



**Budapest University of Technology and Economics
Department of Organic Chemical Technology**

**Thiacalixarenes and the Mitsunobu reaction – new
perspectives for the synthesis of calix[4]crowns**

Ph. D theses

by:

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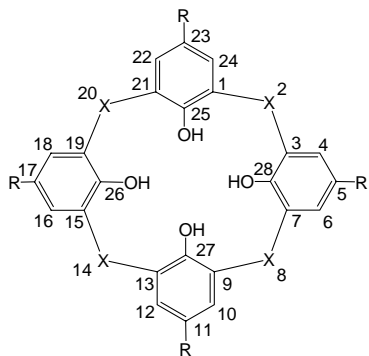
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Introduction

Calix[4]arenes and thiacalix[4]arenes are of cyclic tetramers of phenols containing methylene or sulfur bridges. The great number of calixarene derivatives is partly ascribed to the regio- and conformation selective reactions developed in the last decades. Among them the partial *O*-alkylation and acylation, along with aromatic nitration, halogenation, formylation, etc. of calix[4]arenes provide important synthetic tools for designing supramolecules of great variety. Similar regioselective reactions, at least with the same efficiency, have not been found in thiacalixarene chemistry. The lack of regio- and stereoselectivity in the weak base (K_2CO_3 , Et_3N) mediated partial *O*-alkylation and acylation reactions of thiacalix[4]arenes can be attributed to the substantially less differences between the hydroxyl acidities and the 15% larger cavity comparing with the calixarene counterpart.



R	X	
Bu ^t	S	1a
H	S	1b
Bu ^t	SO	1c
H	SO	1d
Bu ^t	SO ₂	1e
H	SO ₂	1f
Bu ^t	CH ₂	2a
H	CH ₂	2b

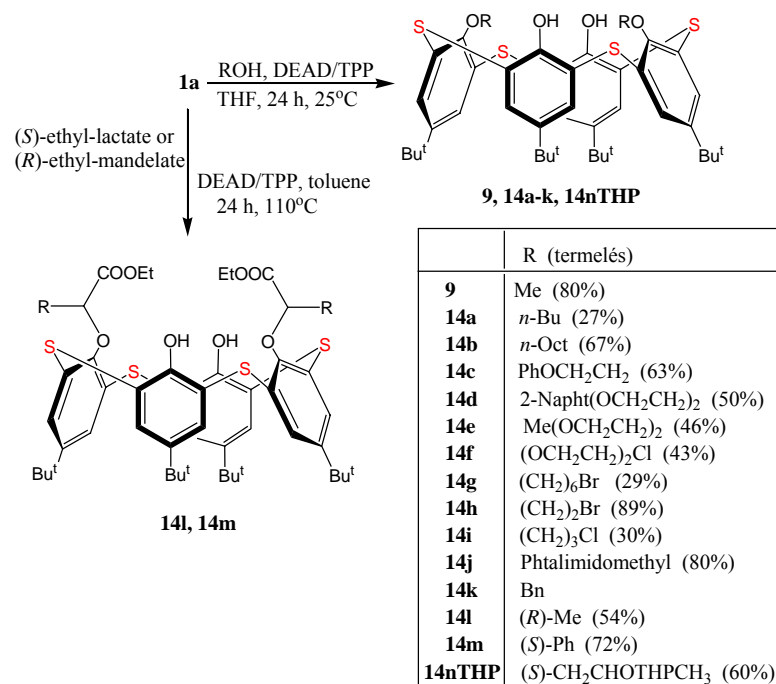
Among calixarene derivatives, calix[4]crowns have attracted great interest due to their exceptionally selective cation complexing ability, which can be influenced by the conformation of the calixarene core. At the beginning of my work the relating thiacalix[4]crowns have not been described yet, therefore we focused on the synthetic availability of these novel macrocycles. It has turned out soon, that the traditional base-promoted ring closures applied successfully in calixarene chemistry cannot operate with the thia counterpart, therefore new alkylation method has to be found to achieve our goal. The Mitsunobu reaction was expected to fulfill the selectivity requirements, thus my work was mainly devoted to explore its utility in thiacalixarene chemistry.

Results

1. Thiacalix[4]bis(crown-5, and 6)ethers were synthesized by the cyclization of thiacalix[4]arenes with tetra- and pentaethylene glycol derivatives in the presence of alkali carbonates and revealed that the reaction does not stop at monocrown level. The latter were prepared from 1,3-thiacalix[4]diethers by the same method. The complexing abilities of ligands were determined by alkali (Li^+ , Na^+ , K^+ , Rb^+ , Cs^+) picrate extraction method and found these mono- and bis(crown-6) derivatives exhibited excellent cesium selectivities,

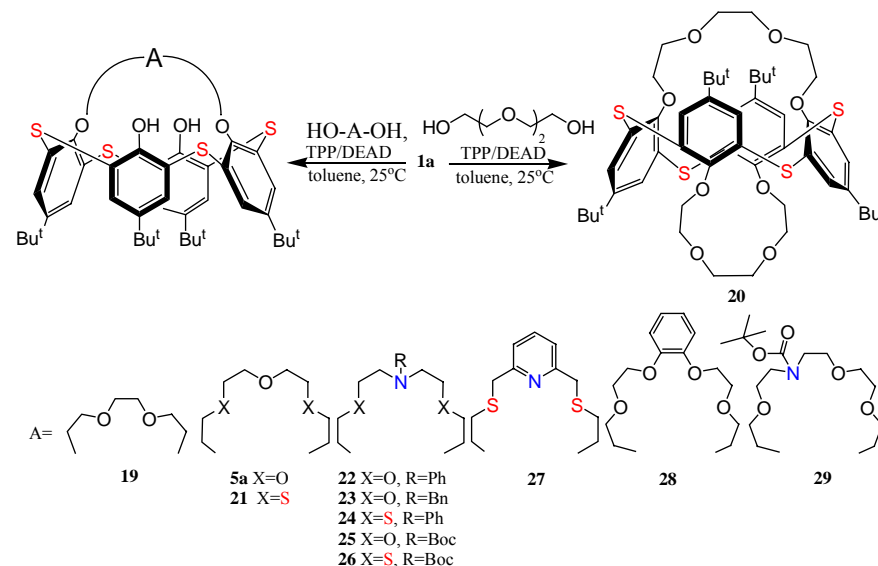
suitable for analytical purposes as ion-selective potentiometric PVC membrane electrodes.

2. The selective 1,3-di-*O*-alkylation of *p*-*tert*-butylthiacalix[4]arene with a series of alcohols was demonstrated for the first time under the Mitsunobu protocol and the method was expanded to the synthesis of tetraethers.

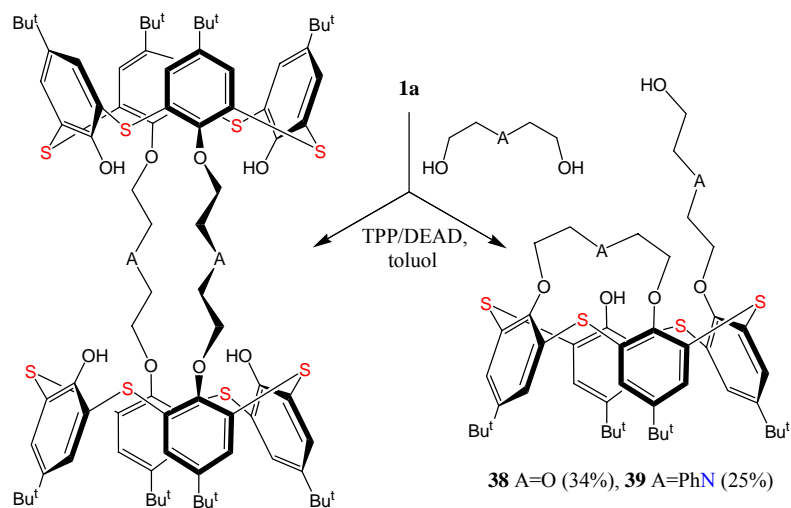


3. The first regioselective cyclization of *p*-*tert*-butylcalix[4]arenes with oligoethylene glycols was accomplished under Mitsunobu

protocol and a mechanistic pathway was suggested to describe the outcome of the reaction. The scope of cyclisation was expanded to a series of aza- and thia analogues, and a number of novel 1,3-thiacalix[4]aza- and/or thiacrowns were synthesized.



4. I have synthesized for the first time *p*-*tert*-butylthiacalix[4]dimers by the Mitsunobu coupling of *p*-*tert*-butylthiacalix[4]arene and diethylene glycols. Depending on the glycol used dimers and/or the inherently chiral 1,2-thiacalix[4]crown-3 derivatives were formed.

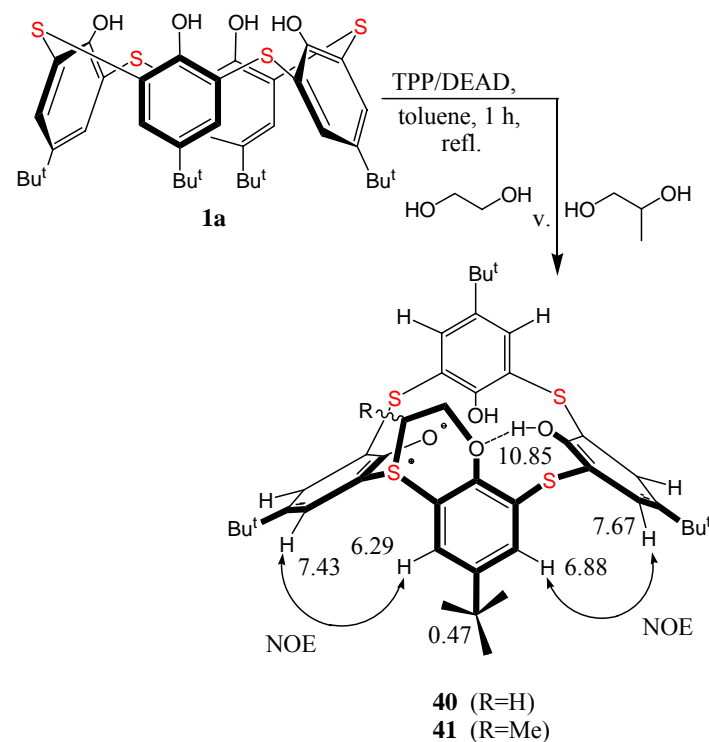


The enantiomeric separation of the 1,2-thiacalix[4]mono(phenylazacrown-3) derivative was achieved by chiral HPLC and the CD spectra of the fractions confirmed their enantiomeric nature.

5. On the basis of the products obtained in the reactions of calix[4]arene and thiacalix[4]arene with several long chained 1,*n*-diols I have established that the regioselectivity of cyclizations described in thesis points 3. and 4. depends on the intramolecular distances of the reactive groups in the open chained betaine intermediate formed after the first alkylation step. The different behaviour of calix[4]arene and its thia analogue can be attributed to

the difference in the ring size of the macrocycles and to the acidity of the hydroxyl groups.

An unprecedented *O,S*-cyclization was observed in the Mitsunobu reaction of *p*-*tert*-butylthiacalix[4]arene and 1,2-diols affording the unique sulfonium phenoxide betaines **40,41** and their structure was elucidated by NMR and chemical methods.



6. Efforts have been made to synthesize thiacalix[4]tubes i.e. dimers containing terminal crown rings which may be mimetics of the iontransport in cell membranes. All attempts with the Mitsunobu coupling and with base-mediated cyclizations of dimers or monocrowns failed, instead half-crowned dimers or 1,3-*alt* biscrowns were formed. Therefore, the reactivity of the hydroxyl groups in dimers was studied in base-promoted exhaustive alkylations and found that in most cases only partially alkylated products were formed with different stereoselectivity.

7. A part of the macrocycles was further transformed to ionophores (with or without chromogenic function) and preliminary binding studies were carried out to estimate the ion-sensing properties by ¹H NMR, UV/VIS spectroscopic and potentiometric methods.

We found that ligands with cyclic *O*₂*S*₂*N* binding site recognise soft metal ions such as Ag⁺, Hg²⁺, Zn²⁺, Cu²⁺.

8. I have synthesized thiacalix[4]monocrown-6 based cesium ionophore which can be immobilized by chemisorption on the surface of a gold plate. The sensor fabricated from these ligands are expected to eliminate the problems of the classical membrane

technics, providing at the same time variable possibilities for the analytical detection.

Publications

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2. István Bitter, Zsolt Török, Viktor Csokai, Alajos Grün, Barbara Balázs, Gábor Tóth, György M. Keserű, Zoltán Kovári, Mátyás Czugler.: Synthesis and conformational analysis of dicationic N,N'-bridged bis(benzimidazolium) and bis(imidazolium) macrocycles, *European Journal of Organic Chemistry*, **2001**, *15*, 2861.

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2. Csokai Viktor, Grün Alajos, Parlagh Gyula, Bitter István: Mono- és bisz-tiakalix(korons) ionoforok előállítása és ionszelektivitásuk vizsgálata, Magyar Kémikusok Egyesülete, XXV. Kémiai Előadói Napok, Szeged, 2002, október 28-30.

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4. Csokai Viktor, Bitter István: Szelektív reakciók a tiakalix[4]arének körében, Budapesti Műszaki és Gazdaságtudományi Egyetem, Vegyészmérnöki Kar Ph.D. iskolájának konferenciája, Budapest, 2003, november 26.