxacalix[4]arene, or [3.1.3.1]homooxacalixarene: the order of digits in the brackets designates the position of triatomic (C–O–C) and monoatomic bridges in the molecule.



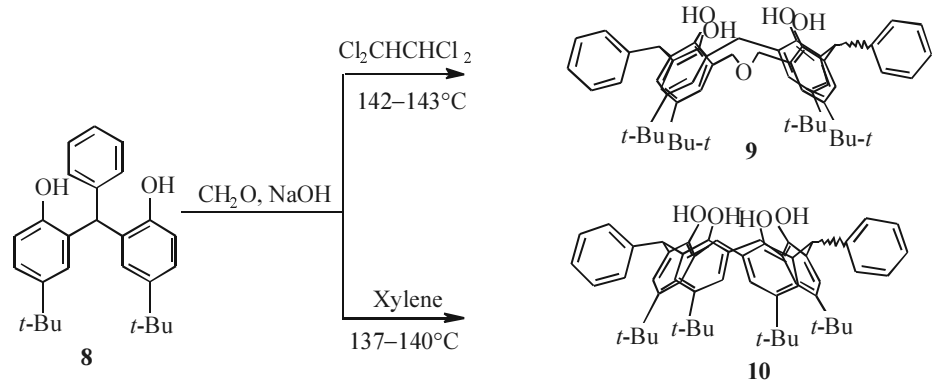
4-*tert*-butylphenol condensation with formaldehyde in the presence of bases isolated alongside three 4-*tert*-butylcalix[4]-, -[6]-, and -[8]arenes **2**–**4** also the fourth reaction product, heteroanalog of 4-*tert*-butylcalix-[4]arene with three CH_2 and one CH_2OCH_2 bridge. This compound was named 4-*tert*-butylbishomooxacalix[4]arene (**5**). The reaction with KOH in xylene gave rise to the product in 20% yield [8].

Monooxacalix[4]arene **5** is stable at heating in xylene at 210–220°C and at heating in xylene in the presence of a small amount of KOH, i.e., under conditions similar to those of calixarenes formation [8, 11]. The dimension of the cavity in monooxacalixarene **5** is somewhat larger than that in the "classic" calix[4]arene **2** and is comparable to that of the cavity in calix[5]arene **6** [8–11]. This fact is confirmed by the weakening of hydrogen bonds (according to IR spectral data νOH in compound **5** is 3300 cm^{-1}, in "classic" tetramer **2** 3160 cm^{-1}, in pentamer **6** 3290 cm^{-1}, in hexamer **3** 3170 cm^{-1}, in heptamer 3155 cm^{-1}, in octamer **4** 3200 cm^{-1}), and by change in activation energy in $CHCl_3$ (15.7 kcal mol^{-1} for compound **2**, 13.2 kcal mol^{-1} for compound **6,** and 13.0 kcal mol^{-1} for compound **5** [8–10]).

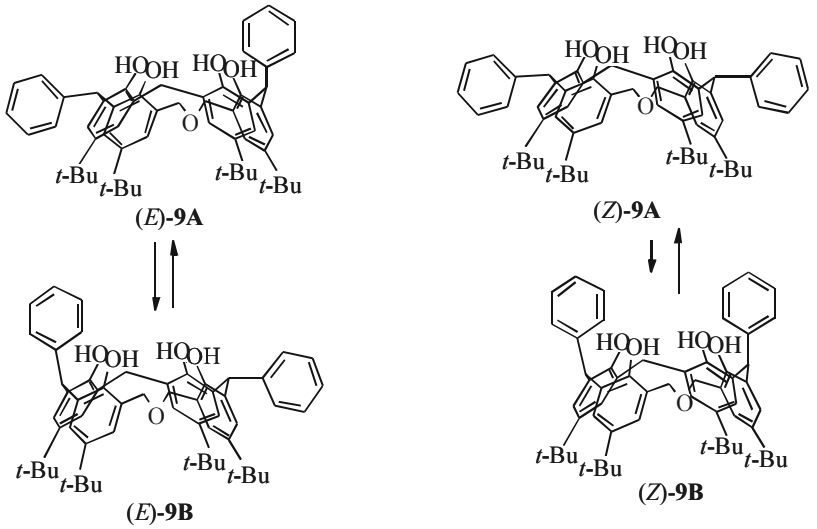
Scheme 1.



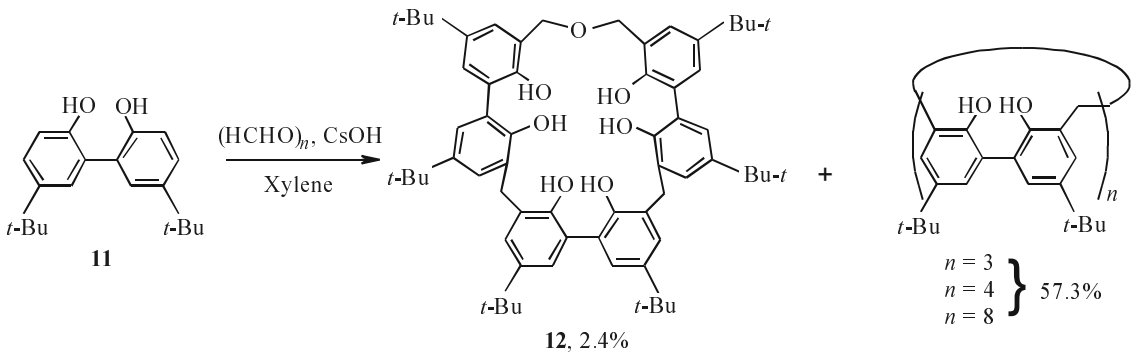
Scheme 2.



Scheme 3.



Scheme 4.



From reaction products obtained by treating 4-octadecylphenol with paraform in tetralin in the presence of KOH 4-octadecylhomooxacalix[4]arene **7** was isolated in 8% yield (Scheme 1) [12].

In 1995 [13] into the reaction with formaldehyde in $Cl_2CHCHCl_2$ in the presence of NaOH was brought 2,2'-dihydroxy-5,5'-di-*tert*-butyltriphenylmethane **8** giving rise to monooxacalix-[4]arene **9** as a mixture of two isomers

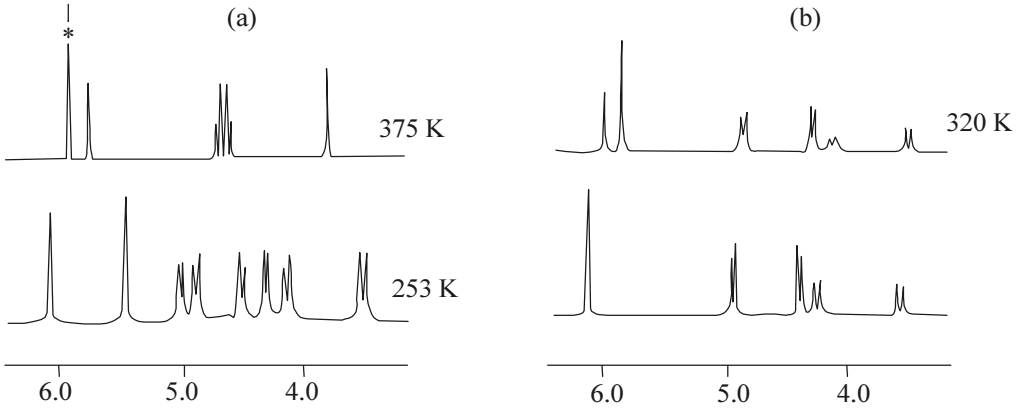
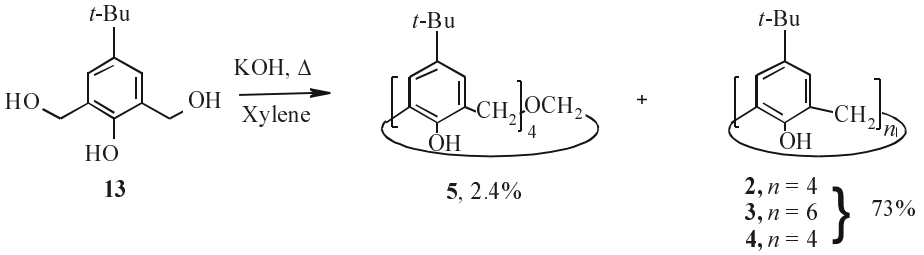
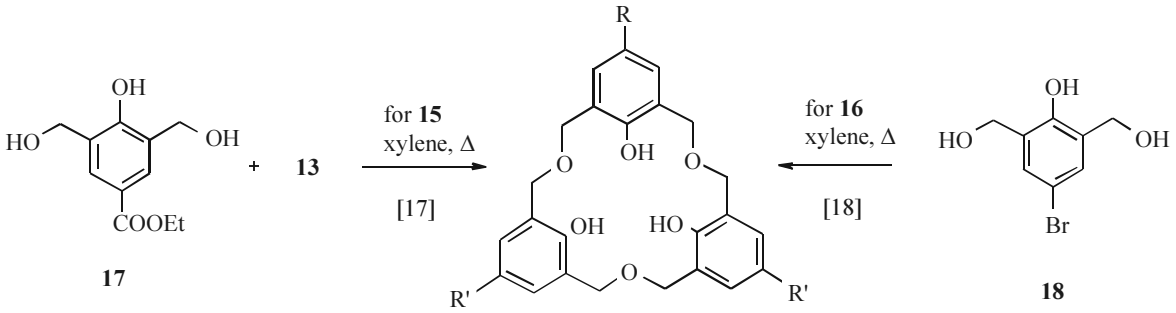


Fig. 1. Variable-temperature ^1H NMR spectra of compounds (*E*)-**9** (a) and (*Z*)-**9** (b) in $CDCl_3$ or $Cl_2CDCDCl_2$ (*).

Scheme 5.

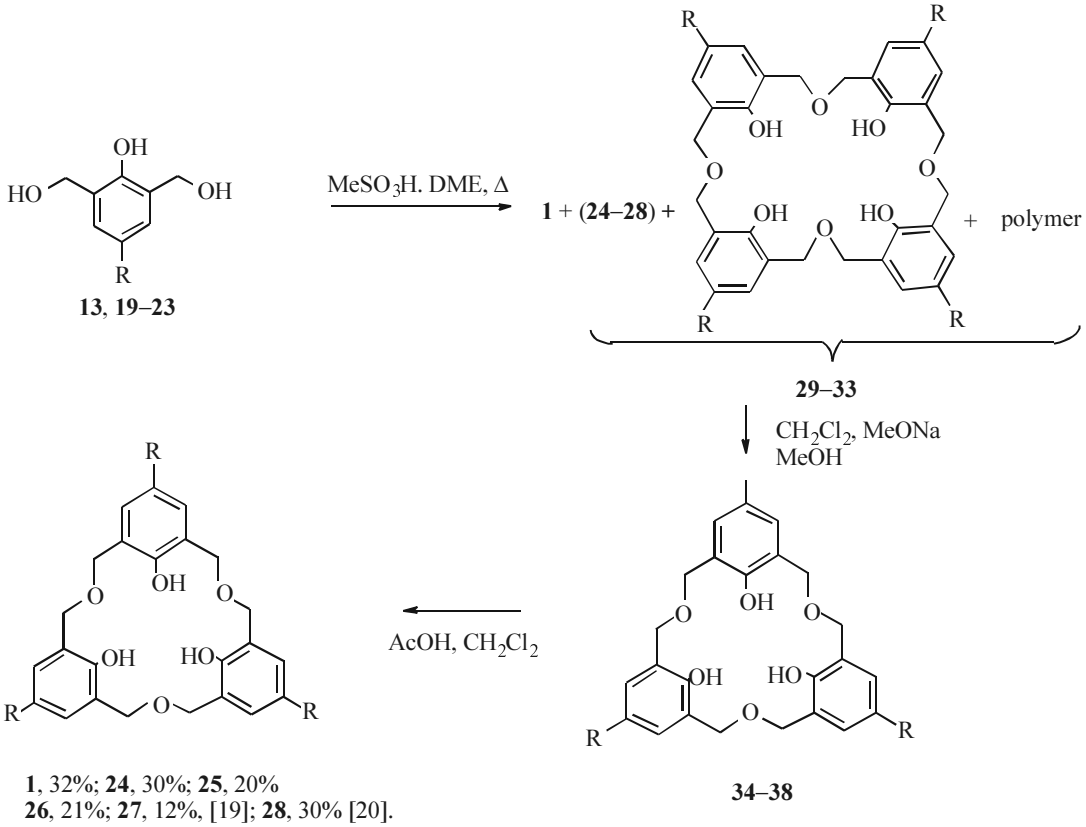


Scheme 6.



15, 26%; **16**, 16%; **15,** R= COOEt, R' = *t*-Bu; **16,** R = R' = Br

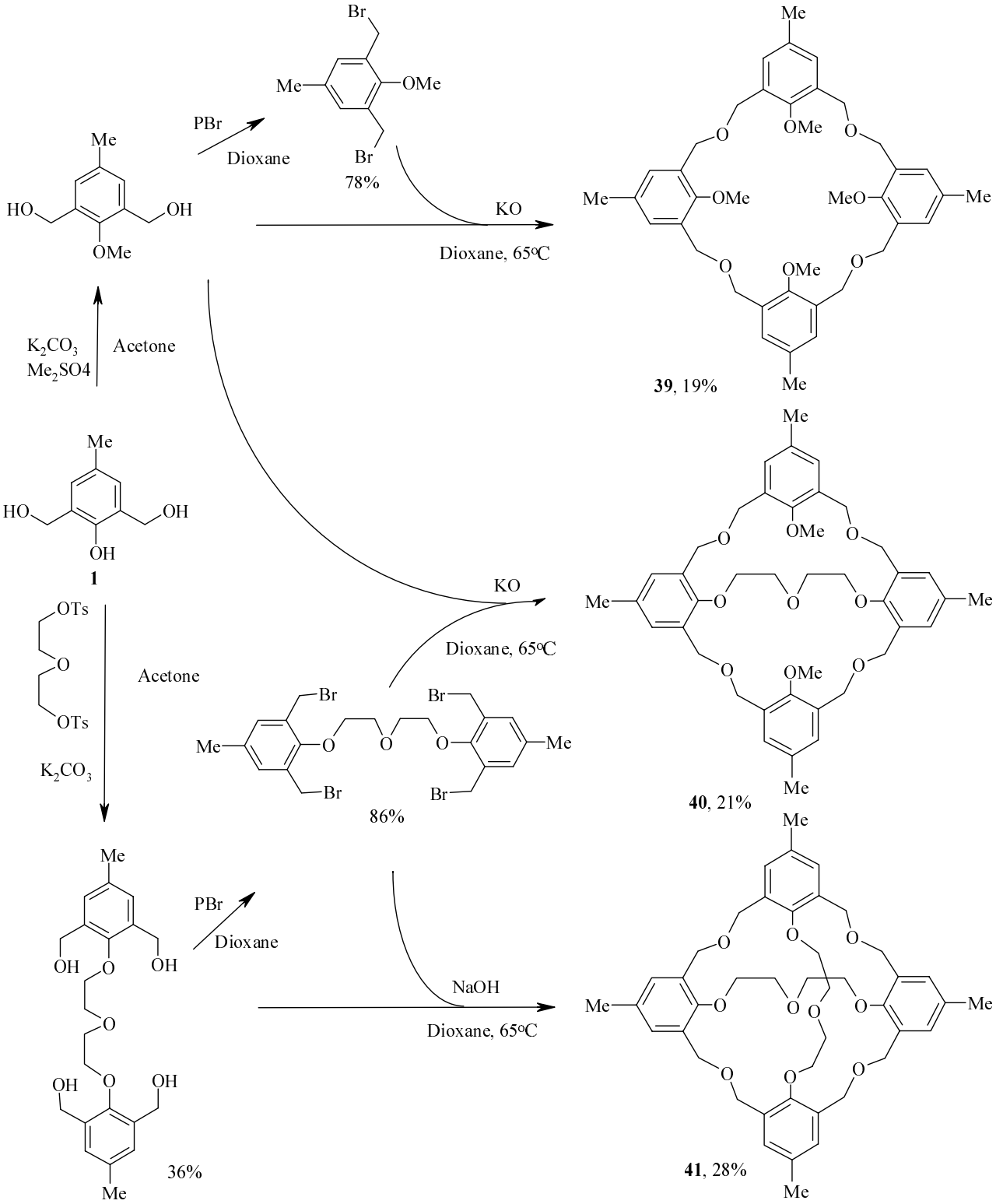
Scheme 7.



1, 32%; **24**, 30%; **25**, 20%
26, 21%; **27**, 12%, [19]; **28**, 30% [20].

R = *t*-Bu (**1, 13, 29, 34**); *i*-Pr (**20, 24,30, 25**);
Et (**21**, **25**, **31**, **36**); Me (**19**, **26**, **32**, **37**);
Cl (**22**, **27**, **33**, **38**); CH_2Ph (**23**, **28**).

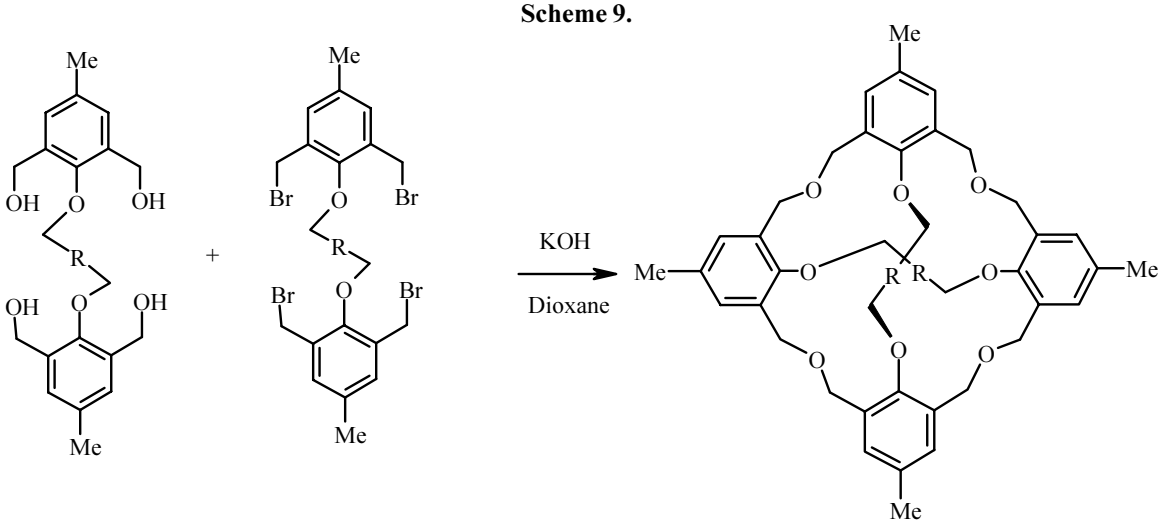
Scheme 8.



in respective yields 14% (*Z*) and 11% (*E*) (overall yield 25%). On replacing $Cl_2CHCHCl_2$ by xylene resulted in formation of only "classic" calix[4]arene **10** [yield 20%, a mixture of (*E*)- and (*Z*)-isomers] (Scheme 2).

The conformational lability of (*Z*)- and (*E*)-isomers of oxacalix[4]arene **9** was investigated by recording their ^1H NMR spectra at variable temperature (Fig. 1) [13].

Scheme 9.



42, 7%; **43**, 18%

R = $(CH_2)_3$ (**42**), *o*-phenylene (**43**)

The (*E*)-isomer of oxacalixarene **9** was shown to be conformationally fluxional compound existing in braked *cone* conformation at 253 K, and at higher temperature (375 K) undergoing fast interconversion of conformers (*E*)-(**9**A**)** and (*E*)-(**9**B) (Scheme 3)**.** The coalescence temperature (T_c) 283 K for the methine proton signals corresponded to the free energy of activation $\Delta G^{\#}$ for the *cone*-inversion equal to 13.1 kcal mol^{-1}. The corresponding $\Delta G^{\#}$ value for the "classic" calixarene **10** is larger by 1.2 kcal mol^{-1}.

The ^1H NMR spectra of (*Z*)-(**9**)-isomer were unchanged while recording at 320 and 253 K. Apparently at both temperature the equatorial (*Z*)-(**9A**) conformer considerably prevailed. Besides at 215 K and below a conformational transition of the CH_2OCH_2 bridge "inside–outside" was revealed..

Monooxacalixarene **12** was isolated in 2.4% yield at condensation of biphenyl derivative **11** with formaldehyde in xylene in the presence of CsOH (Scheme 4) [14].

2.2. Formation of homooxacalix[3]- and [4]arenes as a result of thermal and catalytic condensation of 2,6- bis(hydroxymethyl)-4-R-phenols. Dehydration of 2,6-bis(hydroxymethyl)phenols is one of the best studied preparation methods of homooxacalixarenes. Monooxacalix[4]-arene **5** was found in the reaction mixture resulting from the condensation of 2,6-bis(hydroxymethyl)-4-*tert*-butylphenol (**13**) in the presence of KOH in xylene [8]. The main reaction product (39%) of the reaction was "classic" octamer **4** (Scheme 5).

In 1991 g. [15] from the mixture of products obtained by thermal dehydration of of 2,6-bis(hydroxymethyl)-4-*tert*-butylphenol (**13**) in xylene hexahomotrioxa- (**1**) and octahomotetraoxa- (**14**) calix[4]-arenes were isolated in 6 and 1% yield respectively.

It was shown [16] that the yield of oxacalix[3]arene **1** obtained by cyclization of bis(hydroxymethyl)phenol **13** in boiling xylene depended on the acid used and on the state of purity of the initial phenol. Acetic, methanesulfonic, and *p*-toluenesulfonic acids were tested. The best yield (64%) was obtained from a recrystallized phenol at the use of *p*-toluenesulfonic acid.

Trioxacalix-[3]arenes **15** and **16** selectively and totally modified at the upper rim were prepared from the corresponding 4-derivatives of 2,6-bis(hydroxymethyl)-phenols **17** and **18** (Scheme 6) [17, 18].

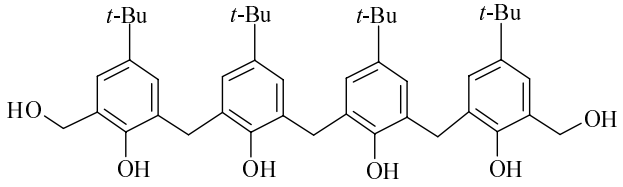
Condensation of 2,6-bis(hydroxymethyl)-4-R-phenols **13, 19–23** in the presence of $MeSO_3H$ at high degree of dilution with ethylene glycol dimethyl ether or in CH_2Cl_2 gave rise to a mixture of oxacalix[3]- **1, 24–28** and oxacalix[4]-arenes **29–33** [19]**.** The yield of oxacalix-[3]arenes **1, 24–28** largely depended on the amount of the sulfonic acid used. No "classic"calixarenes arise under these conditions. The addition of sodium methylate or *t*-BuOK to the reaction products mixture dissolved in THF or CH_2Cl_2 resulted in precipitation of individual monosodium or potassium salts of oxa-calix[3]-arenes **34–38** that on acidification afforded pure oxacalix-[3]arenes (Scheme 7).

The analysis of ^1H NMR spectra revealed [19] that in salts **34–38** the sides of the macroring are equivalent. It is probably caused by transition of the metal from one to the other side of the macrocycle either intramolecularly ("metal through the ring") or intramolecularly.

In 1993 a multistage synthesis of methyltetraoxacalix-[4]arenas modified at the lower rim (mono-, bi-, and tri-

cyclic ethers **39–43**) was carried out starting with 2,6-bis-(hydroxymethyl)-4-methylphenol (**19**) (Schemes 8, 9) [21].

2.3. Homooxacalixarenes from bis(hydroxymethyl)polyphenols. Monooxacalix-[4]arene **5** was obtained in a quantitative yield by intramolecular dehydration of a linear bis(hydroxymethyl)tetramer (**44**) prepared at least in three stages from 4-*tert*-butylphenol [11].



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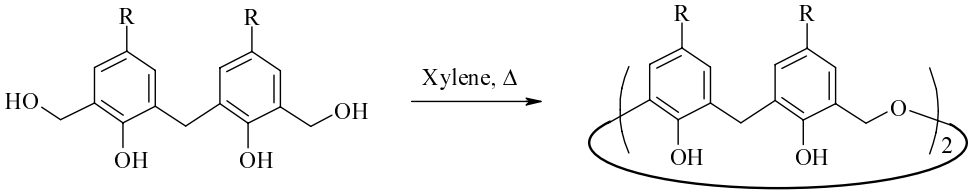
Xylene, Δ → **5**

Intramolecular dehydration of linear dimers **45–47** gave rise to butyl, methyl, and phenyl derivatives of tetrahomodioxacalix[4]-arene **48–50** respectively [11, 22, 23]. Oxacalix[3]arene **1** was obtained from dimer **45** in a yield below 1% (Scheme 10) [24].

Dioxacalixarene **48** differs from monooxa derivative **5** with respect to stability against bases: the boiling of compound **48** in xylene in the presence of KOH gives rise to a mixture of classic calixarenes and initial compound **2**, **3**, **4**, **48** in a ratio 4: 1: 1: 2 respectively [11]. Thus the arising mixture is similar to that obtained in the synthesis of calixarenes directly from 4-*tert*-butylphenol and CH_2O.

Recording the ^1H NMR spectra at variable temperature [9] revealed the coalescence temperatures and thus permitted to estimate the activation energies (kcal mol^{-1}) for mono- and dioxacalix[4]arenes **5** and **48**. The following

Scheme 10.

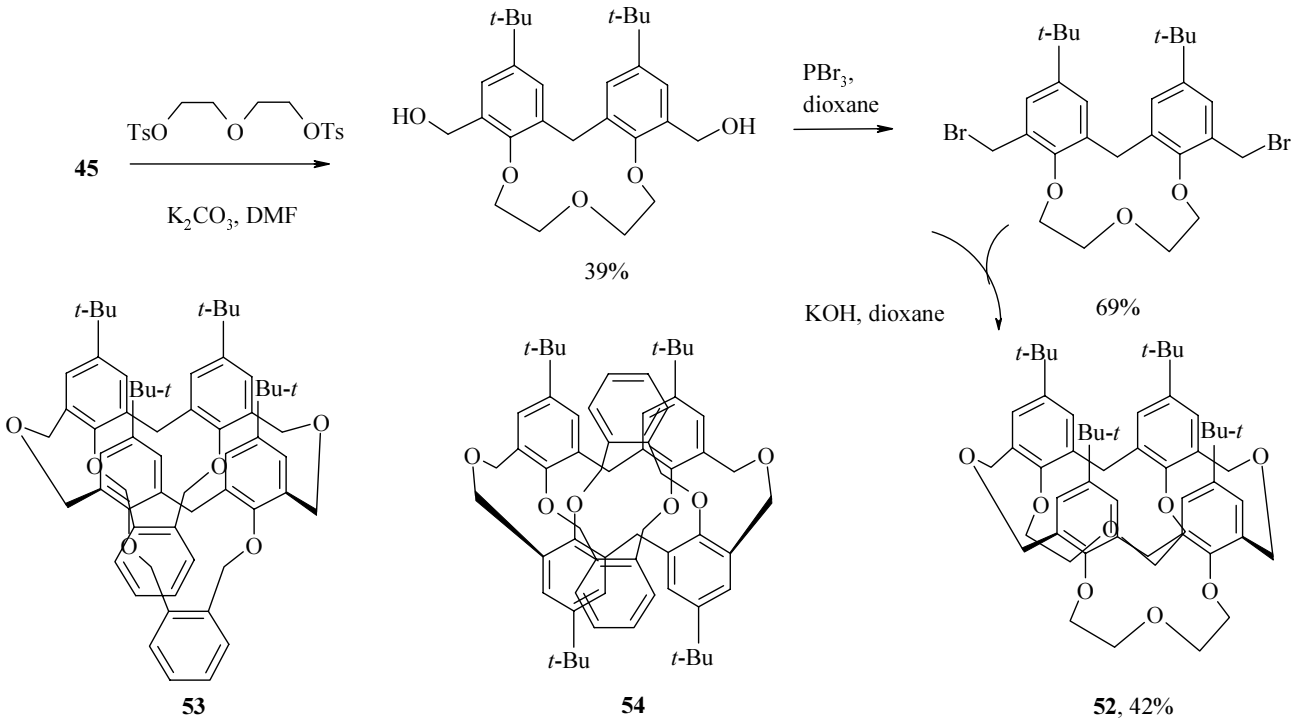


45–47

48, 65%; **49**, 6–10%; **50**, 79%

R = *t*-Bu (**45, 48**), Me (**46, 49**), Ph (**47, 50**)

Scheme 11.

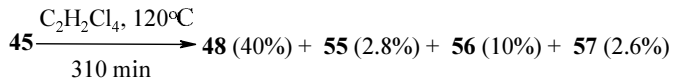


values were obtained: compound **5,** T_c –8°C (CH_2OCH_2), –2°C (CH_2), $\Delta G^{\#}$ 12.9 and 13.0 respectively in $CDCl_3$ and T_c –32°C, $\Delta G^{\#}$ 10.0 in C_5D_5N; compound **48,** T_c –24°C, $\Delta G^{\#}$ 11.9 in $CDCl_3$ and T_c below –70°C in C_5D_5N. It was shown that conformational lability of compounds under study was closely associated with the macroring size and with the existence of intramolecular hydrogen bonds. Monooxacalix[4]arene **5** is present in *cone* conformation, whereas the dioxa derivative **48** exists in a "*flattened*" *cone* conformation. Trioxa derivative **1** is the most flexible, and no signs of braked rotation were observed in the spectra down to –90°C.

According to the values of activation energies of conformational inversion in $CDCl_3$ for oxacalix-arenas and classic 4-*tert*-butyl-calix[*n*]arenes (*n* = 4–8) these compounds form the following series: calix[4]arene **2** ≅ calix[8]-arene **4** > calix-[5]arene **6** ≅ oxacalix[4]arene **5** ≅ calix[6]arene **3** > calix[7]arene **51** > dioxacalix[4]arene **48** > trioxacalix[3]arene **1** [9]. In pyridine the Intramolecular hydrogen bonds are destroyed, and the barrier to inversion is closely connected with the macroring size. The activation energies then decrease in the following seies: **2** > **6** > **5** > **3** > **48** > **4** > **1**.

Conformationally rigid dioxacalix[4]arenas bound at the distal positions of the lower rim with polyoxyethylene **52** or *o*-phenylene **53** and **54** bridges were prepared by condensation of preliminary modified bis(hydroxymethyl)phenols (Scheme 11) [25].

The synthesis of isomeric dioxacalixarenes **53** and **54**) was not described in [25]. It was shown later that at heating a concn. solution (0.75 M) of bis(hydroxymethyl)-diphenol **45** in $Cl_2CHCHCl_2$ or in xylene at 120°C afforded a mixture of four oxacalixarenes which were separated by column chromatography: dioxacalix[4]arene **48**, dioxa- and trioxacalix[6]arenes **55** and **56**, and tetraoxacalix-[8]arene **57** [26].



The reaction conditions (temperature, dehydration time, quality of solvent) are very important for the synthesis of large oxacalixarenes, especially of compound **57** [26]. The variations in the composition of the oxacalixarenes mixture as a function of dehydration time of diphenol **45** indicate that compounds **56** and **57** are consumed in the course of heating partially due to decomposition and partially by transforming into lower cyclooligomers; therewith the thermal lability increases in going from the cyclic dimer to trimer and tetramer. This conclusion was proved by special experiments using pure samples of compounds **48**, **56**, and **57**.

Dioxacalix[6]arene **58** was prepared in 63% yield by heating bis(hydroxymethyl)triphenol **59** in xylene at 120°C [27]. Monooxacalix[6]arene **60** and trioxacalix[9]arene **61** formed as side products (Scheme 12).

The prevailing formation of compound **58** was due to a template effect of the intramolecular hydrogen bonds [27].

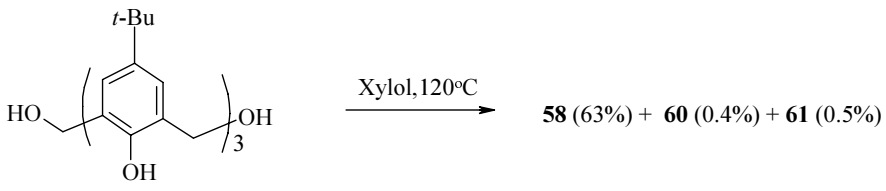
2.4. Linear oligomers of 2,6-bis(hydroxymethyl)-4-R-phenols and their analogs in the synthesis of homooxacalix[3]- and -[4]arenes. Oxacalix[4]arene **32** with four ether bridges can form at heating of bisphenol derivative **62** [10] but in a very low yield.

In 1998 was for the first time carried out a synthesis [28] of trioxacalix[3]arenes **1, 16, 63–77** by intramolecular cyclization of linear trimers **78** with preliminary ketal protection of the terminal hydroxyls. Treating trimers **78** with $HClO_4$ at high dilution with $CHCl_3$ saturated with water afforded trioxacalixarenes with various substituents on the upper rim of the molecule. The easy isolation and purification of the reaction products was specially mentioned (Scheme 13).

Tsubaki *et al.* described the formation of oxacalixarenes from the corresponding linear trimers as successive protonation first of aliphatic (A) and then also aromatic (B) ether oxygens of the ketal fragments followed by cyclization resulting from intramolecular attack of the primary benzyl OH group in the dioxonium intermediate (C) (Scheme 14).

Oxacalixarenes **69** and **74** were shown by X-ray diffraction study to exist in *cone* conformation forming a supramolecular network of strong hydrogen bonds. Each

Scheme 12.



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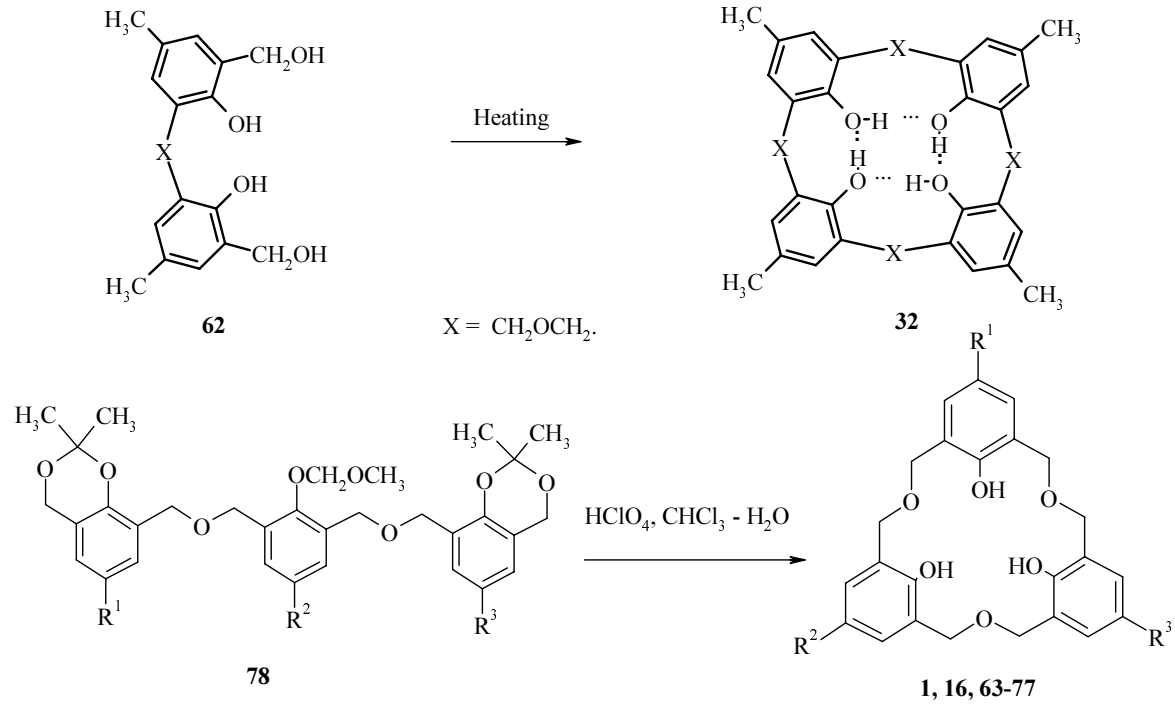
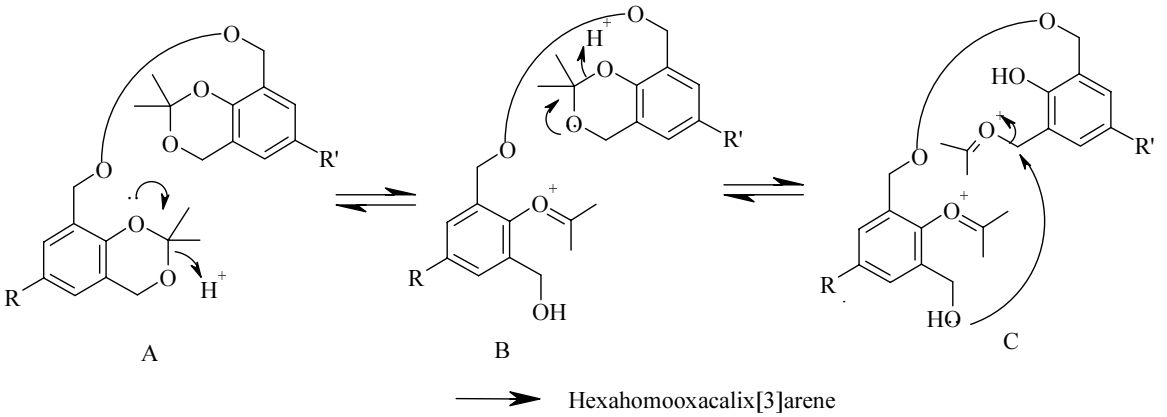
Scheme 13.



62 **32** **78** **1, 16, 63-77**

$R^1 = R^2 = R^3 = t$-Bu (**1,** 48%), H (**63,** 22%), OMe (**64,** 20%), Br (**16,** 4%); R^2 = H, $R^1 = R^3$ = Me (**65,** 44%), Et (**66**, 42%), *i*-Pr (**67**, 42%), *t*-Bu (**68**, 54%);$R^2 = t$-Bu, $R^1 = R^3$ = H (**69**, 22%), Me (**70**, 43%), Et (**71**, 50%), *i*-Pr (**72**, 54%); R^1 = Me, R^2 = H, R^3 = Et (**73**, 45%); R^1 = Et, $R^2 = t$-Bu, $R^3 = i$-Pr (**74**, 53%); $R^1 = R^3 = t$-Bu, R^2 = Br (**75**, 51%), NO_2 (**77**, 55%) [28]; $R^1 = R^2$ = Br, $R^3 = t$-Bu (**76**, 34%).

Scheme 14.

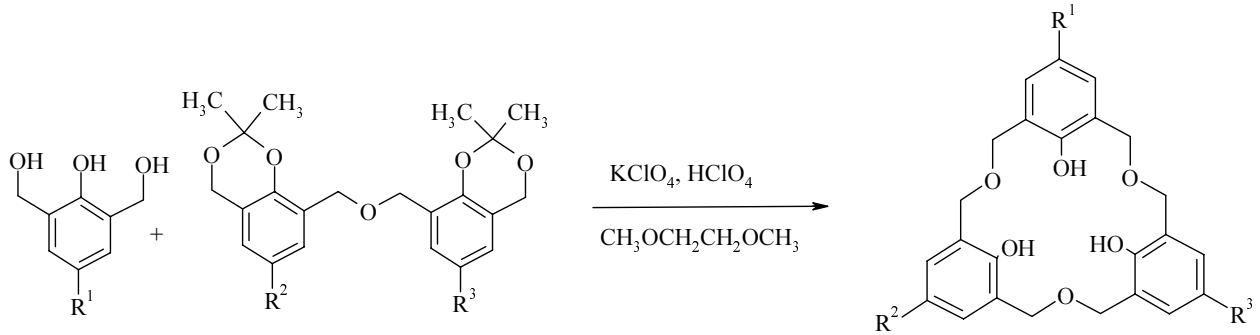


phenol hydrogen atom of the oxacalixarene interacts with two oxygens (a phenol and a dibenzyl ether ones). Therewith the angles O–H···O are not equal to 180°. These angles in compound **69** are between 102° and 163°. The distance between the phenol and the dibenzyl ether oxygens are equal to 2.77–2.92 Å in oxacalixarene **69** and to 2.70–2.98 Å in compound **74**.

In 2000 the synthesis of homooxacalix[3]arenas with various alkyl substituents attached to the upper rim of the molecule **79**–**86** was performed as a condensation of 4-substituted dihydrooxymethylphenol dimers with a monomer (condensation of "2+1" type) in acid medium at high dilution (Scheme 15) [29].

The procedure [29] for preparation of oxacalixarenes with substituents on the upper rim in quite a number of cases is more favorable than linear trimer cyclization [28]. Compound **74** was prepared by 6-stage procedure involving "2+1" condensation in 12.4% yield [29] whereas in the 9-stage synthesis including condensation of a linear trimer the target product was obtained in only 2.4% yield [28].

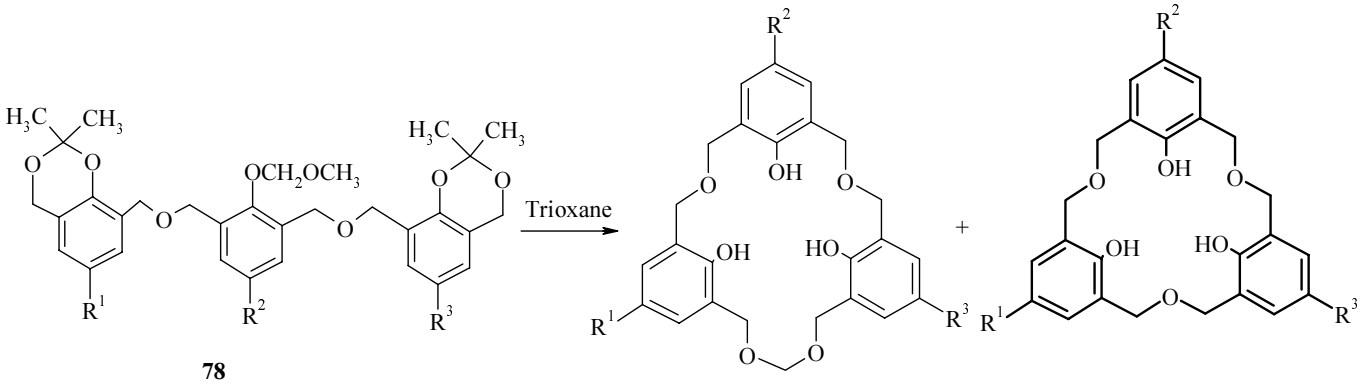
Scheme 15.



73, 74, 79- 86

R^1 = H, R^2 = Me, R^3 = Et (**73,** 8%), *i*-Pr (**79,** 9%), *t*-Bu (**80,** 9%); R^1 = H, R^2 = Et, R^3 = *i*-Pr (**81,** 10%), *t*-Bu (**82,** 10%); R^1 = H, R^2 = *i*-Pr, R^3 = *t*-Bu (**83,** 7%); R^1 = Me, R^2 = Et, R^3 = *i*-Pr (**84,** 14%), *t*-Bu (**85,** 16%); R^1 = Me, R^2 = *i*-Pr, R^3 = *t*-Bu (**86,** 13%); R^1 = Et, R^2 = *i*-Pr, R^3 = *t*-Bu (**74,** 20%).

Scheme 16.



78 **87 – 92** **1, 68, 82, 93–95**

R^1 = R^3 = *t*-Bu: R^2 = H (**87,** 40%**; 68**, 8%), Me (**89**, 23%; **93,** 7%), Et (**90**, 26%**; 94,** 8%), *i*-Pr (**91**, 29%; **95**, 8%), *t*-Bu (**92**, 30%; **1**, 10%); R^1 = *t*-Bu, R^2 = H, R^3 = Et (**88**, 25%; **82**, 8%).

The cyclization of trimer **78** in the presence of $HClO_4$ in wet $CHCl_3$ afforded alongside the trioxacalix[3]arene derivatives also side products, derivatives of new type oxacalixarenes, heptahomotetraoxacalix[3]arenes. Tsubaki et al. [30] studied the possibility of preparation of this type compounds. It turned out that addition of trioxane as the second initial compound resulted in 23-40% yield of tetraoxacalixarenes **87–92** (Scheme 16).

The new type of oxacalixarenes synthesized possesses a skeleton of unique structure, a 20-membered macroring composed of three aromatic fragment and having *pseudo- C_2* symmetry. The size of the macroring is comparable to that of the "classic" calyx[5]arene. The study of ^{1}H NMR spectra of compound **87** in CD_2Cl_2 at variable temperature provided a possibility to evaluate the barrier to OH groups rotation through the annulus. It proved to be less than 8 kcal mol^{-1} [30]. This value is comparable with the barrier to OH groups rotation in trioxa-calix[3]arene **1** (< 9 kcal mol^{-1} [3]) and less than in calix[5]arene **6** (13.2 kcal mol^{-1} [3]). T_c of compound **87** was not determined since it was below–90°C.

The crystalline structure of tetraoxacalixarene **88** was determined by X-ray diffraction analysis (Fig. 2). The molecule turned out to exist in the so-called *flattened cone* conformation, and two phenol atoms H^1 and H^2 participated in hydrogen bonds with phenol and ether oxygen atoms (H^1 with O^2 and O^6; H^2 with O^3 and O^7); atom H^3 is not involved into hydrogen bonds apparently since it is remote from the neighboring oxygen atoms.

The first synthesis of naphthalene analogs of oxacalixarenes, *C_3*-symmetrical and unsymmetrical hexahomotrioxacalix[3]naphthalenes **96–99**, was achieved in 2001 (Scheme 17) [31]. As the initial substance was used the naphthalene analog **100** of the linear trimer **78** involved

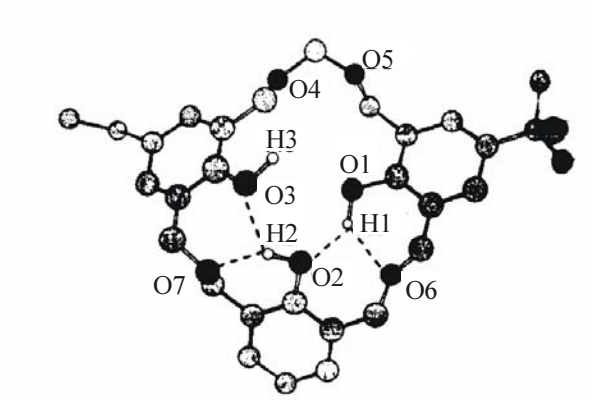


Fig. 2. Crystal structure of compound **88**

in the synthesis of trioxacalixarene **1** derivatives [28]. The reaction was carried out on similar conditions (Scheme 17).

Quite unexpectedly the oxacalixnaphthalenes proved to form in a one-stage process from monomers **101** or **102** under the same conditions as in reaction with the trimer (Scheme 18).

The high conformational lability of compound **96** was demonstrated by ^{1}H NMR spectroscopy. It is characterized by fast interconversion of *cone*-like conformers where all three OH groups are located on the same side of the 18-membered macroring.

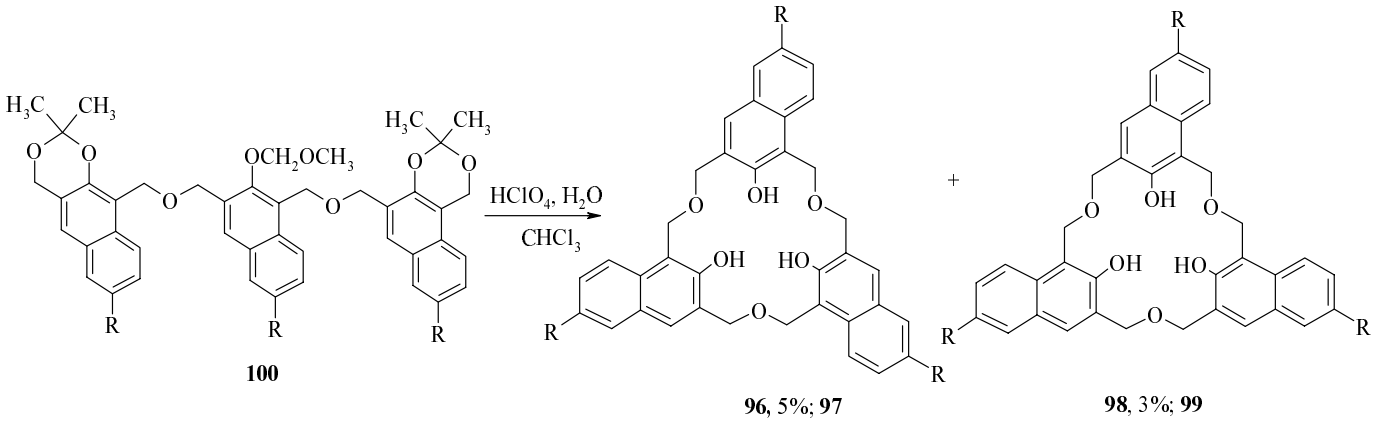
2.5. 2,6-Diformylphenols in the synthesis of homooxacalix[*p*]arenes. In 2001 Komatsu [32] developed a new synthetic procedure for homooxacalix[*n*]arenes (*n* = 3, 4): reductive homo- or heterocoupling of 4-substituted 2,6-diformylphenols. Treating a mixture of substituted phenola and Me_3SiOTf in CH_2Cl_2 with triethylsilane at cooling to –78 till 0°C afforded a mixture of tri- and tetraoxacalixarenes **1, 16, 26–28, 103–105** and **29, 32, 33, 106–109** respectively (Scheme 19).

The reductive heterocoupling involves reaction of triethylsilane with two aromatic substrates, a substituted diformylphenol (**D**·R^1), and tri(trimethylsilyl) ether of 4-substituted 2,6-bis(oxymethyl)phenol (**E**·R^2) (Scheme 20).

It was demonstrated that the ratio of initial compounds **D**·R^1 and **E**·R^2 brought into the reaction of reductive heterocoupling significantly affected the distribution of the cyclization products. The developed procedure provided a possibility at an appropriate choice of reaction conditions, initial substrates, and their ratio to prepare derivatives of homooxa-calix[3]- and –[4]arenas with one or two types of substituents (Scheme 21).

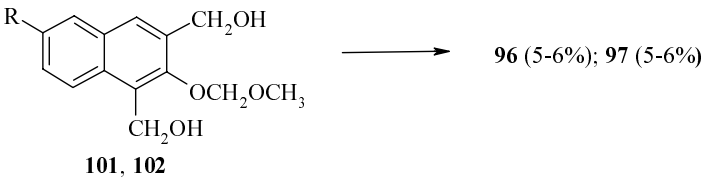
Applying as initial diformyl derivatives for reductive homocoupling the corresponding methyl ethers of phenols

Scheme 17.



R = H (**96**, **98**); *t*-Bu (**97**, **99**).

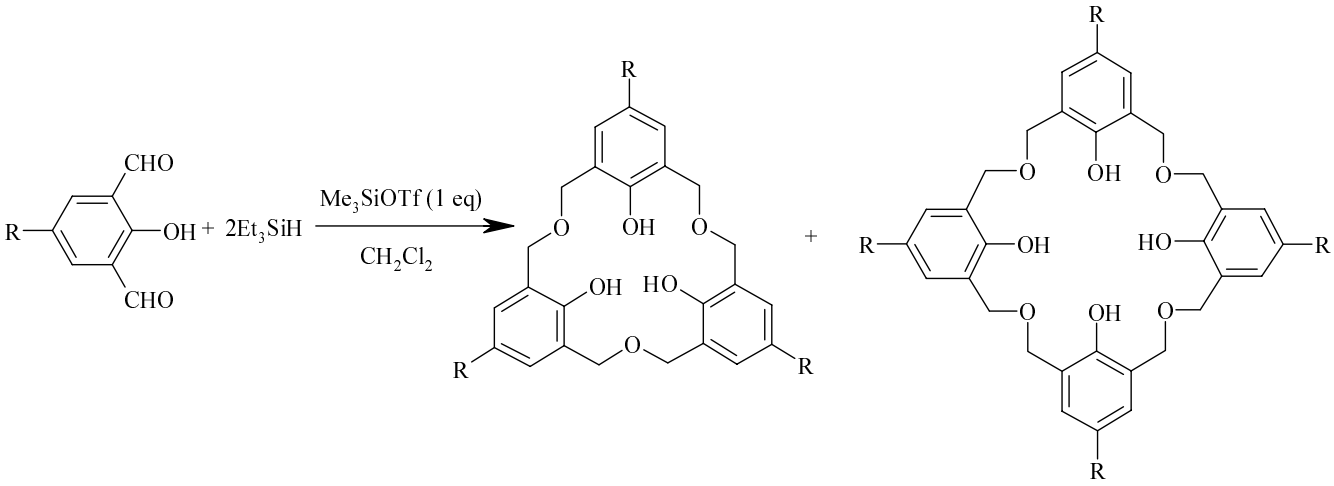
Scheme 18.



101, **102**

R = H (**96**, **101**); *t*-Bu (**97**, **102**).

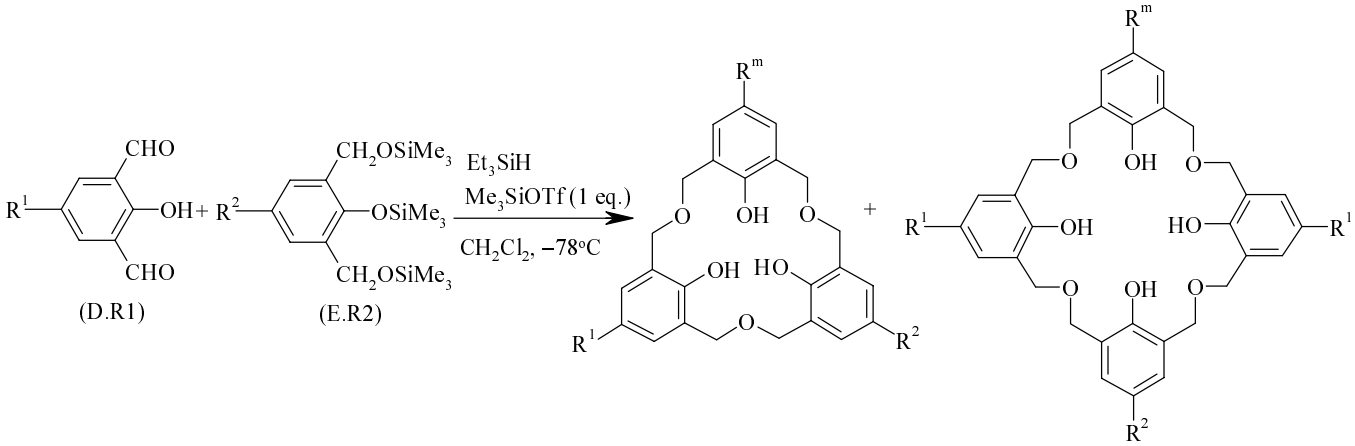
Scheme 19.



1, **16**, **26-28**, **103–105** **29, 32**, **33**, **106–109**

R: = *t*-Bu (**1**, 38%), (**29**, 22%); Me (**26**, 35%), (**32**, 12%); CH_2Ph (**28,** 32%)**, (106,** 14%); Ph (**103**, 11%), (**107**, 18%); F (**104**, 29%), (**108**, 24%); Cl (**27**, 29%), (**33**, 22%); Br (**16**, 28%), (**109**, 26%); I (**105**, 13%).

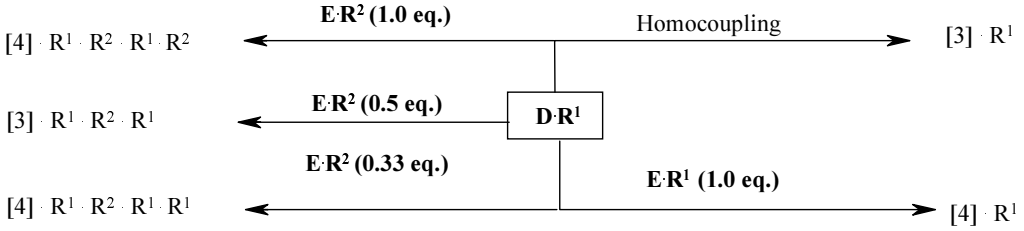
Scheme 20.



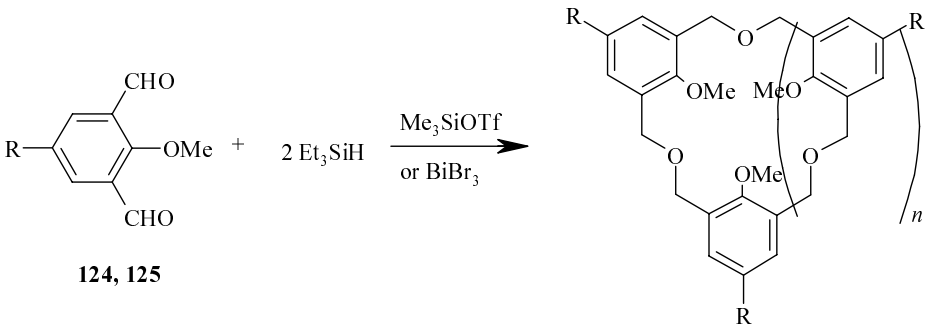
(D.R1) (E.R2)

[3] · R^1 · R^2 · R^m (m = 1 or 2): $R^1 = R^2 = R^m$ = *t*-Bu (**1**, 26%); R^2 = *t*-Bu, $R^1 = R^m$ = Me (**70**, 19%), Br (**76**, 8%), $PhCH_2$ (**110**, 15%), Cl (**111**, 5%), F (**112**, 24%); $R^2 = R^m$ = *t*-Bu, R^1 = Br (**75**, 6%), Me (**92**, 12%), $PhCH_2$ (**114**, 8%), Cl (**115**, 7%); $R^1 = R^m$ = *t*-Bu, R^2 = F (**113**, 22%). [4] · R^1 · R^2 · R^m (m = 1 or 2): $R^1 = R^2 = R^m$ = *t*-Bu (**29**, 42%); $R^1 = R^m$ = F, R^2 = *t*-Bu (**116**, 20%); $R^1 = R^m$ = *t*-Bu, R^2 = F (**117**, 13%); R^1 = *t*-Bu, $R^2 = R^m$ =Me (**118**, 28%); $R^2 = R^m$ = *t*-Bu, R^1 = Me (**119**, 32%), $PhCH_2$ (**120**, 26%), Cl (**121**, 20%), Br (**122**, 13%), F (**123**, 26%).

Scheme 21.



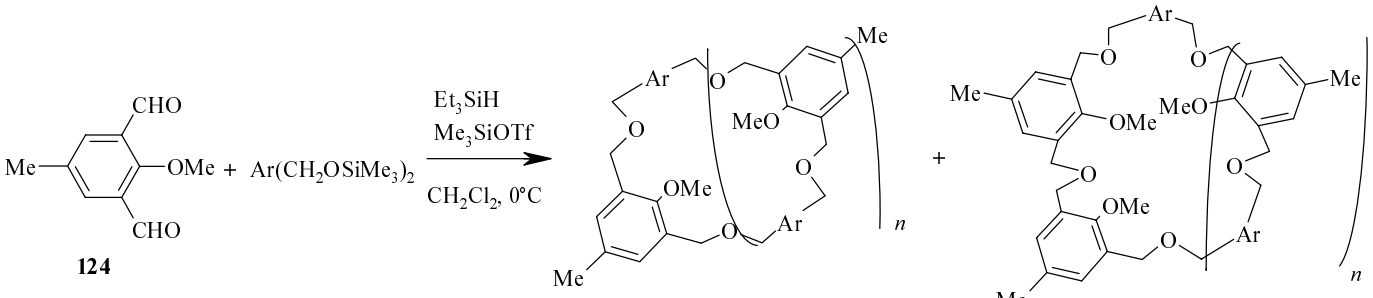
Scheme 22.



124, 125 **126 - 136**

R = Me (**124**), (**131**, *n* = 1), (**132**, *n* = 2), (**126**, *n* = 3), (**127**, *n* = 4), (**128**, *n* = 5), (**129**, *n* = 6), (**130**, *n* = 7); SMe (**125**), (**133**, *n* = 2), (**134**, *n* = 3), (**135**, *n* = 4), (**136**, *n* = 5).

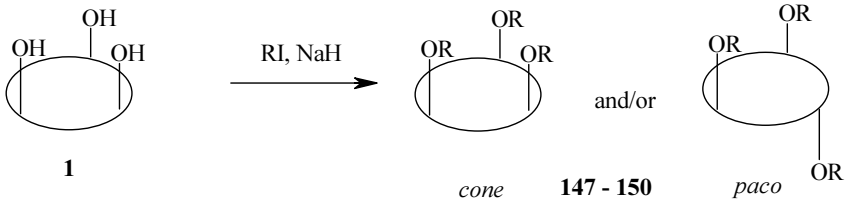
Scheme 23.



124 **137 - 142** **143 - 146**

Ar = *m*-phenylene, *n* = 2 (**137**, **145**), *n* = 3 (**139**, **146**), *n* = 4 (**140**); *p*-phenylene, *n* = 2 (**138**, **143**), *n* = 3 (**141**, **144**), *n* = 4 (**142**).

Scheme 24.



1 *cone* **147 - 150** *paco*

R = Me (**147**, 32%), Et (**148**, *paco*, 70%), Pr (**149**, *cone : paco* = 1 : 6, 77%), Bu (**150**, *paco*, 63%).

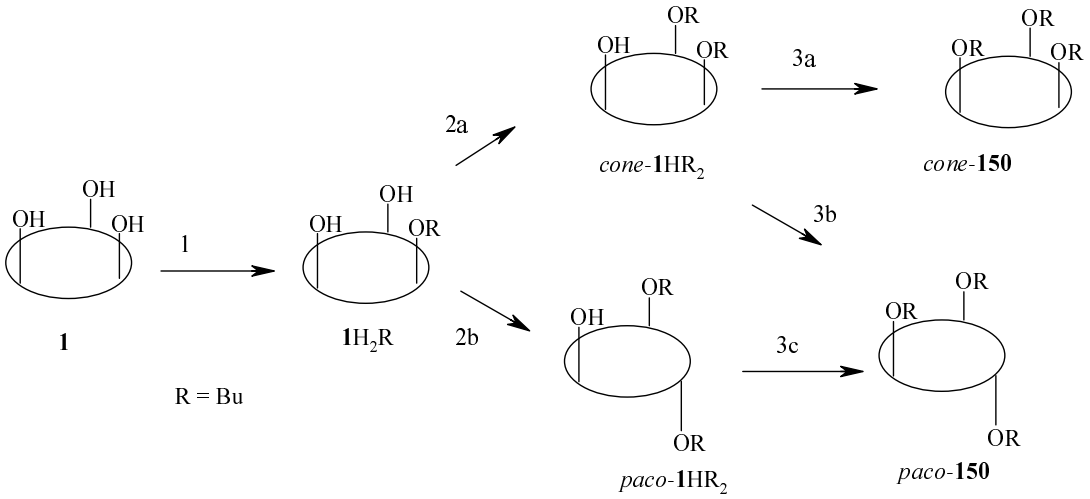
124 and **125** Komatsu et al. [33] succeeded to prepare a mixture of homooxacalix[*n*]arenas having from 3 to 9 ether bridges **126–136.**

The highest yield of reaction products (46% for diformyl derivative **124** and 37% for derivative **125**) was attained in reaction carried out in CH_2Cl_2 in the presence of Me_3SiOTf. In the first case the reductive homocoupling afforded a mixture of compounds **132**, 16%, **126**, 8%, **127**, **128**, 6% each, **129**, **130, 131**, 3–4% each; in the second case formed a mixture of derivatives **133**, 13%, **134**, 10%, **135**, 8%, **136**, 6%.

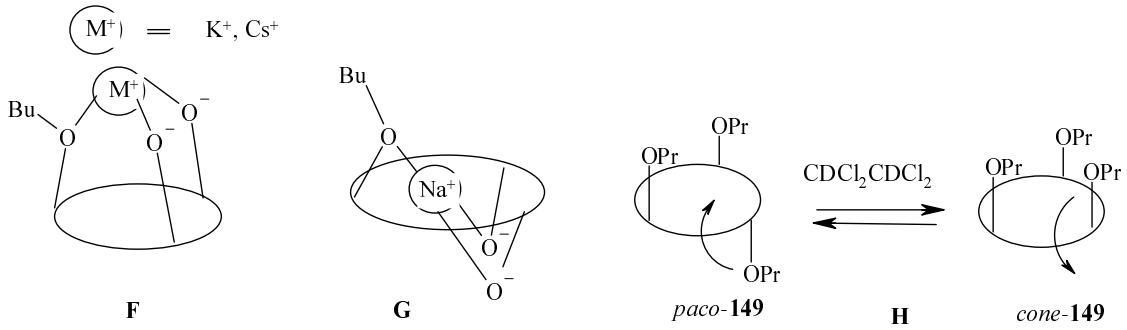
By the reaction of the reductive heterocoupling a novel type of homooxalixarenes was synthesized that alongside a fragment of homooxacalixarene contained in the molecule also a fragment of oxa[3_n]cyclophane **137–146** (Scheme 23) [33].

The highest yield of reaction products at the use of 1,3-dihydroxymethylbenzene bis(trimethylsilyl) ether as initial compound was 40%, at the use of the corresponding derivative of 1,4-dihydroxymethylbenzene was 24%. In the first case the main reaction product was oxacyclophane **137** (25%), in the second case oxacyclophane **138** (11%).

Scheme 25.



Scheme 26.



According to X-ray diffraction study the homooxacalixarenes **127, 132, 137,** and **138** exist in 1,2,3-*alt*, 1,2-*alt*, 1,3-*alt*, and alternate conformations respectively.

3. CHEMICAL PROPERTIES OF HOMOOXACALIXARENES

3.1. Total modification of the lower rim of hexahomotrioxacalix[3]arenes. Araki *et al.* [6] performed a total *O*-alkylation of homooxacalixarene **1** with alkyl iodides in the presence of bases, and the conformational structure of ethers **148** and **149** obtained was investigated by ^{1}H NMR spectroscopy. It was found that the molar ratio compound **1**–RI–NaH = 1:3.2:16 favored predominant formation of *paco* conformer (Scheme 24).

The effect of reaction conditions (first of all, the base used) on the conformers distribution was studies by an example of oxacalixarene **1** alkylation with butyl iodide [6]. In the presence of Cs_2CO_3, K_2CO_3, *t*-BuOK, and potassium metal a mixture of *cone* and *paco* conformers formed with the latter, *paco*-**150**, prevailing. At the use of NaH the *cone* conformer was lacking. The routes leading from calixarene **1** to tributyl ether **150** in *cone* and *paco* conformations are shown on Scheme 25 [6].

These data suggest that cations K^+ and Cs^+ prefer interaction with three phenol oxygen atoms located on the same side of the ring (F), whereas Na^+ favors the oxygens position "across the ring" (G). In the first case the reaction results in the *cone* conformer, in the latter arose the *paco* conformer. The temperature effect on the *cone*/*paco* (H) ratio was studied on tripropyl ether **149**. The following values were obtained: 0.168 (at 30°C), 0.162 (at 50°C), 0.137 (at 80°C), and 0.126 (at 100°C) .

Thermodynamical parameters (ΔH –0.94 kcal mol^{-1}, ΔS –6.6 e.u., ΔG_{298} 1.02 kcal mol^{-1}) indicate that isomerisation of *paco*-**149** into *cone*-**149** is favored by decrease in ΔH and disfavored by increase in ΔS. On the contrary, for the tetramethoxy derivative of "classic" calix[4]arene **151** having ΔH 1.15 kcal mol^{-1}, ΔS 2.78 e.u., ΔG_{298} 0.32 kcal mol^{-1} [34] the isomerization of *paco*-**151** into *cone*-**151** was accompanied with increase in ΔH and decrease in ΔS. Hence the reasons of *paco* conformer stability are dissimilar for "classic" calix[4]arene and trioxacalix[3]arene (Scheme 26).

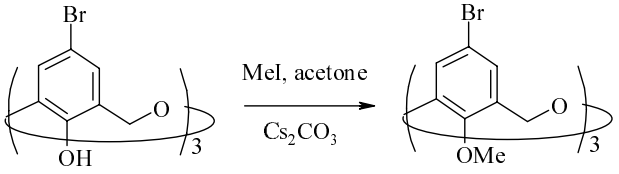
Table 1. Effect of *O*-substituents on rotation"oxygen-through-the-annulus" in calix[4]arenes and in homooxacalix[3]arenes **147–150**

Compd. no.	R	Calix[4]arene[a]	Homooxacalix[3]-arene
147	Me	Labile, T_c 60°C	Labile, T_c < –50°C
148	Et	Frozen out at room temperature	Labile, T_c 50° C
149	Pr	Frozen out	Labile
150	Bu	Frozen out	Frozen out

[a] Data from [35, 36].

^{1}H NMR spectroscopy was applied to investigation of the effect of alkyl substituent in triethers **147–150** on the possibility of ring inversion as a result of oxygen rotation through the annulus. The results compared to the corresponding data for derivatives of the classic calix[4]arene are presented in Table 1.

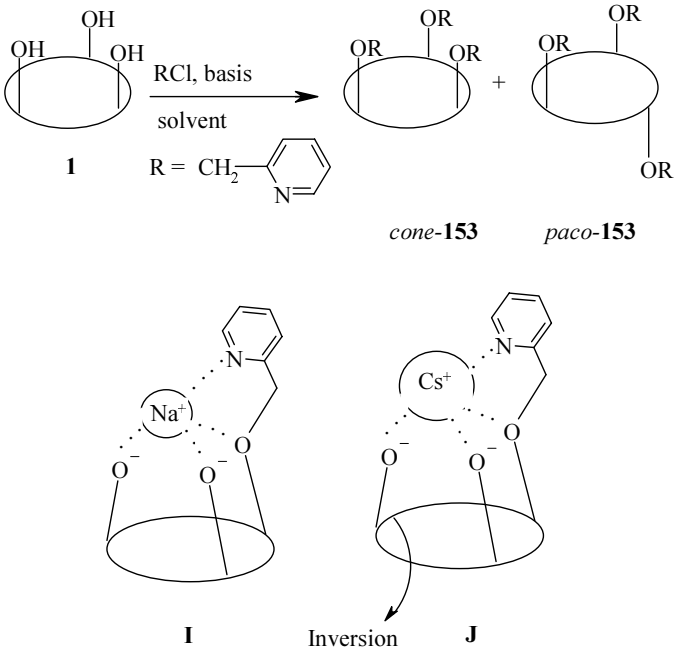
O-Benzylation of oxacalixarene **1** with benzyl bromide in acetone in the presence of Cs_2CO_3 afforded tribenzyl derivative **152** in *paco* conformation in 95% yield [37]. Under similar conditions 4-bromooxacalixarene **16** with CH_3I afforded trimethyl ether **9** [38].



16 **9**, 93%

2-Pyridylmethyloxy derivatives of oxacalixarene **1** were obtained by treating compound **1** with 2-(chloromethyl)pyridine in the presence of bases [37].

The template effect of alkali metal cation plays an important role in the *O*-alkylation and is reflected in the ratio of formeing conformers of compound **153**. In reaction carried out in acetone in the presence of Cs_2CO_3 the overall yield of products was 70%, and conformers ratio *paco*/*cone* ≅ 7.5 : 1; in the presence of NaH in a mixtureTHF–DMF the initial compound conversion reached 45%, and conformers ratio in the reaction product was ≈ 2 : 1. Hence the larger cation Cs^+ favored formation of the thermodynamically feasible conformation *paco* (**I, J**).



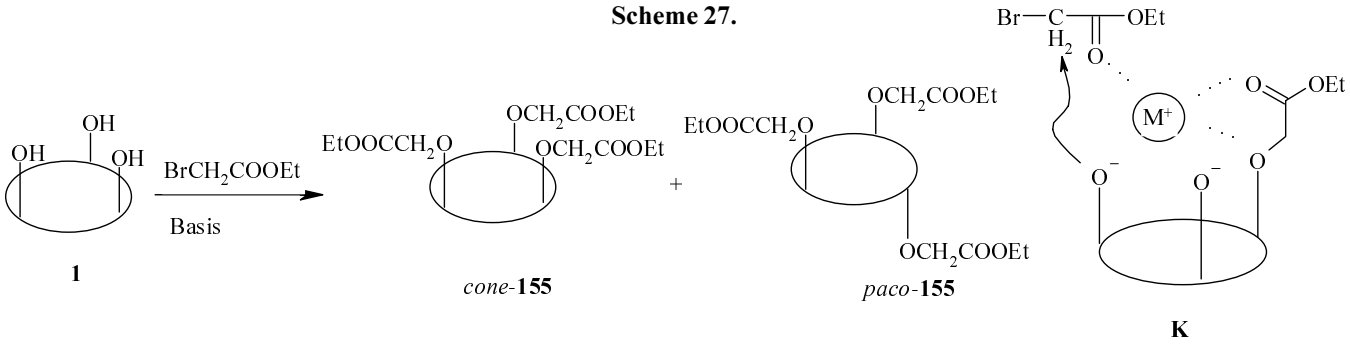
1 *cone*-**153** *paco*-**153**

I **J**

O-Alkylation of oxacalixarene **1** with 4-(chloromethyl)-pyridine in the presence of Cs_2CO_3 afforded a single stereoisomer, *paco*-**154** , in 89% yield [39]. In the presence of NaH or K_2CO_3 formed a mixture of two conformers, *paco*- and *cone*-**154**, in the former case in the ratio 22:78, in the latter 85:15. The overall yield in reaction with NaH was 9% (91% of the initial compound **1** was recovered), in reaction with K_2CO_3 the yield reached 93%.

The reaction of oxacalixarene **1** with ethyl bromoacetate in the presence of bases resulted in the total alkylation of the hydroxy groups on the lower rim of the

Scheme 27.



1 *cone*-**155** *paco*-**155**

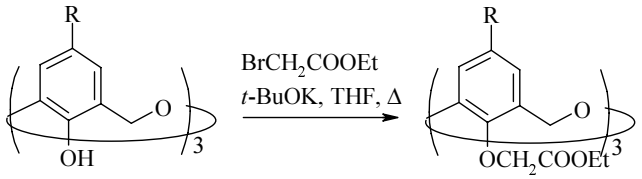
K

molecule [5]. The arising triethoxycarbonyl derivatives **155** were predominantly in *paco* conformation.

The trialkylation of compound **1** with ethyl bromoacetate was presumed to proceed analogously to the reaction with BuI [6] (Scheme 27). The lack of mono- and di-*O*-alkylated products [**1** (H_2R, R = CH_2COOEt), **1**(HR_2, R = CH_2COOEt)] suggests that stage *3* is the fastest, and stage *1* is the slowest. Stage *1* is a common Williamson reaction, yet in stage *2* the ether group in the monosubstituted compound [**1** (H_2R, R = CH_2COOEt)] may be already linked to a metal cation, and the second $BrCH_2COOEt$ molecule may already coordinate to the bonded metal cation. As a result the process in (**K**) complex becomes pseudointramolecular. This trend is still stronger in stage *3*, and thus the reaction undergoes self-acceleration resulting in the selectivity of the process, namely, in the total alkylation of the OH groups.

The conformers ratio depends on the template effect of the metal cation. The reaction performed in acetone in the presence of K_2CO_3 or Cs_2CO_3 afforded *paco*-**155** in quantitative yield. Araki *et al*. pointed out that conformers *cone*-**155** and *paco*-**155** did not suffer interconversion even at 100°C (24 h in $Cl_2CHCHCl_2$). Thus OCH_2COOEt is sufficiently bulky to stop the rotation "oxygen-through-the-annulus". Considerable amounts of *cone*-**155** conformer (20–22%) were obtained at the use in the reaction of cations Na^+ and K^+ in the form of strong bases (NaH and *t*-BuOK, but not K_2CO_3). Apparently in this case the template cation is able to retain the ether and oxide groups on the same side of the calixarene bowl in the position favorable for *cone* conformation synthesis. At the use of a weak base the nondissociated OH groups form intramolecular hydrogen bonds with dissociated

Scheme 28.



16, 26 **156,** 22%; **157**, 21%

R = Br (**16**, **156**); Me (**26**, **157**).

O^- groups thus weakening the template effect of the cation and facilitating formation of *paco* conformer..

4-Bromo- and 4-methyltrioxacalixarenes **16** and **26** also undergo complete alkylation by ethyl bromoacetate in THF in the presence of *t*-BuOK affording the corresponding products **156** and **157** (Scheme 28)[18].

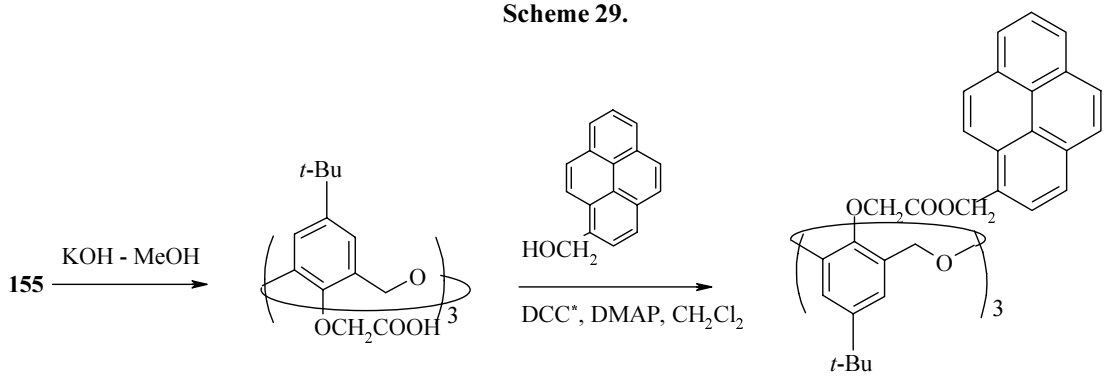
Tricarboxy derivative **158** was obtained in 90% yield at treating the corresponding ester **155** with KOH in MeOH at reflux [40] or with NaOH in aqueous dioxane [41]. Compound **158** was used for preparation of modified receptors **159** [41] and **160**, **161** (Schemes 29, 30) [42].

In 1995 the OH groups in oxacalixarene **1** were modified by introducing amide substituents [43].

The reaction carried out in the presence of NaH in THF afforded exclusively *cone*-conformer of trisubstituted calixarene **162** (yield 23%), whereas in DMF formed a mixture of nearly equal amounts of *cone*- and *paco*-conformers. In the presence of K_2CO_3 or Cs_2CO_3 in acetone only *paco*-conformer **162** was obtained (yield 45%) (Scheme 31).

A complete modification of the lower rim of oxacalixarene **155** molecule afforded well soluble in water cationic derivative **163** [44] (Scheme 32).

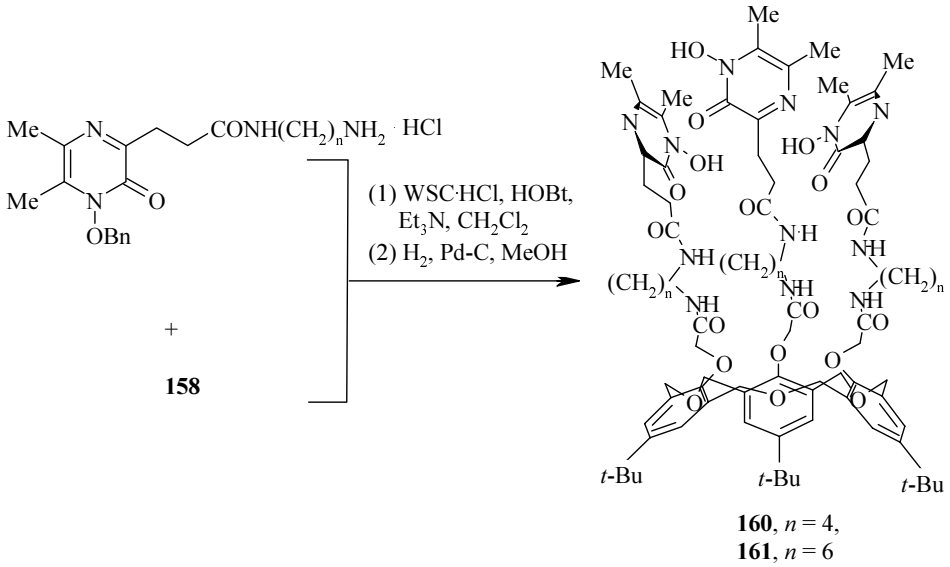
Scheme 29.



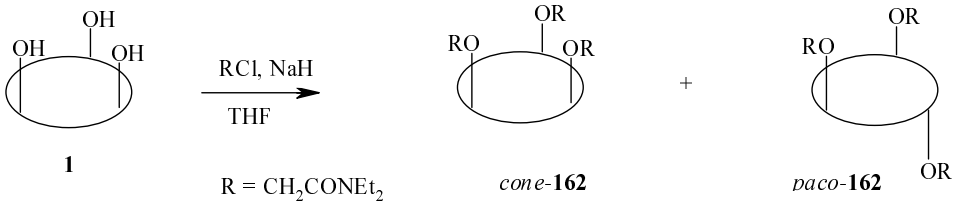
cone-**158**, *paco*-**158** *cone*-**159**, *paco*-**159**

* The following abbreviations were used in reaction equations: DCC is dicyclohexylcarbodiimide; DMAP is 2-(dimethylamino)-pyridine; WSC·HCl – $CH_3CH_2N{=}C{=}N(CH_2)_3NMe_2{\cdot}HCl$ is a water-soluble carbodiimide; EDC is 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide; HOBt is 1-hydroxybenzotriazole hydrate; $PyBEt_2$ is diethyl(3-pyridyl)borane; *t*-BOC is *tert*-butoxycarbonyl; BOP-reagent is benzotriazolyl(N-oxy)tris(dimethylamino)-phosphonium hexaphosphate; THT is tetrahydrothiophene.

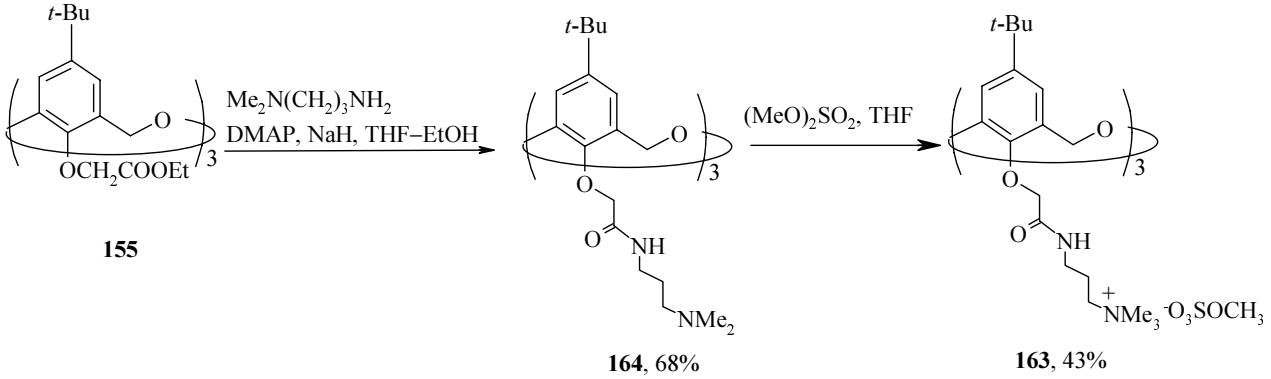
Scheme 30.



Scheme 31.



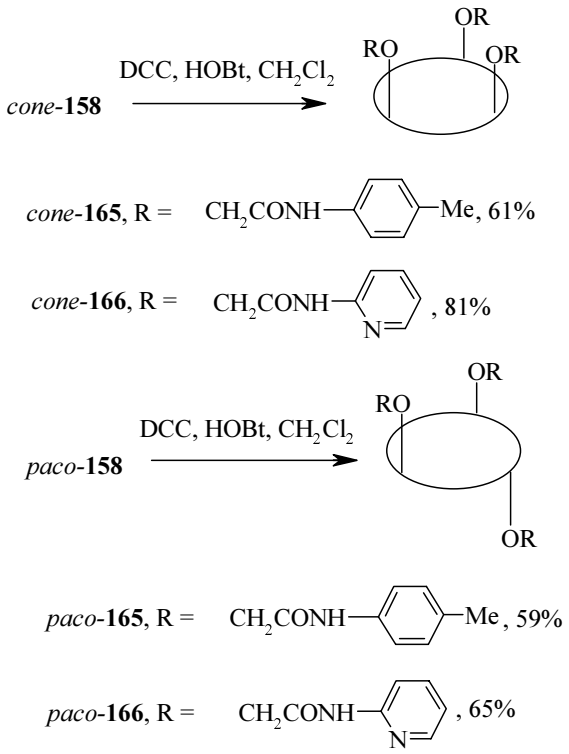
Scheme 32.



Tricarboxy derivative **158** in *cone* and *paco* conformations was applied to preparation of amides **165** and **166** (Scheme 33) [45].

The conformations of the amides obtained were in agreement with those of initial compounds as was demonstrated by ^{1}H NMR spectroscopy. *cone*-Conformers **165** and **166** possess C_3 symmetry and contain intramolecular hydrogen bonds between NH groups and adjacent carbonyls. In *paco*-conformers **165** and **166** two substituents are directed upward with respect to aromatic rings, and the third one is tightly located in a hydrophobic cavity formed by two aryl fragments as in «*self-inclusion*» complexes. Between two substituents directed upward arise hydrogen bonds. In conformer *paco*-**166** the nitrogen atoms of pyridine rings are oriented outward from the cavity due to repulsion. *paco*-Conformers **165** and **166** possess C_2 symmetry.

Scheme 33.



In 2001 a synthesis was performed for the first time of cycloenantiomeric homooxa-calixarenes **167** and **168** containing three different substituents on the upper rim of the molecule [46] by modification of the lower rim of compounds **74** [28] and **82** [29] with chloroacetic acid *N,N*-diethylamide [43].

Oxacalixarene **167** in a crystalline state exists in the *cone* conformation (Fig. 3a) although considerably distorted, whereas the initial **74** exists in an ideal *cone* conformation (Fig. 3c). The three benzene rings of oxacalixarene **167** form a cylindrical cavity (Fig. 3b). The shortest distance from the carbon atom of the CH_3 group of *tert*-butyl substituent to the neighboring benzene ring is equal to 3.85Å, and it is comparable with the sum

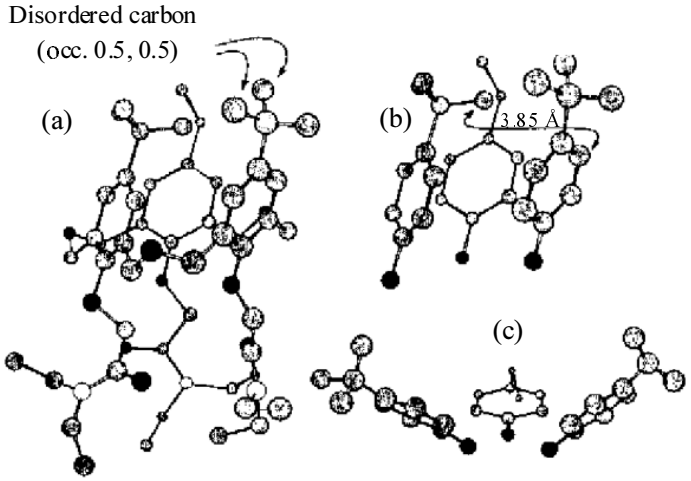


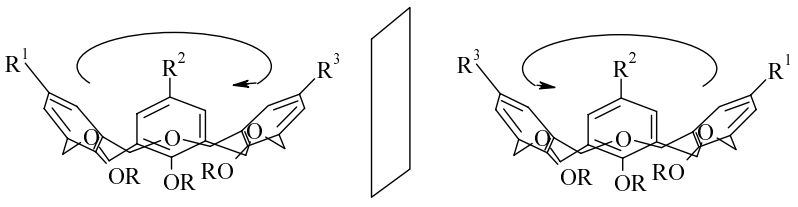
Fig. 3. (a) Crystal structure of oxacalixarene **167**; (b) position of three benzene rings in oxacalixarene **167** forming a cylindrical cavity; (c) position of three benzene rings in compound **74** according to data from [28].

of van der Waals radii of the CH_3 group (~2.0Å) and sp^2-hybridized C atom(1.7–1.8Å). This fact indicates that the dominant factor in conserving the distorted *cone* conformation is the CH-π interaction. The structure of compound **168** is similar to that of oxacalixarene **167** Scheme 34. The distortion of the cavity in oxacalixarene **168** is caused by self-inclusion thereto of the *tert*-butyl group.

Enantiomers of oxacalixarene **168** were separated. Preliminary study using ^{1}H NMR spectroscopy suggests that optically active oxacalixarene **168** is capable to recognize enantiomers of phenylalanine ethyl ester hydrochloride [46].

In 1995 the silylation of OH groups in substituted oxacalix[3]arenes **1, 24, 26**, and **27** was carried out for the first time [47]. Reactions of these compounds with 1-trimethylsilyl)imidazole (TMSIM) or with bis(trimethylsilyl)trifluoroacetamide (BSTFA) gave rise to a mixture of *cone* and *paco* conformers of compounds **169–172** (Scheme 35).

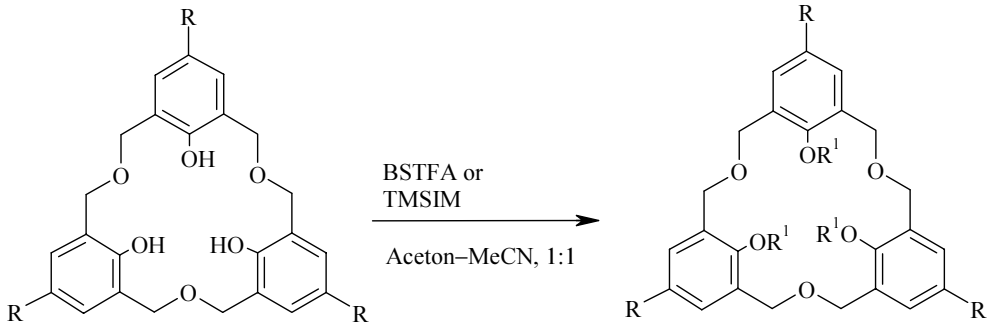
Scheme 34.



167, 168

167, R^1 = *t*-Bu, R^2 = *i*-Pr, R^3 = Et, R^4 = CH_2CONEt_2; **168**, R^1 = *t*-Bu, R^2 = Et, R^3 = H, R^4 = CH_2CONEt_2.

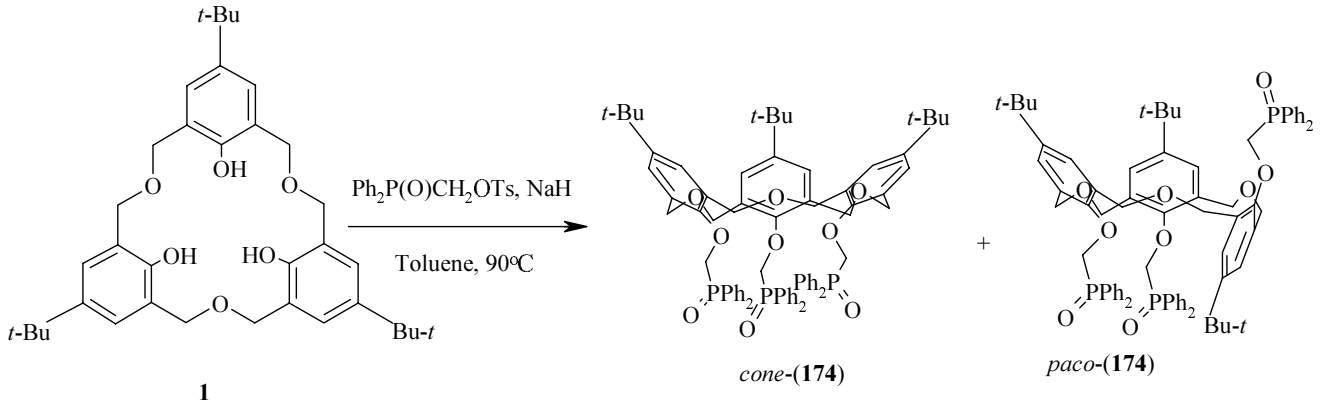
Scheme 35a.



1, **24**, **26**, **27** — *cone*-(**169-172**) + *paco*-(**169-172**)

R = *t*-Bu (**1**, *paco*-**169** + *cone*-**169**, 2.9:1; 82%), *i*-Pr (**24**, **170**), Me (**26**, **171**), Cl (**27**, **172**).

Scheme 35b.



1 — *cone*-(**174**) + *paco*-(**174**)

(*cone* - *paco*-, 4 : 1)

The ratio of *paco/cone* conformers of compounds **169–172** was directly dependent on the silylating agent, and the following values were obtained at the use of BSTFA at 297 K: for **169**, 2.9; **170**, 4.8; **171**, 9.1; **172**, >100; at the use of TMSIM at 320 K: for **169**, 46; **170**, 38; **171**, 30; **172**, >31. The *paco* conformer prevailed in all cases (Scheme 35a).

The first triphosphine ligands **173** and the corresponding oxides **174** were synthesized in 1999 [48].

cone-Conformer **174** was isolated in 72% yield. The reduction of *cone* and *paco* phosphinoxides **174** with $PhSiH_3$ in toluene at reflux afforded in quantitative yield triphosphines *cone*- and *paco*-**173** respectively (Scheme 35b). The structure of compounds obtained was established using ^1H NMR spectroscopy and X-ray diffraction analysis.

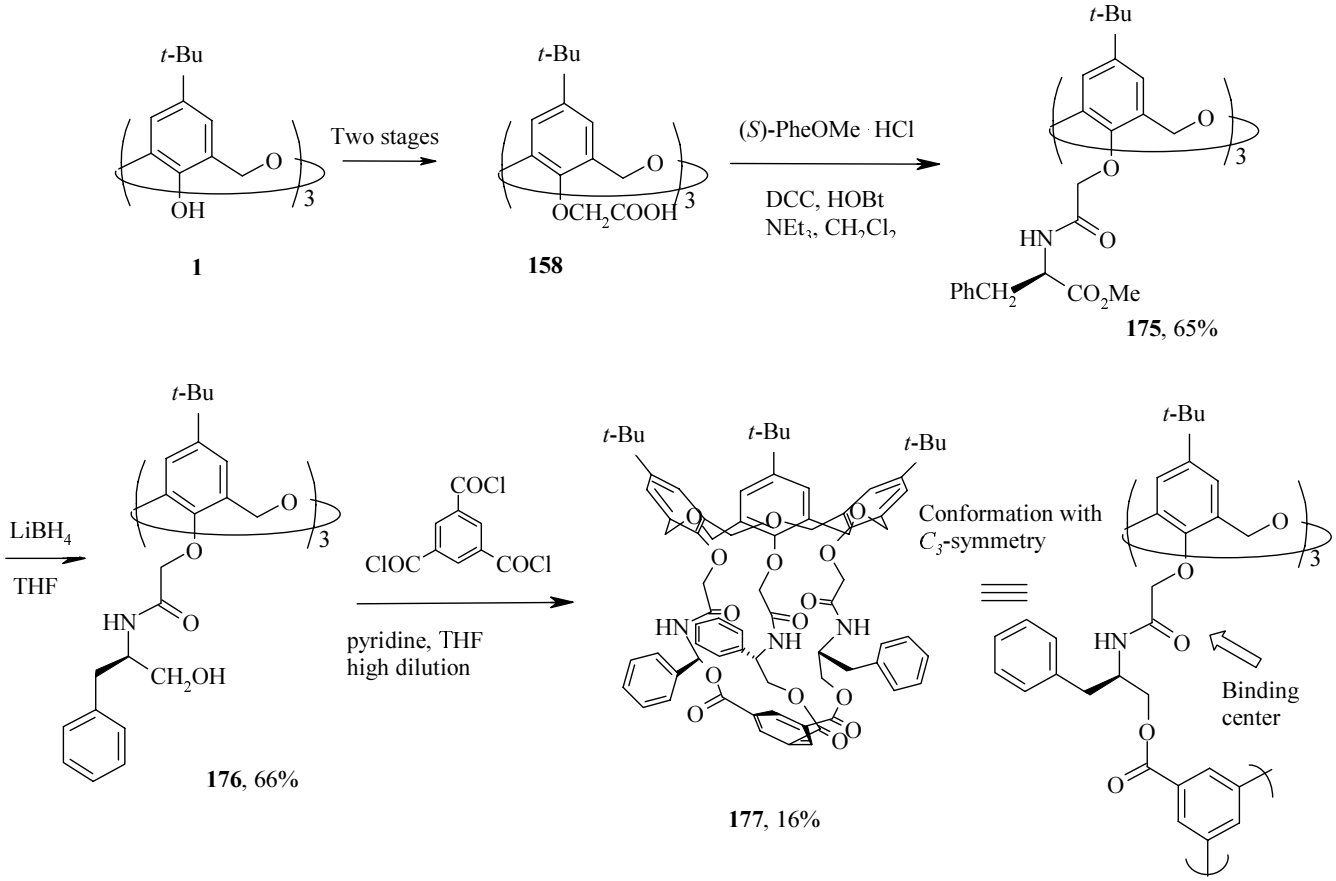
In 1995 starting with oxacalixarene **1** a conformationally rigid receptor **177** was synthesized [49]. The building up of this molecule was performed through derivative of oxacalixarene with (*S*)-phenylalanine **176** where amide substituents were "capped" with 1,3,5-benzenetricarbonyl trichloride

From tricarboxy derivative **158** and 4-methylbenzyl alcohol in the presence of DMAP and DCC compound **178** was prepared [7].

The treatment of compound **158** with 1,3,5-tri(bromomethyl)benzene **I** DMF in the presence of Na_2CO_3 gave rise to oxacalixarene **179** "*capped*" at the lower rim (Scheme 37) [7].

At the use of K_2CO_3 instead of Na_2CO_3 compound **179** failed to form. This fact evidences the importance of the template effect of the Na^+ cation in the condensation process. The conformational structure of oxacalixarene **179** was proved by ^1H spectra and X-ray diffraction study. It exists in solution in a leveled *cone* conformation, and in the solid state in a somewhat distorted *cone* conformation with C_3 symmetry. The concave cavity of compound **179** is hydrophobic and is readily solvated in

Scheme 36.



1

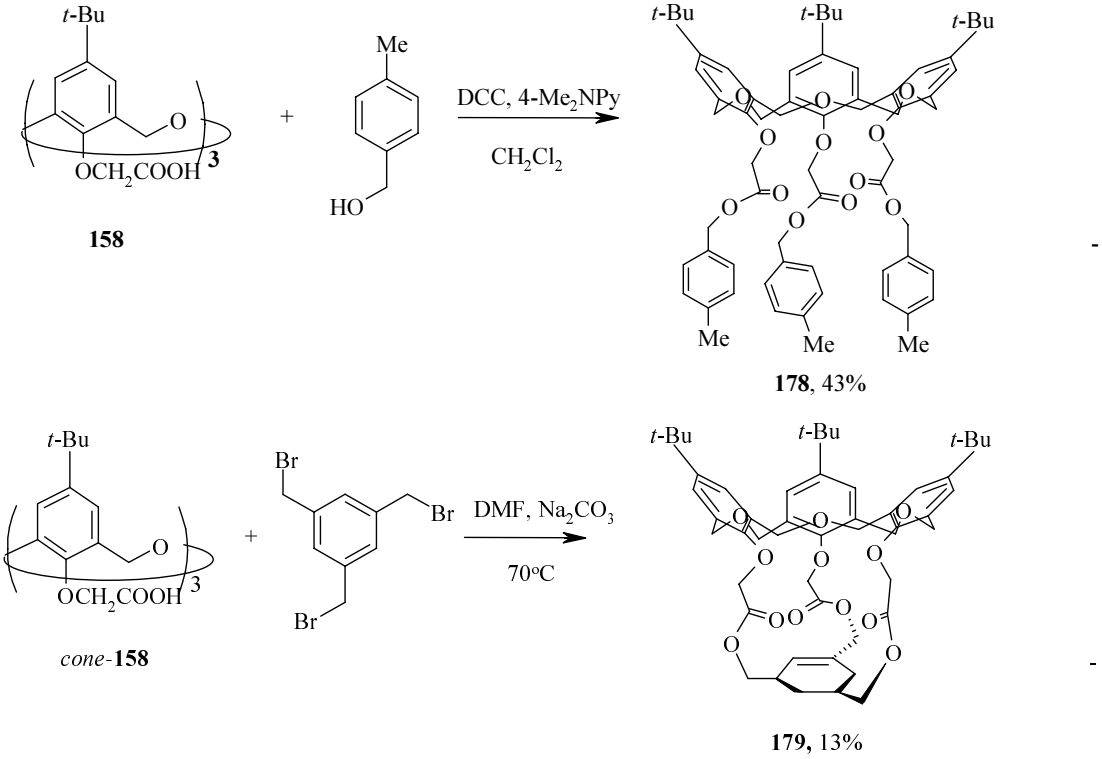
158

175, 65%

176, 66%

177, 16%

Scheme 37.



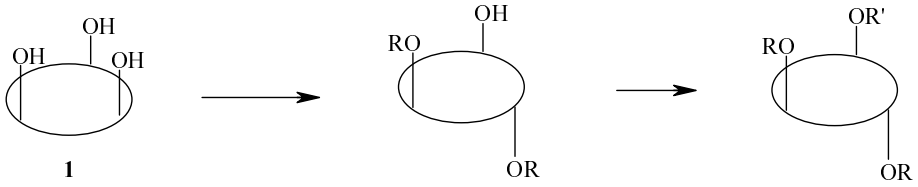
158

178, 43%

cone-**158**

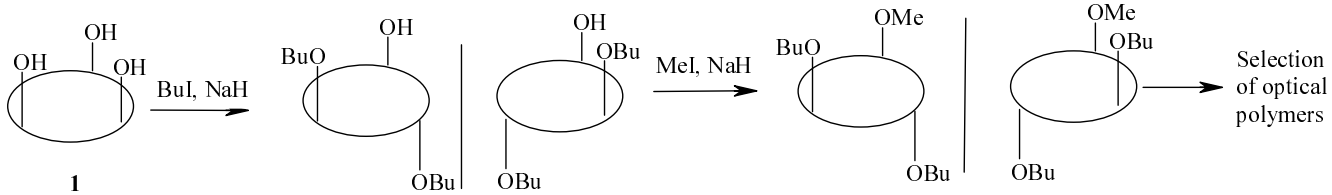
179, 13%

Scheme 38.



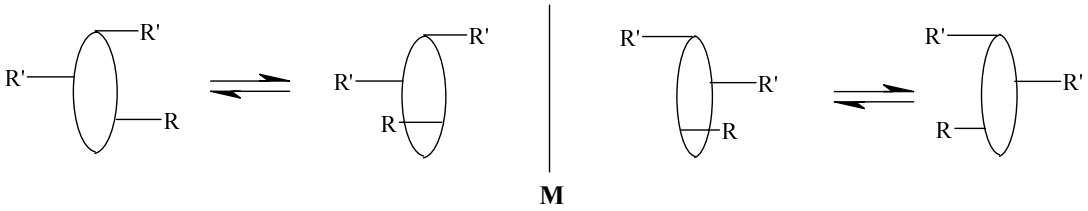
180, R = Bu; **181**, R = Bu, R' = $CH_2C_6H_5$.

Scheme 39.



anti-**180** *anti*-**182**, 70%

Scheme 40.



organic phase as has been observed during the X-ray analysis on single crystals.

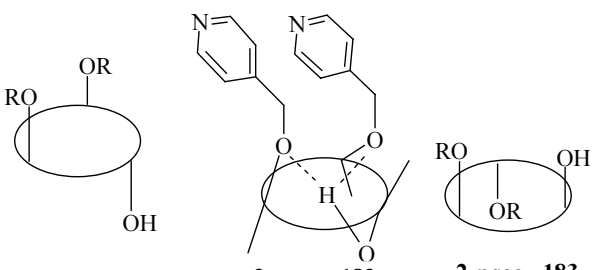
3.2. Selective modification of the lower rim of hexahomotrioxacalix[3]arenas. Selective alkylation of oxacalixarene **1** was done with C_4H_9I in the presence of NaH (molar ratio 1:2.2:2) in DMF [6]. The reaction in 52% yield afforded dibutyl ether **180**. The presence of unmodified OH group capable of rotation through the annulus results in equivalence of both butyl groups in the NMR spectra disregarding of conformation (*cone* or *paco*) taken by ether **180**. To discriminate between conformations the free OH group was subjected to benzylation by treating diether **180** with benzyl bromide in the presence of NaH to obtain derivative **181** in 53% yield. Its ^{1}H NMR spectrum proved to belong to *paco* conformation. Since in this compound rotation of the type "oxygen-through-the-annulus" was inhibited, Araki et al assigned to precursor **180** also *paco* conformation where the butyl groups are in *anti*-orientation (Scheme 38).

The selectively modified derivative **180** was applied to a synthesis of optically active triether **182** [50] that according to the ^{1}H NMR spectrum consisted of a mixture of two enantiomers. The latter were separated by HPLC (Scheme 39).

Due to the free rotation of the methoxyphenyl fragment compound **182** behaves like macrorings possessing C_2 symmetry (**L**) (Scheme 40).

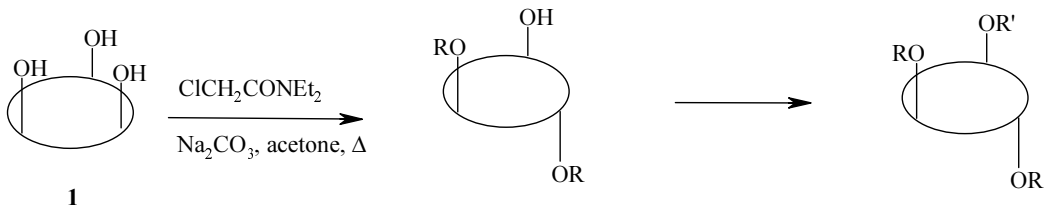
Thus from a macroring **1** of C_3 symmetry was built up derivative **182** of *pseudo*-C_2 symmetry.

O-Alkulation of oxacalixarene **1** with 4-(chloromethyl)-pyridine in the presence of Na_2CO_3 gave exclusively disubstituted calixarene **183** in 52% yield [39]. The structure of di(4-pyridylmethyl)oxacalixarene **183** was established by spectral methods (IR and ^{1}H NMR spectroscopy). The data obtained suggest the presence of intramolecular hydrogen bonds between OH and 4-$PyCH_2O$ groups in a *paco* conformer **183**. Yamato *et al*. believed that of two possible forms (3-*paco* and 2-*paco*) the first existed where both 4-$PyCH_2O$



3-*paco* - **183** **2**-*paco* - **183**

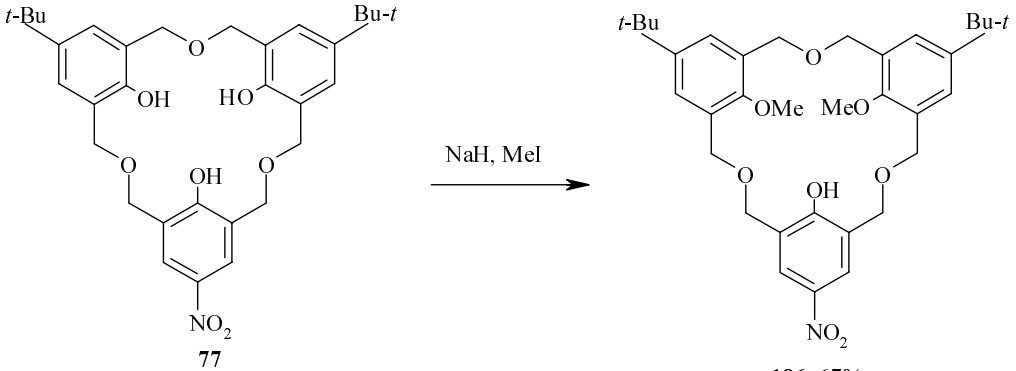
Scheme 41.



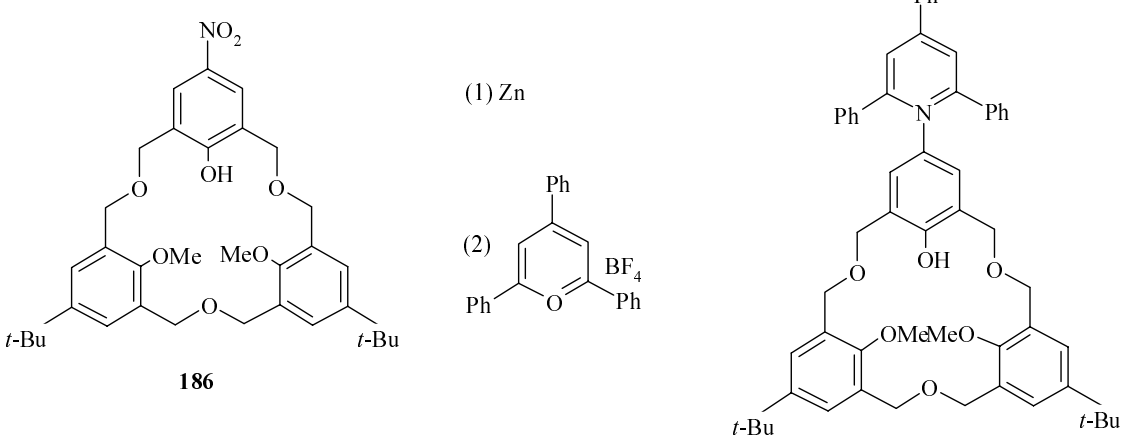
1

184, R = CH_2CONEt_2; **162**, R = R' = CH_2CONEt; **185,** R = CH_2CONEt_2, R' = CH_2CO_2Bu-*t*.

Scheme 42.



77 **186,** 67%



186 **187,** 96%

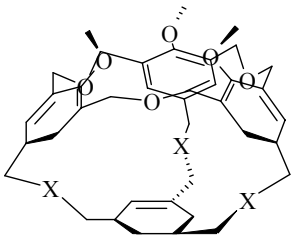
substituents occurred on the same side of the cyclophane ring, and OH group was inverted into the calixarene cavity. A form arose favoring hydrogen bonds formation.

In 1995 selective amidation of oxacalixarenea **1** with N,N-diethylchloroacetamide was carried out in acetone in the presence of Na_2CO_3, and in 38% yield a disubstituted derivative *paco*-**184** was isolated [43]. The further alkylation of the free OH group with diethylchloroacetamide both in acetone in the presence of Na_2CO_3 and in THF in the presence of NaH afforded conformer *paco*-**162**, and alkylation with *tert*-butyl bromoacetate (THF, NaH) resulted in diamidomonoether derivative **185** (55%) (Scheme 41).

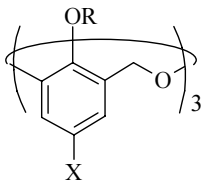
In 2002 was performed a selective methylation of two OH groups 4-nitrooxacalixarene **77** [51]**.**

The X-ray diffraction study of the structure of dimethyl ether **186** synthesized revealed that in the solid state it existed in the *paco*-conformation (Scheme 42).

Scheme 43.



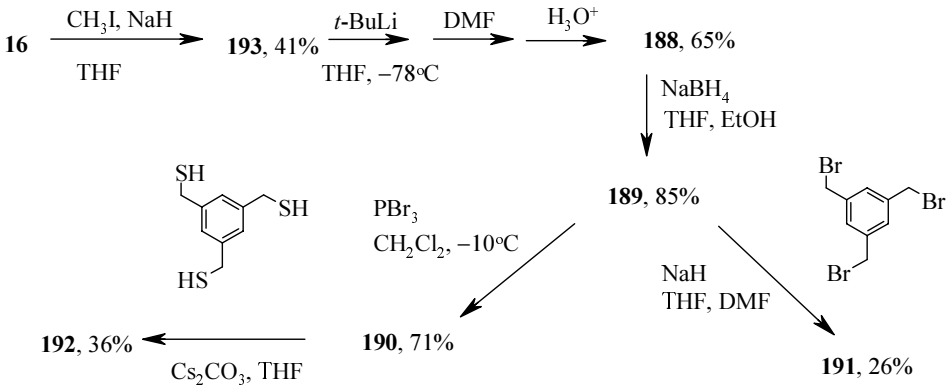
191, X = O;
192, X = S



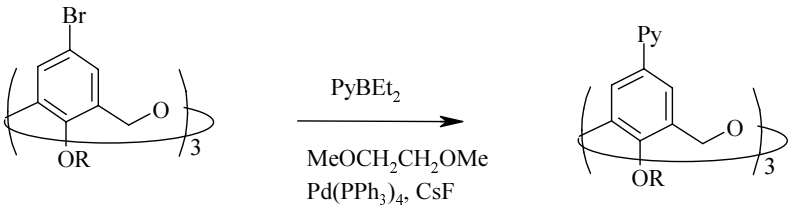
16, 188–190, 193

R = H, X = Br (**16**), R = CH_3, X = CHO (**188**); R = CH_3, X = CH_2OH (**189**); R = CH_3, X = CH_2Br (**190**); X = O (**191**); S (**192**); R = CH_3, X = Br (**193**).

Scheme 44.

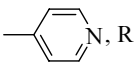
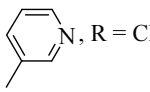


Scheme 45.



156, 193

194, 30%; **195**, 35%; **196**, 53%

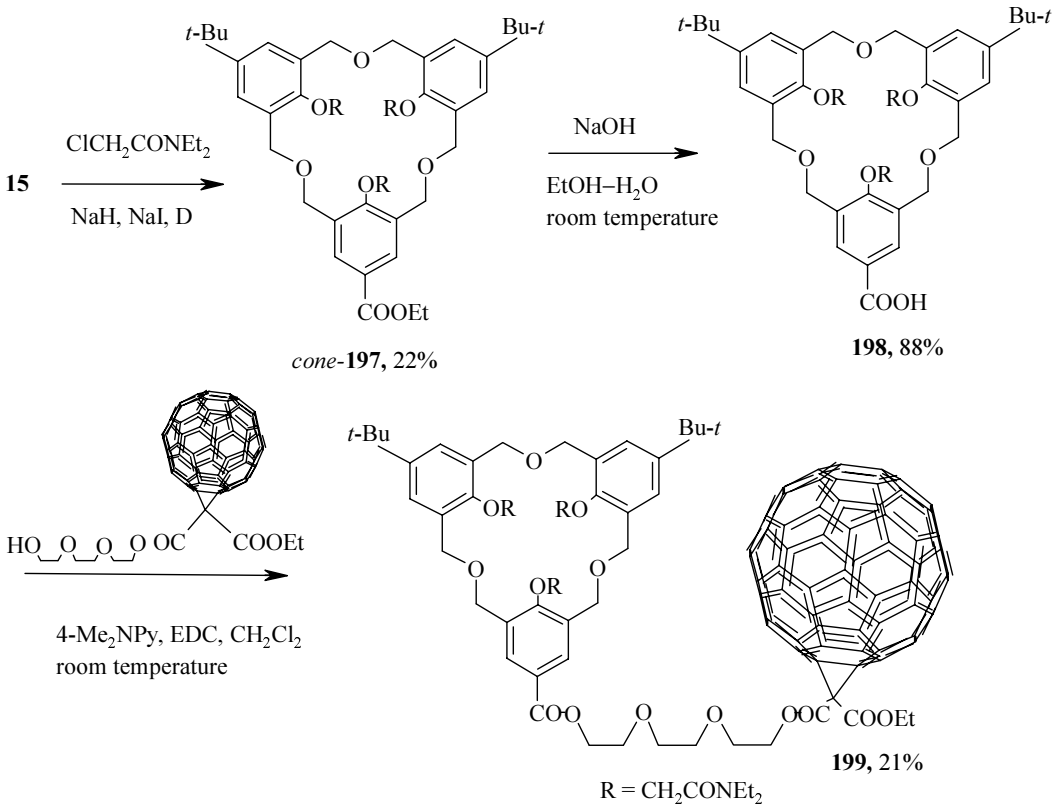
Py =  R = CH_2COOEt (**156**, **194**), Me (**193**, **195**); Py =  R = CH_2COOEt (**196**)

Dimethylated *p*-nitrooxacalixarene **186** was used in preparation of receptor **187** containing a fragment of pyridinium N-phenolate dye (Reichardt dye E_t1) [52].

3.3. Modification of the upper rim of hexahomotrioxacalix[3]arenes. Proceeding from 4-bromooxacalixarene **16** oxacalixarenes **188–190** with functional groups on the upper rim of the molecule were synthesized, and two among them (**189** and **190**) were used to prepare compounds **191** and **192** immobilized in *cone* conformation and having $C_{3\gamma}$ symmetry (Scheme 44) [53].

From 4-bromooxacalixarenes **156** and **193** modified at the lower rim were prepared derivatives with pyridyl substituents at the upper ring **194–196** (Scheme 45) [38, 54].

The strongest difference in the properties of these reaction products consists in rigidity of oxacalixarene **194** that is immobilized in the *cone* conformation whereas compound **195** is conformationally labile. Oxacalixarene derivative with an ester group at the upper rim of the molecule **15** was used in the synthesis of calixfullerene **199** where the calixarene part is connected with C_{60}-



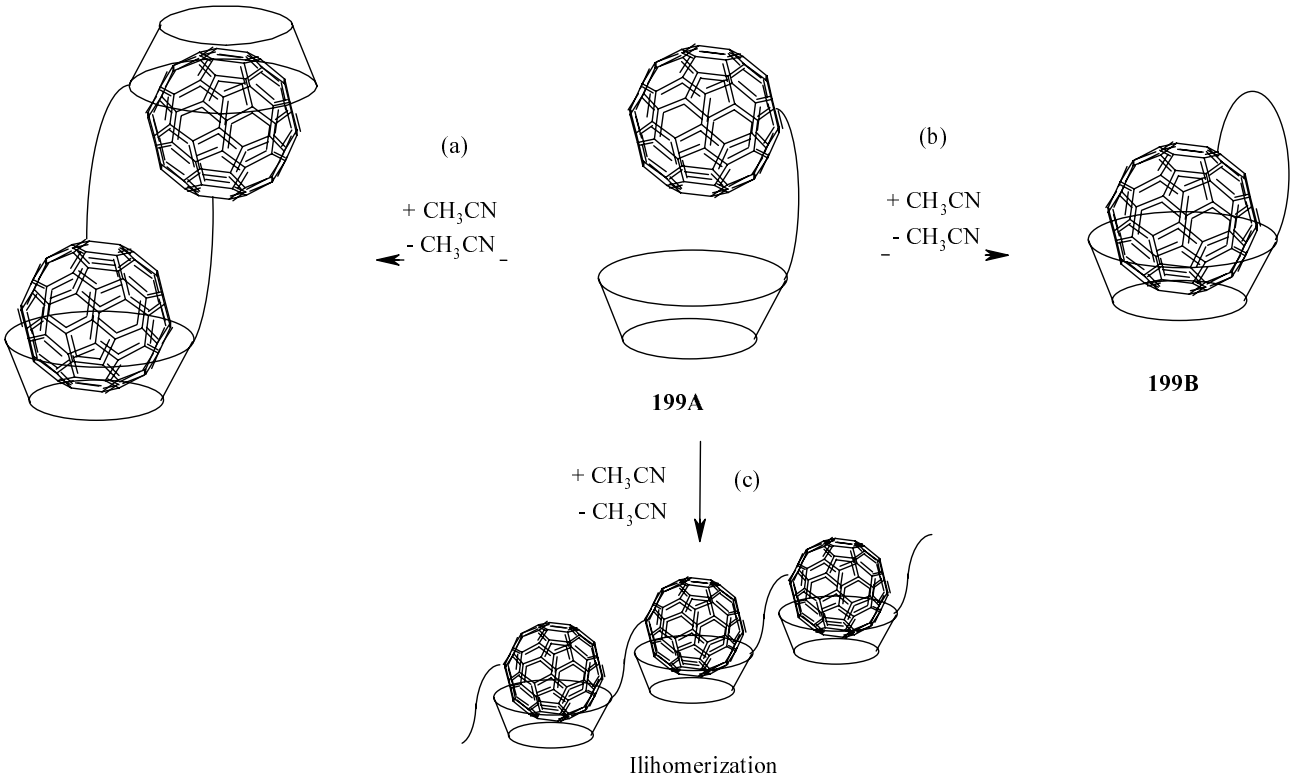
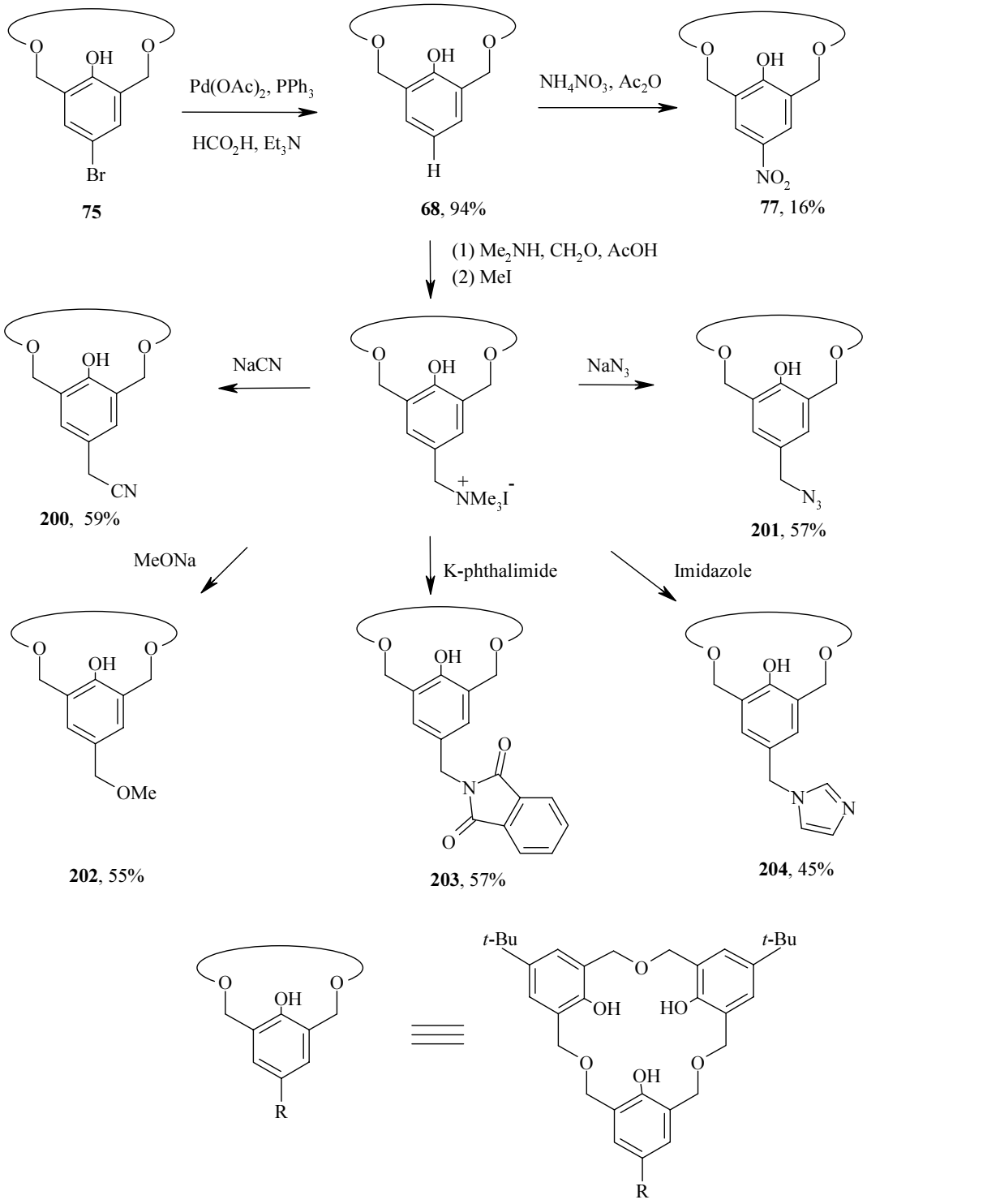


Fig. 4. Options (*a–c*) of intra- and intermolecular interactions in calixfullerene **199**.

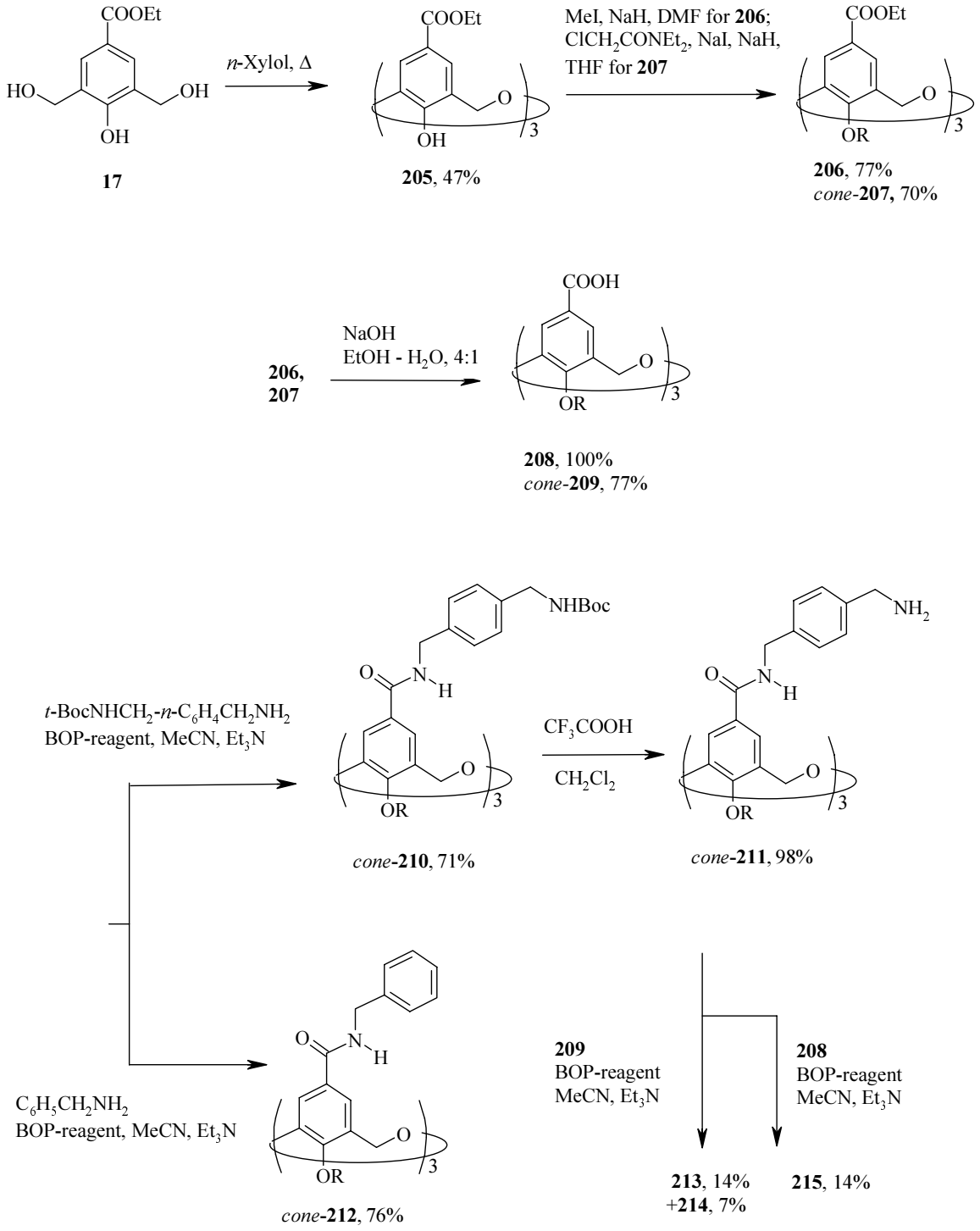
Scheme 46.



fullerene one through a flexible triethylene glycol bridge [17].

The conformational behavior of compound **199** was studied by spectral methods (absorption spectra in UV and visible region, ^{1}H NMR spectra) and by computer molecular simulation [17]. The data obtained suggest that there is a possibility of interaction between the C_{60}-fullerene fragment with the oxacalixarene cavity. It turned out that among three options of such interaction (Fig. 4) the *a* mode came true.

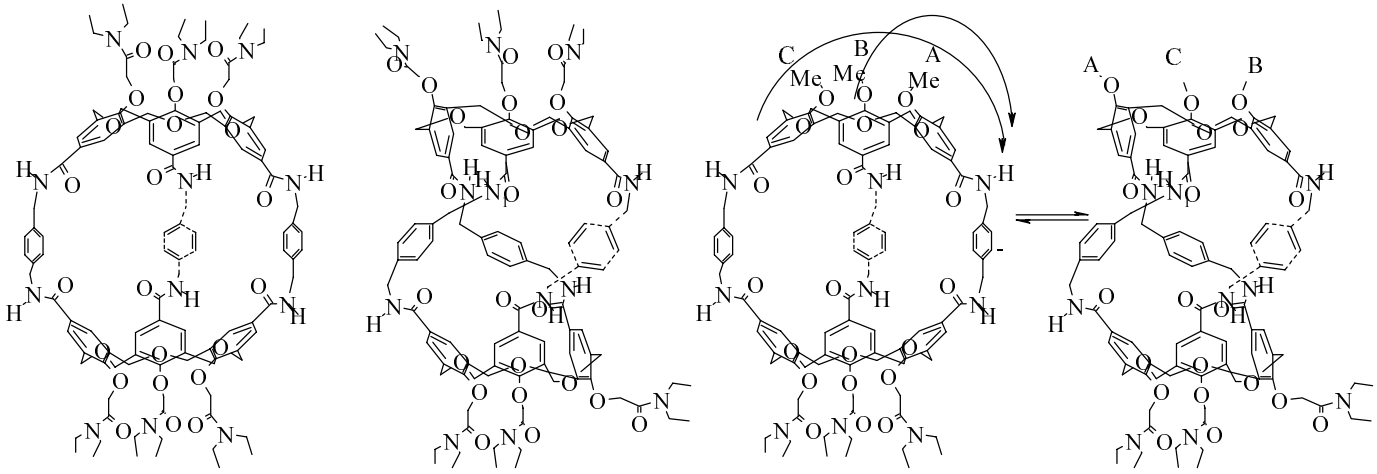
Scheme 47.



R = Me (**206**, **208**), CH_2CONEt_2 (**207**, **209 - 215**)

The synthesized calixfullerene **199** was shown to exist in $CDCl_3$ solution predominantly in **199A** conformation with an open oxacalixarene cavity and free fullerene fragment. In a mixed solvent $CHCl_3$–CH_3CN (1:1 by volume) due to intramolecular self-inclusion of the fullerene fragment into the calixarene cavity formed 100% of conformer **199B**. The equilibrium constant [conformer **199B**/conformer

Scheme 48.



213 **214** **215**

199A = 0.72] in $CHCl_3$–CH_3CN (24:1 by volume) at 27°C was evaluated.

Mono-4-bromooxakalixarene **75** served a key compound for direct introduction of functional substituents into position *4* of oxacalixarene **68** by Mannich reaction [51] (Scheme 46)).

3.4. Molecular capsules based on hexahomotrioxacalix[3]arenes. Calixarenes and their analogs of hemisphere form are excellent building blocks for construction of molecular capsules, "host" molecules with well developed inner cavities [1, 2]. Basing on the derivatives of oxacalix[3]arenes **205**–**212** new types of dimeric molecules **213**–**215** were synthesized where two oxacalixarene fragments are bound with each other with three bridges (Scheme 47). Compound **213** is a molecular capsule, compound **214** is a self-threaded rotaxane, and compound **215** is a conformationally labile dimer (Scheme 48) [55].

Molecular capsule **213** possesses a large inner cavity favorable for inclusion of large "guest" molecules. The molecule has three sufficiently large windows providing a possibility for guests to come in and go out. Finally, the molecule possesses two types of recognizing centers: on the lower rim of the calixarene fragments, and the binding bridges. The reaction between compounds **211** and **209** unexpectedly [55] alongside the molecular capsule **213** provided also its isomer **214** as a self-threaded rotaxane with no inner cavity. Inasmuch as on the lower rim of the oxacalixarene fragments are located diethylaminoacetamide substituents the formation of compound **214** due to internal inversion of one of the calixarene parts of the molecule is ruled out. The pathways of compounds **213** and **214** formation are independent. In the unsymmetrical compound **215** with anisyl substituents this conformational inversion is probable, and as a result the reaction affords compound **215** as a mixture of a molecular capsule and a molecular self-threaded rotaxane (Scheme 49).

In 2001 from oxacalixarene **209** and porphyrin molecular capsule **216** was synthesized composed of two oxacalixarene fragments connected with three porphyrin-containing bridges [56].

Molecular capsules, "constructed" from oxacalixarenes in the presence of metal cations will be considered in our next review treating the receptor properties of the homooxacalixarenes (Scheme 50).

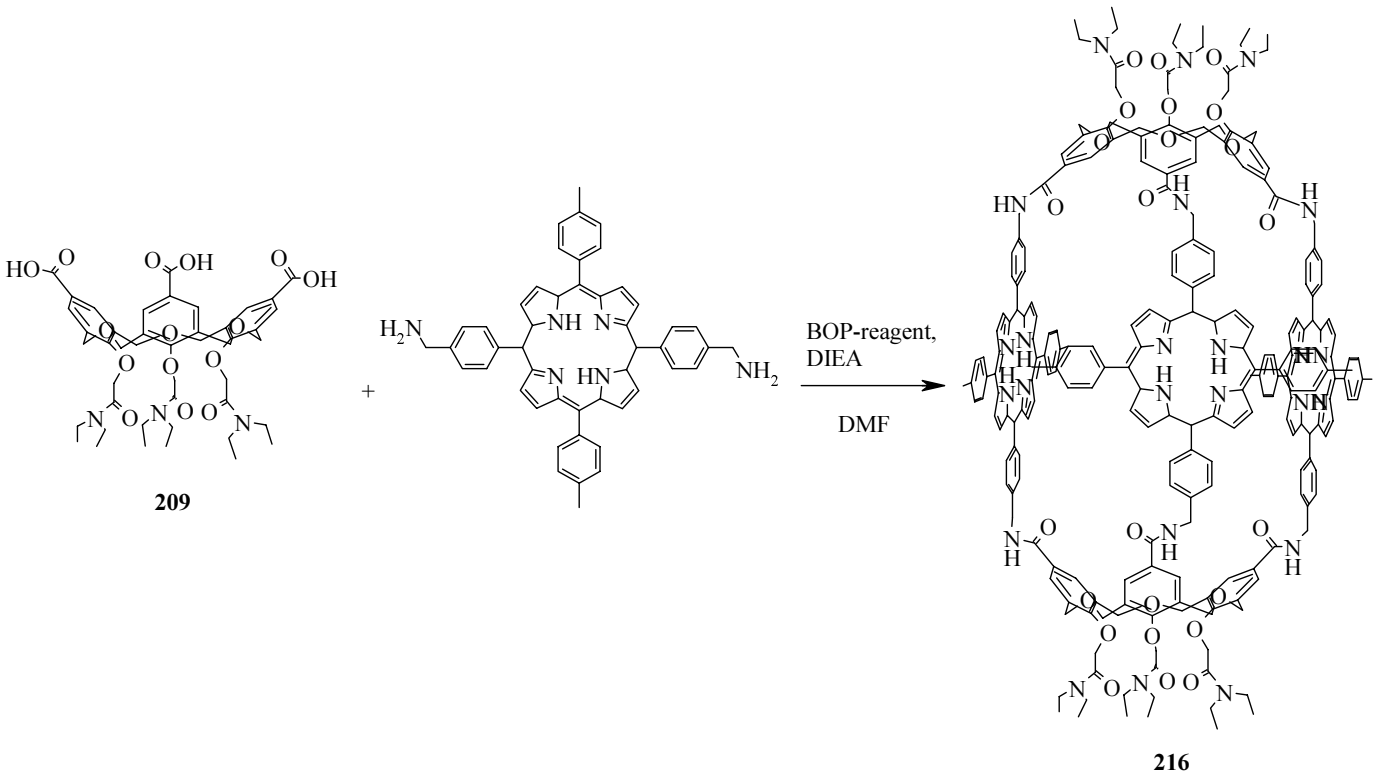
3.5. Modification of dihomomonooxacalix[4]- and tetrahomodioxacalix[6]arenes. Complete modification of OH groups in monooxacalix[4]arene **5** was performed by its reaction with haloalkyls [57], haloketones [58], and chlorodiethylacetamide [58] in the presnce of bases.

The conformational isomerism of monooxacalix[4]-arene **5** is somewhat more complicated than that of "classic" calix[4]- **2** and calix[5]- **6** arenes [9, 35, 57, 59]; the latter compounds may exist in four conformations (*cone, paco,* 1,2- and 1,3-*alt*) whereas the oxacalix-[4]arene **5** may occur in six conformations (Scheme 51).

The spectral characteristics of oxacalixarene **5** conformers are compiled in Table 2.

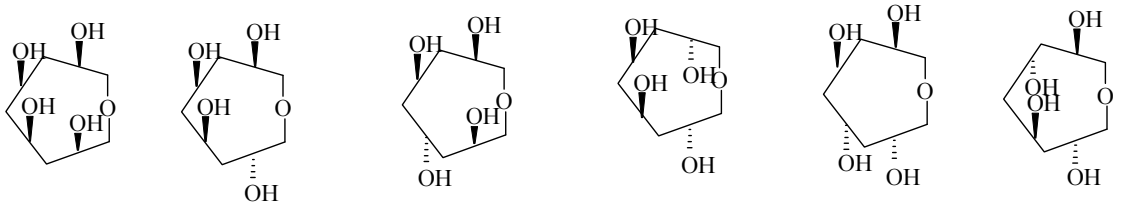
Oxacalixarene **5** was shown by means of dynamic spectroscopy [57] to be conformationally labile at room temperature. In going to its ethers the conformational flexibility of compounds diminished, and some of them

Scheme 49.



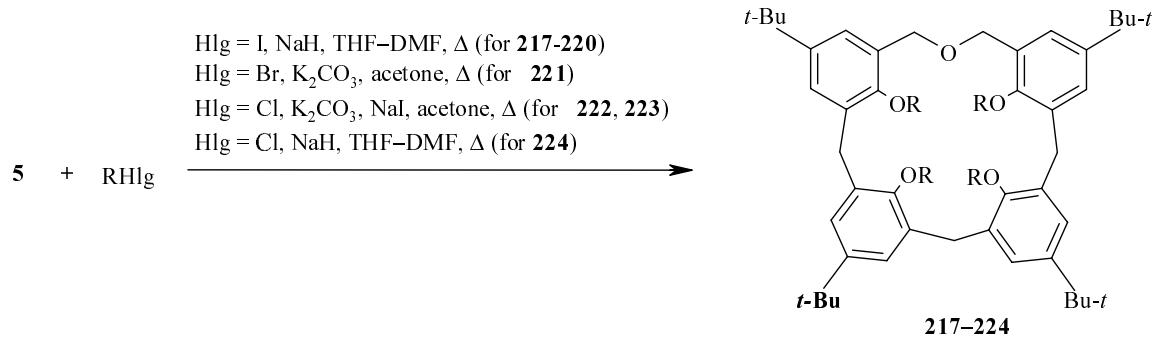
209 **216**

Scheme 50.



cone *paco*-**A** *paco*-**B** 1,2-*alt*-**A** 1,2-*alt*-**B** 1,3-*alt*

Scheme 51.



217–224

R = Me (**217**), Et (**218**), $CH_2CH{=}CH_2$ (**219**, 62%), CH_2Ph (**220**, 64%), CH_2CO-1-Ad (**221**, 34%), CH_2COCH_3 (**222**, 48%), CH_2CO-*t*-Bu (**223**, 18%), CH_2CONEt_2 (**224**, 30%).

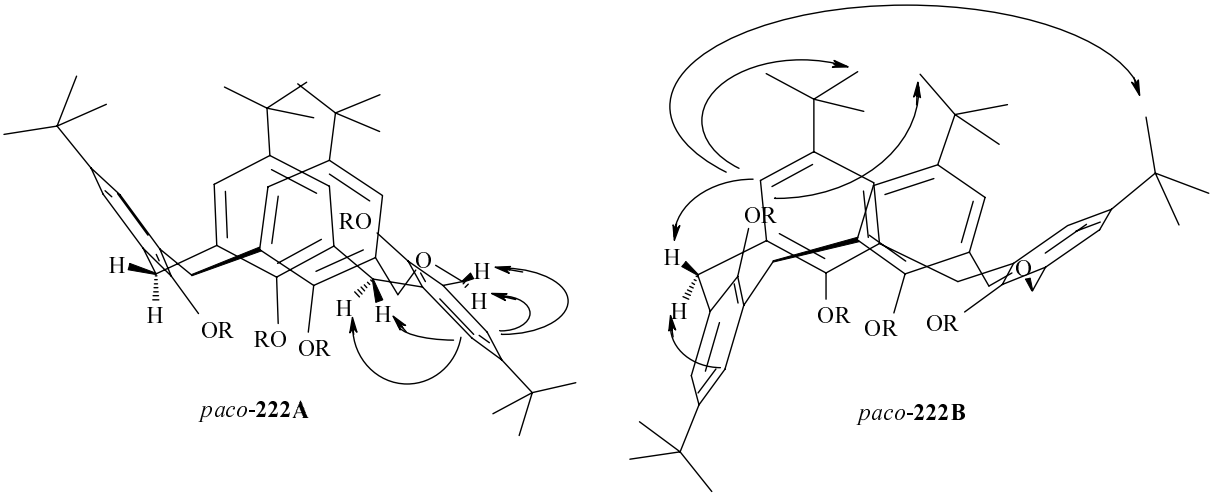
Table 2. Features of ^{1}H and ^{13}C NMR spectra of oxacalix[4]arene **5** conformers [57]

Conformation (symmetry element)	^{1}H NMR spectrum, number of signals (intensity)			^{13}C NMR, number of signals (δ, ppm)				
	ArH	CH_2	$C(CH_3)_3$	Ar	CH_2	$\mathbf{C}(CH_3)_3$	$C(\mathbf{C}H_3)_3$	$ArCH_2Ar$
cone (plane)	2 pairs of doublets (1:1)	3 pairs of doublets (2:2:1)	2 singlets (1:1)	12	3	2	2	1 (~31)1 (~31)
1,2-*alt*-A (plane)								1 (~31)1 (~37)
1,2-*alt*-B (axis)	2 pairs of doublets (1:1)	2 pairs of doublets and 1 singlet (2:2:1)	2 singlets (1:1)	12	3	2	2	1 (~31)1 (~37)
1,3-*alt* (axis)								1 (~37)1 (~37)
paco-A (none)	4 pairs of doublets (1:1:1:1)	5 pairs of doublets (1:1:1:1:1)	4 singlets (1:1:1:1)	24	5	4	4	1 (~31) 1 (~31) 1 (~37)
paco-B (none)								1 (~31)1 (~37)1 (~37)

became conformationally rigid at room temperature. Tetraethers **217–220** by conformational characteristics occupy an intermediate place between the corresponding derivatives of the "classic" calix[4]- and calyx[5]arenes [60–63]. Methyl ether **217** (T_c –56°C, $\Delta G^{\#}$ 10.0 kcal mol^{-1} in $CDCl_3$) is conformationally labile at –100°C; ethyl ether **218** (T_c –49°C, $\Delta G^{\#}$ 15.0 kcal mol^{-1} in $CDCl_3$) is conformationally rigid at –20°C, and ethers **219** (T_c 122°C, $\Delta G^{\#}$ 18.5 kcal mol^{-1} in $CDCl_2CDCl_2$) and **220** (T_c >>130°C, $\Delta G^{\#}$ >>20.0 kcal mol^{-1} in $CDCl_2CDCl_2$) are conformationally rigid at room temperature. Whereas the majority of calix[4]arenes tetraethers were isolated in *cone* or *paco* conformations [64] the preferred conformation of oxacalix[4]arene derivatives **217**–**219** is 1,2-*alt*-B, and benzyl ether **220** has been obtained in the *cone* conformation.

As to compounds with ketone and acetamide groups on the lower rim of oxacalix[4]arene, three among them, **221**, **223**, and **224** were obtained in the *cone* conformation [58] similar to the corresponding derivatives of "classic"calix[4]arene [65–67]. Methyl ketone **222** was isolated in two different conformations: *paco*-A and *paco*-B (Fig. 5), whereas the corresponding ketone from 4-*tert*-butylcalix[4]arene **2** was obtained in the *cone* conformation.

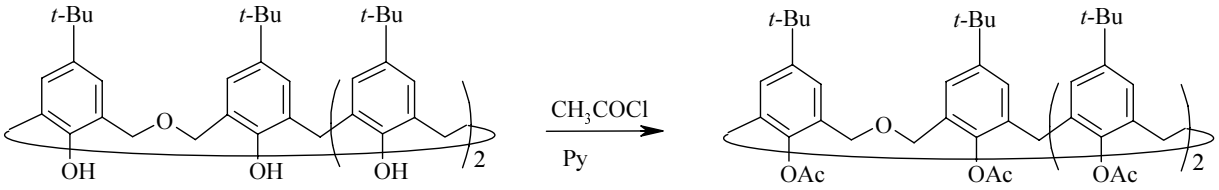
The study of the conformational lability of *paco*-A and *paco*-B conformers by ^{1}H NMR spectroscopy



paco-**222A** *paco*-**222B**

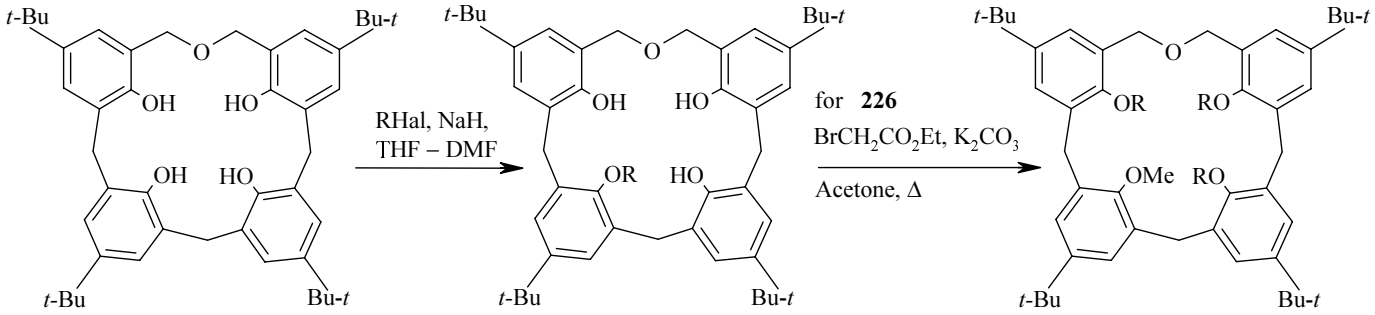
Fig. 5. Conformations of derivatives *paco*-**222A** and *paco*-**222B**; R = CH_2COOCH_3

Scheme 52.



5 **225**

Scheme 53.



5 **226 - 229** **230**

226, R = Me, 57%; **227,** R = Et, 36%; **228,** R = $CH_2CH{=}CH_2$, 51%; **229,** R = $CH_2C_6H_5$, 32%; **230**, R = CH2COOEt, 55%.

demonstrated that although the *paco*-B isomer is less rigid then the *paco*-A one, nonetheless the rigidity of both conformers was still high, and the methylene proton signals did not coalesce even at 120°C [58].

Treating compound **5** with acetyl chloride in pyridine afforded tetraacetate **225** in 95% yield (Scheme 52) [8].

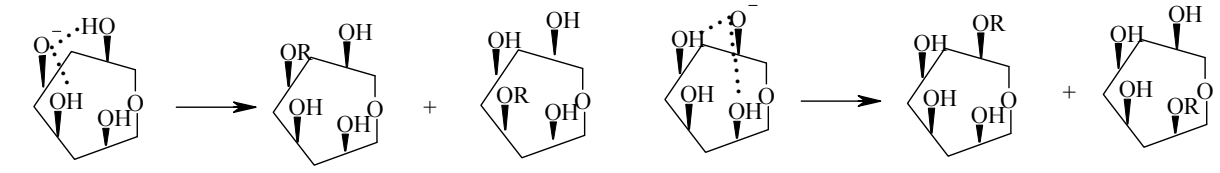
Selectively modified at the lower rim chiral derivatives of monooxacalix[4]arene **5,** monoethers **226–229** [68], and compound **230** [69] with two types of substituents (methoxy and alkoxycarbonyl groups) were described (Scheme 53).

The investigation by means of ^1H and ^{13}C NMR spectroscopy (recording at variable temperature in different solvents, at Pirkle's reagent addition), NOESY, NOE 1D, COSY, HMQC INEPT experiments demonstrated that all synthesized monoethers **226–229** are present in the *cone* conformation; the chirality of compounds was proved, coalescence temperature and energy barriers to the conformational inversion were evaluated. The T_c values, °C ($\Delta G^{\#}$, kcal mol^{-1}) for ether **226** equaled to 86 (16.6) in $CDCl_2CDCl_2$, 23 (13.6) in $(CD_3)_2CO$, and –8 (12.0) in pyridine-d_5. These characteristics for the other three compounds **227–229** were over 130 (≫ 20) in $CDCl_2CDCl_2$ and over 110 (≫ 20) in pyridine-d_5. Compound **230** in $CDCl_3$ at room temperature is present in a *distorted cone* conformation [69].

The monoalkylation [68] afforded racemic monoethers **226–229** in the *cone*-**A1** and *cone*-**A2** conformations. Marcos et al. [68] belive that just these conformations and not racemic *cone*-**B1**and *cone*-**B2** formed due to more efficient stabilization of phenoxide anion in *cone*-**A** by hydrogen bonds (Scheme 54).

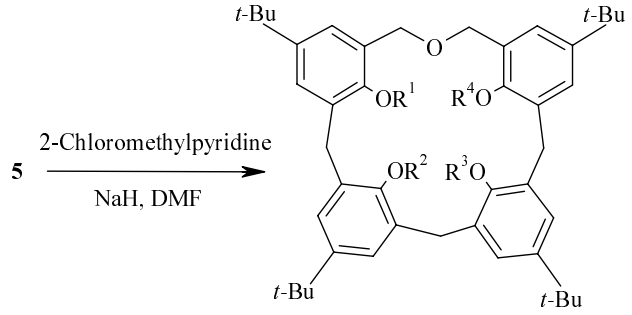
The alkylation of oxacalix[4]arene **5** with 2-(chloromethyl)pyridine in DMF in the presence of NaH gave rise to a mixture of six from nine possible pyridylcalixarenes, among them mono- **231**, di- **232–235**, and tetra- **236** derivatives (Scheme 55) [70]. The mixture was separated by chromatography. Mono- and dipyridyl derivatives were in *cone* conformation, the tetra derivative was in *cone* and *alt* conformations.

Scheme 54.



cone **A** **A1** **A2** **B1** **B2**

Scheme 55.



231 - 236

231, $R^1 = R^3 = R^4 = H$, $R^2 = 2\text{-}CH_2Py$, 22%; **232**, $R^1 = R^3 = H$, $R^2 = R^4 = 2\text{-}CH_2Py$, 26%; **233**, $R^3 = R^4 = H$, $R^1 = R^2 = 2\text{-}CH_2Py$, 2%; **234**, $R^1 = R^4 = H$, $R^2 = 2\text{-}CH_2Py$, <1%; **235**, $R^2 = R^3 = H$, $R^1 = R^4 = 2\text{-}CH_2Py$, <1%; **236**, $R^1 = R^2 = R^3 = R^4 = 2\text{-}CH_2Py$, 40%.

The composition of the alkylation products depends on the reaction time, the base used (NaH or K_2CO_3), and to a large extent is governed by the possibility of the intermediate phenolate ions stabilization with hydrogen bonds (Scheme 56).

Proceeding from monooxacalix[4]arene **5** the corresponding crown-derivatives **237–239** were obtained, and their conformational behavior was studied [71, 72].

The analysis of variable-temperature ^1H NMR spectra showed that in a nonpolar solvent $CDCl_2CDCl_2$ compound **239** is more rigid conformationally than calixcrown **238**. Compound **239** exists in the *paco* conformation, and calixarenes **237** and **238** in the *cone* conformation (Scheme 57).

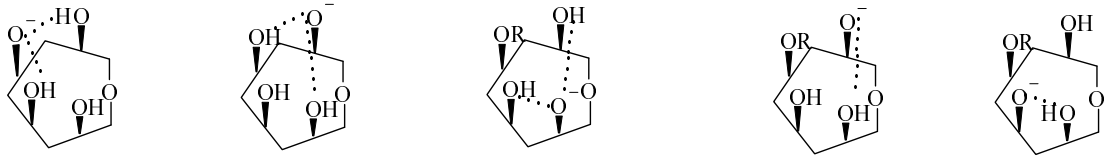
The total modification of the lower rim of tetrahomodioxacalix[4]arene **48** resulted in the corresponding tetraester **240** that on hydrolysis afforded dioxacalix[4]-arene with free COOH groups at the lower rim of molecule **241** [73, 74] (Scheme 58).

Synthesis of tetraamides **242** and **243** and tetrathioamides **244** and **245**, derivatives of dioxacalix[4]arene with 4 phenyl substituents on the upper rim of the molecule **50**, was carried out in [23, 75]. The tetraamides were obtained in reaction of calixarenea **50** with the N-substituted chloroacetamide in MeCN in the presence of K_2CO_3 [23, 75], the tetrathioamides formed at treating the appropriate amides with the Lawesson's reagent [75] (Scheme 59).

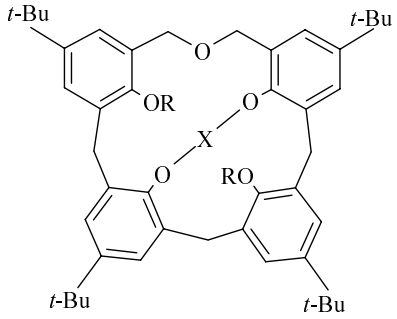
Derivatives of dioxacalix[4]arene **48** alkylated at the lower rim can exist in five different conformations.

The conformations of compounds synthesized were established with the aid of ^1H and ^{13}C NMR spectroscopy and X-ray diffraction analysis. It turned out that the reaction of oxacalixarene **50** with *N,N*-diethylchloro-

Scheme 56.

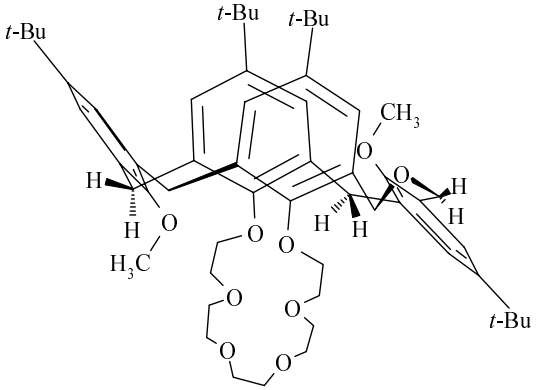


Scheme 57.



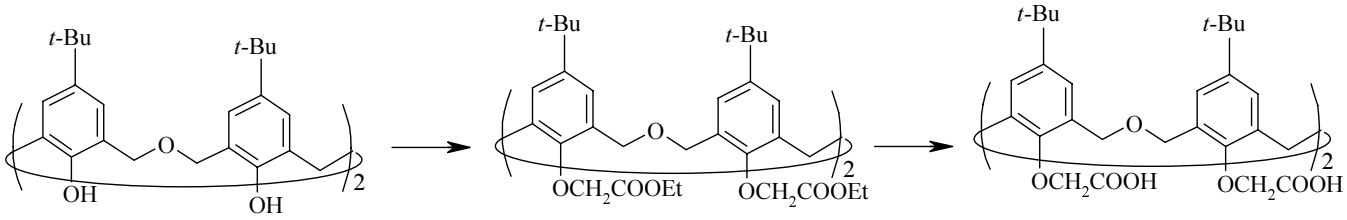
237–239

237, $X = (CH_2CH_2O)_3CH_2CH_2$, R = H;
238, $X = (CH_2CH_2O)_4CH_2CH_2$, R = H;
239, $X = (CH_2CH_2O)_4CH_2CH_2$, $R = CH_3$.



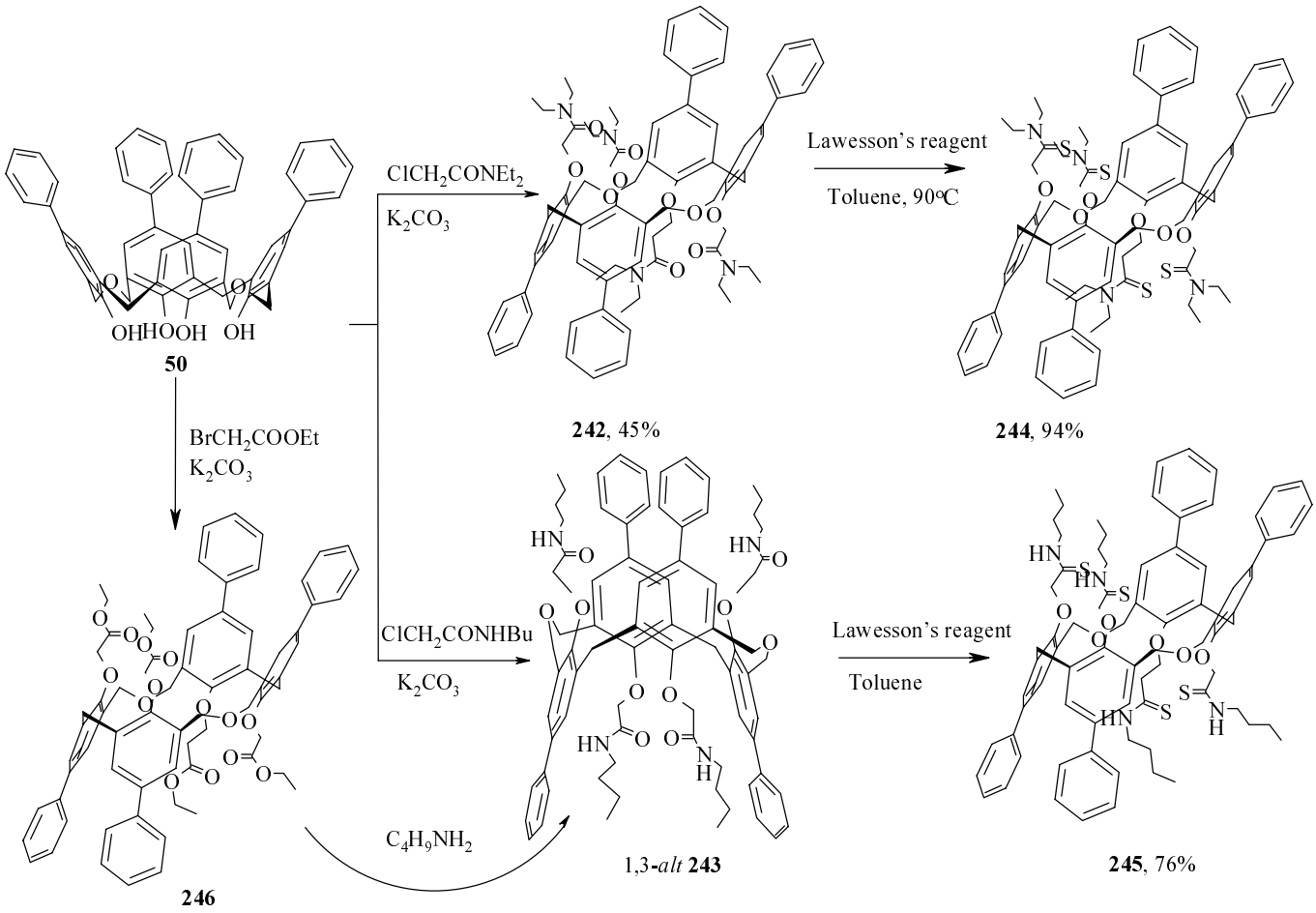
paco-**239**

Scheme 58.



48 **240** **241**

Scheme 59.



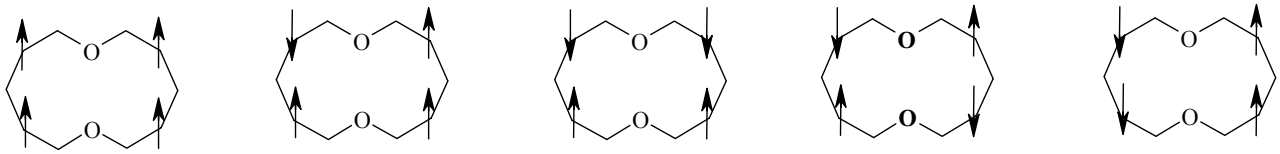
50 **242**, 45% **244**, 94% **246** 1,3-*alt* **243** **245**, 76%

acetamide afforded amide **242** in the 1,2-*alt* conformation which was retained at treating the amide with the Lawesson's reagent, and thioamide **244** also was present in the 1,2-*alt* conformation.

The reaction of oxacalixarene **50** with *N*-butylchloroacetamide gave in 6 h a mixture of 1,3-*alt* and 1,2-*alt* conformers of amide **243,** but in 12 h exclusively 1,3-*alt* conformer was isolated. The treatment of the latter with the Lawesson's reagent caused a reverse transformation of the conformer, and from 1,3-*alt*-**243** 1,2-*alt*- **245** was obtained. The sufficiently strong hydrogen bonds in the N-monoalkylamido derivative **243** apparently stabilize the 1,3-*alt* conformation. The change from 1,3-*alt* to 1,2-*alt* conformation in going from *N*-butylamide **243** to *N*-butylthioamide **245** is due apparently to weakening of the hydrogen bonds in the latter.

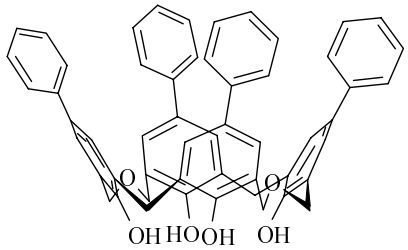
Amination with butylamine of 1,2-*alt* tetraethyl acetate **246** also gave rise to a mixture of two conformers, 1,3-*alt* (55%) and 1,2-*alt* (45%), of amide **243** within 6 h, and afforded conformer 1,3-*alt* in 24 h. The conformation

Scheme 60.



cone *paco* 1,2-*alt* 1,3-*alt* 1,4-*alt*

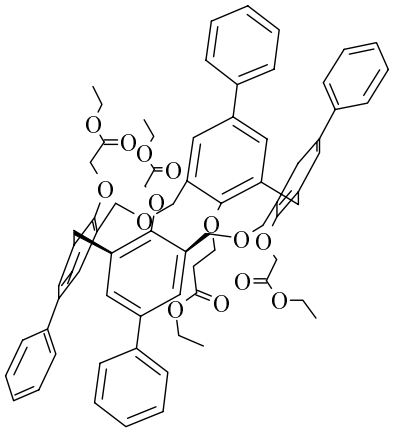
Scheme 61.



50

$BrCH_2COOEt$

K_2CO_3



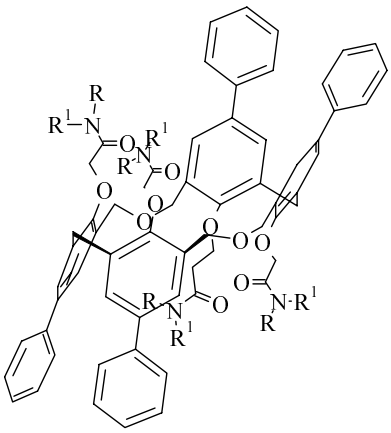
246

Ph_2NCOCH_2Cl,
CH_3CN, K_2CO_3, Δ

$C_5H_{11}NH_2$,
EtOH,PhMe, Δ

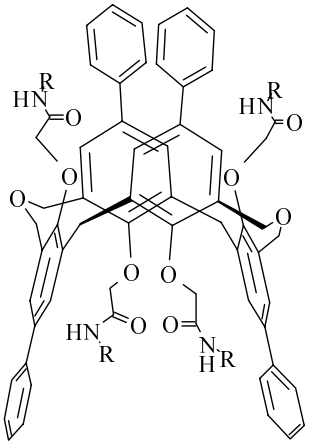
248, 45%

1,2-*alt* **247**, 22.5% + 1,3-*alt* **247**, 51%



1,2-*alt* **247, 248**

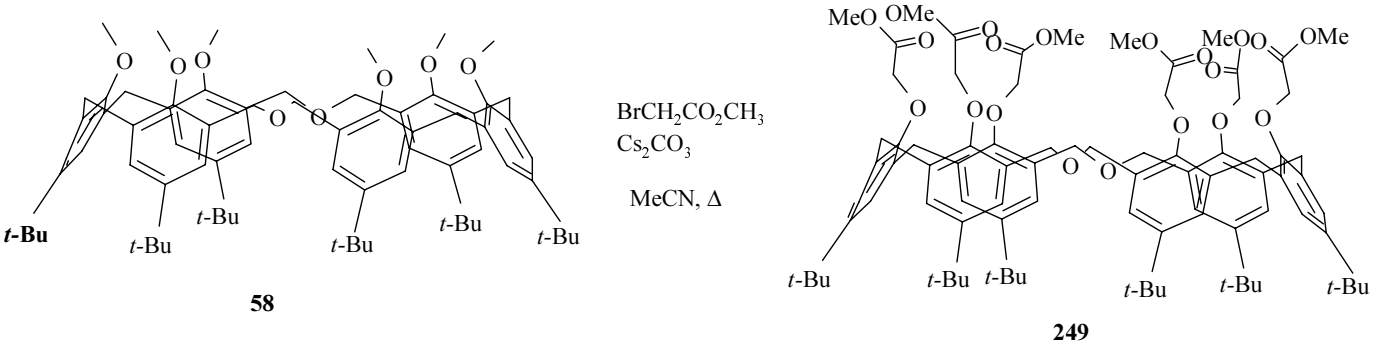
247, R = C_5H_{11}, R^1 = H;
248, R = R^1 = C_5H_{11}.



1,3-*alt* **247**

247, R = C_5H_{11}

Scheme 62.



58 **249**

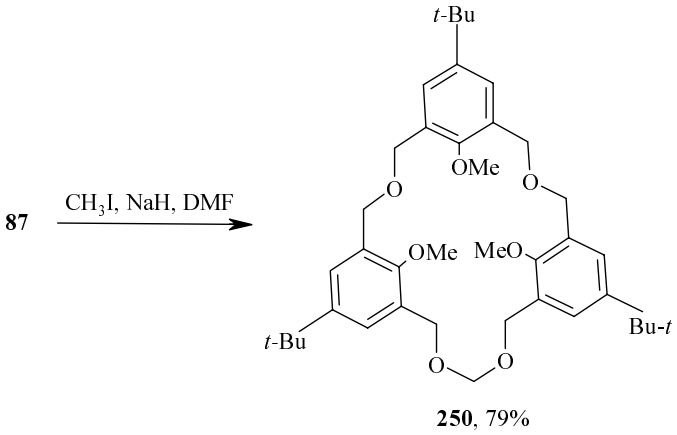
of the initial calixarene **246** did not changed at boiling in EtOH for 7 days.

The presence of intramolecular hydrogen bonds between amide NH groups and directed thereto CO groups in the crystal structure of compound **243** (Fig. 6) is proved by the corresponding crystallographic parameters: $N^1H\cdots O^5$ and $N^4H\cdots O^7$ distances are equal respectively to 2.08 and 2.01 Å, and angles N^1HO^5 and N^4HO^7 are169.8 and 176.8°.

A synthesis of *N*-monopentyltetraamides of tetrahomodioxa-4-phenylcalix[4]arene **247** in 1,2- and 1,3-*alt* conformatins and of *N,N*-dipentyltetraamide **248** in conformation 1,2-*alt* was carried out in 2003 [76]

It should be noted in conclusion that a total modification of the lower rim was performed also in dioxacalix[6]arene **58** [77] and in unususal tetraoxacalixarene **87** [30].

The spectral data are insufficient for unambiguous assignment of compound **249** conformation: it may be either *cone* or 1,2,3-*alt.* X-ray diffraction data for a single crystal of inclusion complex **249**·$2CHCl_3$ revealed the presence of a leveled 1,2,3-*alt* conformation.



250, 79%

4. CONCLUSION

The scope of data compiled in the present review proves the highest intensity of development in the field of calixarenes chemistry [78], compounds named "the third generation of hosts" [79], macrorings of " nearly unlimited opportunities" [2]. This research commenced from the "classic" calix[*n*]arenas with methylene bridges between aromatic fragments, and in the last decade these studies were extended to heterocalixarenes where as bridges between aromatic units served heteroatoms, sulfur or dihomooxa moieties. Thiacalixarene chemistry has been developed within the last 5–7 years [80]. As to homooxacalixarenes, the list of references to the present review evidences, that half of all publications has appeared within the latter five years, and two thirds within the last decade. The results obtained in the synthesis and modification of oxacalixarenes suggest that they are promising for preparation selective receptors for neutral molecules, metal cations and ammonium ions. The

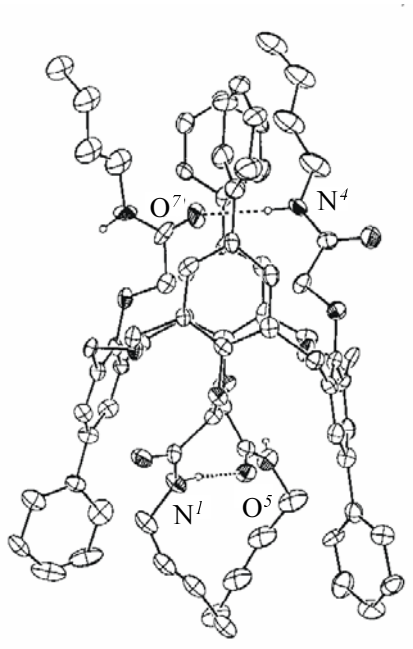


Fig. 6. Crystal structure of tetraamide **243.**

receptor properties of homooxacalixarenes will be treated in the next review.

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