

MODIFICATION OF P-ISOPROPENYLCALIX[4]ARENE WITH AMINO COMPOUNDS

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ABSTRACT

The cyclic *p*-isopropenylcalix[4]arene, recently obtained, possesses a reactive double bond in the *p*-isopropenyl substituent. This enables the easy modification of its structure at the upper rim. The present study traces out the possibility for modification of *p*-isopropenylcalix[4]arene with ethylenediamine and cysteamine hydrochloride (2-aminoethanethiol hydrochloride). The reactions were performed via: 1) an electrophilic addition in the presence of *p*-toluene sulphonic acid (PTSA); 2) a radical mechanism in the presence of benzoyl peroxide (BP) or azobisisobutyronitrile (ABIN). It has been established that a fully modified *p*-isopropenylcalix[4]arene is obtained in the presence of BP and ABIN. The obtained products were characterized by gel permeation chromatography, IR, UV and ¹H NMR spectroscopy.

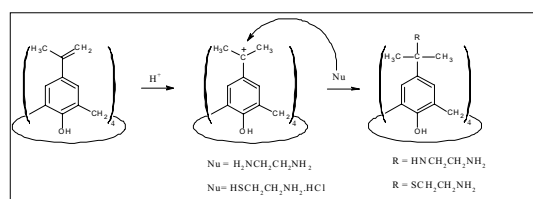
Keywords: *p*-isopropenylcalix[4]arene, modification, ethylenediamine, cysteamine hydrochloride.

INTRODUCTION

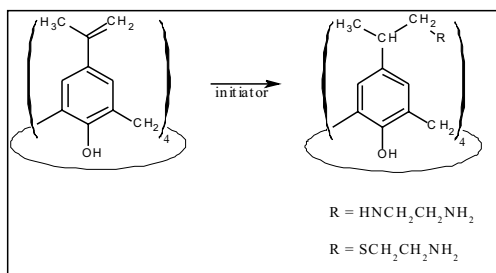
Calixarenes are synthetic macrocyclic compounds derived from the condensation of *p*-substituted phenols and formaldehyde [1]. They can be comprised of different number of aromatic units in the cyclic array. Recently a subject of great interest is the use of calixarenes as building blocks in supramolecular chemistry, for the construction and synthesis of biomimetic receptors [2 - 4].

In contrast to the widely studied *p*-tert-butylcalixarenes [1], *p*-isopropenyl-calixarenes are a novel class of calixarenes, which have a *p*-isopropenyl group at the upper rim. This group contains a double bond, which is conjugated with the aromatic ring. This enables to modify them readily with different compounds. A possible route for selective change of the structure and the properties of these calixarenes is the

modification of the double bond in the isopropenyl substituent via electrophilic addition reaction. The most suitable for the purpose are acids as electrophilic agents. They are able to initiate reaction at the double bond [5]. The reaction will be carried out according to accepted mechanism – an initial electrophilic attack followed by nucleophilic addition:



Alternative route to initiate the reaction at the double bond is the use of BP or ABIN. The reaction follows the radical mechanism [6]:



In previous research the possibility for electrophilic addition of poly(ethylene glycol) to p-isopropenylcalix[n]arenes in the presence of different acidic catalysts has been investigated. A full modification of all p-isopropenyl groups in the macrocyclic products had not been achieved [7]. That is why the investigations were focused on the possibility to add ethylenediamine and cysteamine hydrochloride at the upper rim of p-isopropenylcalix[4]arene in the presence of a catalyst or an initiator.

The aim of this research was to obtain a fully modified p-isopropenylcalix[4]arene at the upper rim, containing terminal reactive amino groups that are able to undergo chemical modification. This compound can be used as a building block for the construction of amino acids calixarene structures in the future experiments.

EXPERIMENTAL

Method for modification of p-isopropenylcalix[4]arene with amino compounds in the presence of different initiating agents

2 g (3.42 mmol) of p-isopropenylcalix[4]arene dissolved in 20 ml ethanol and the corresponding amino compound [0.82 g (0.014 mol, 0.91 ml) ethylenediamine or 1.56 g (0.013 mol) cysteamine hydrochloride dissolved in 5 ml water] were put into a 100 cm³ three-necked flask, equipped with a reflux condenser and a thermometer. Then a catalyst - p-toluene sulphonic acid (PTSA) – in amount 4 mol % per mol calixarene, or an initiator [benzoyl peroxide (BP), azobisisobutyronitrile (ABIN)] - 1 mol % per mol calixarene were added to the mixture. The reaction mixture was heated at the b. p. under stirring for 6 hours. After that it was poured in icy water in 10-fold excess. The precipitate obtained was filtered off and dried under vacuum at 40°C.

Analysis

¹H NMR spectra were recorded on a Bruker spectrometer (TMS was used as an internal standard) at 400

MHz. The IR spectra were recorded with a Perkin-Elmer 1600 Spectrophotometer in KBr pellets. The UV spectra were recorded with a Waters 991 photodiode array UV detector equipped with a data station at $\lambda = 190\text{--}400$ nm. Gel permeation chromatography (GPC) data were obtained with a Waters system using a Waters 484 UV detector and a Waters 410 differential refractometer. The separation was performed with “Plgel” columns 300x6.9 mm large and pore sizes 500 Å. THF was used as an eluent at 0.5 ml min⁻¹ elution rate and at 45°C. The calibration was performed with p-cresol standards, synthesized for the purpose, at 254 nm UV detection.

RESULTS AND DISCUSSION

The p-isopropenylcalix[4]arene subjected to modification was obtained from the cyclization of p-isopropenylphenol and paraformaldehyde according to a procedure described in [8]. The initiation of the reaction at the double bond was performed with different agents: PTSA (4 mol %), BP (1 mol %) and ABIN (1 mol %). The optimum of their quantity had been established in our previous research. Ethylenediamine and cysteamine hydrochloride (2-aminoethanethiol hydrochloride) were used as reagents.

Modification of p-isopropenylcalix[4]arene with ethylenediamine

The products obtained from the reaction of p-isopropenylcalix[4]arene with ethylenediamine in the presence of different initiating agents were first characterized by GPC.

The GPC chromatograms (Fig.1) and molecular mass characteristics (Table1) revealed that irrespective of the nature of the initiating agent used products with similar molecular masses and narrow molecular mass distributions (D) are obtained, but a maximum yield (99 %) is observed when BP is used as initiator.

In the infrared spectra of these products absorption bands at 3368 (OH, NH₂), 2870-2927 (ArC-H, C-H), 1611 (ArC=C), 1496-1477 cm⁻¹ (-CH₂-, -CH₃) are observed. They are similar to the IR spectrum of p-isopropenylcalix[4]arene but a main difference is that the band at 1656 cm⁻¹ (>C=CH₂) is not present (Fig. 2).

The absorption band at $\lambda = 256$ nm, which is typical of the double bond in >C=CH₂ group is missing in the UV spectra of the products. On the basis of

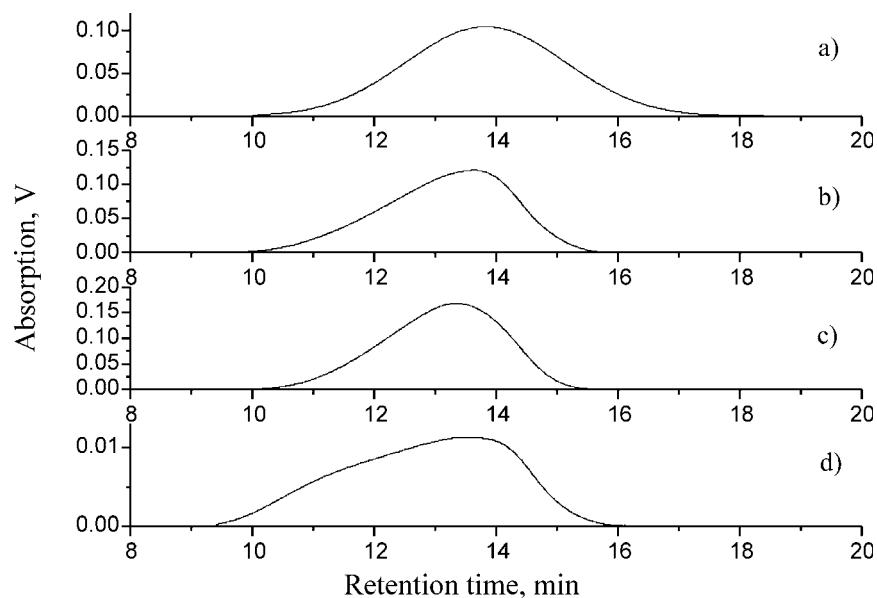


Fig. 1. Gel permeation chromatograms of: a) p-isopropenylcalix[4]arene; p-isopropenylcalix[4]arene modified with ethylenediamine obtained in the presence of: b) 1 mol% ABIN; c) 1 mol% BP; d) 4 mol% PTSA.

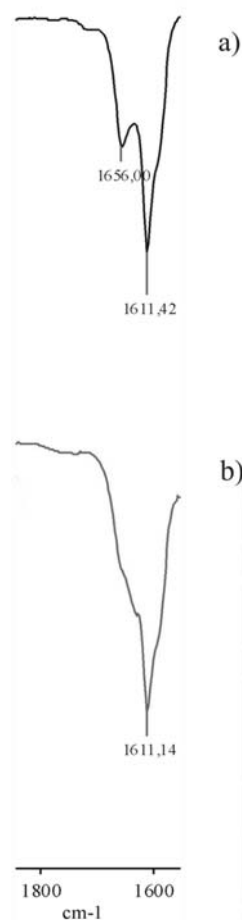


Fig. 2. Partial IR spectra of: a) p-isopropenylcalix[4]arene; b) p-isopropenyl-calix[4]arene modified with ethylenediamine.

Table 1. Molecular mass characteristics of p-isopropenylcalix[4]arene modified with ethylenediamine.

Initiating agents	Modified p-isopropenylcalix[4]arene		
	Mn, Da	Mw, Da	D
4mol% PTSA	827	914	1.1
1mol% ABIN	812	974	1.2
1mol% BP	830	913	1.1

Table 2. Molecular mass characteristics of p-isopropenylcalix[4]arene modified with cysteamine hydrochloride.

Initiating agents	Modified p-isopropenylcalix[4]arene		
	Mn, Da	Mw, Da	D
4mol% PTSA	666	725	1.1
1mol% BP	847	1007	1.2
1mol% ABIN	832	980	1.2

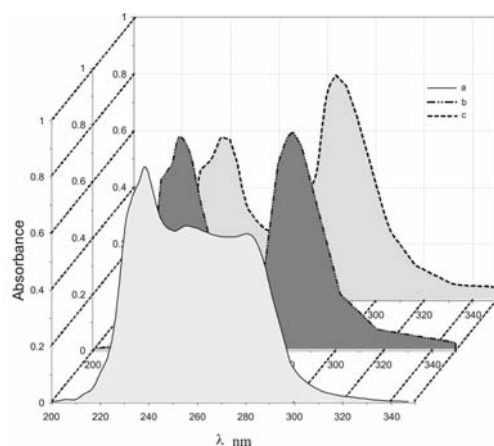


Fig. 3. UV spectra of: a) p-isopropenylcalix[4]arene; p-isopropenyl-calix[4]arene modified with: b) ethylenediamine; c) cysteamine hydrochloride.

this we suggest that a full modification of the double bonds in the isopropenyl groups has been accomplished. Our suggestion is supported by the UV and ^1H NMR spectra of 5,11,17,23-tetra-p-(2'-[(2''-aminoethyl)amino]-1'-methylethyl)-25,26,27,28-tetrahydroxy-calix[4]arene (1), which was obtained with an initiator BP (Fig. 3b and Fig. 4b).

In the ^1H NMR spectrum of 1 the pronounced multiplet at δ 4.38-4.47 ppm characteristic of the protons from the $>\text{C}=\text{CH}_2$ group is not observed (Fig.4). The resonance of the methylene protons (ArC_2Ar) appears at δ 4.40-4.44 ppm (*Hax*) and 3.45-3.50 ppm (*Heq*), as a pair of doublets. The singlet arising from the hydroxyl protons shifts from 9.2 to 8.31 ppm. The peaks at δ 4.29 ppm and δ 7.83 ppm – typical of the protons of $-\text{NH}-$ and $-\text{NH}_2$ groups, as well as multiplets at δ 2.67 ppm and δ 2.95 ppm from the methylene protons of $-\text{CH}_2-\text{NH}_2$ and $-\text{CH}_2-\text{NH}-$ groups represent another proof that an addition reaction has successfully been carried out.

Modification of p-isopropenylcalix[4]arene with cysteamine hydrochloride

From the GPC chromatograms (Fig.5) and molecular mass characteristics (Table2) of the obtained products was established that the results are analogical to those when ethylenediamine was used. The main distinction is that when PTSA was used as catalyst a product with lower molecular mass (666 Da) is obtained; corresponding to a partially modified calixarene connected with one or two molecules cysteamine hydro-

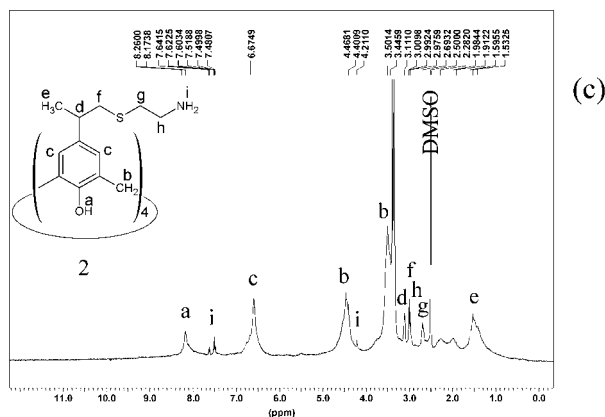
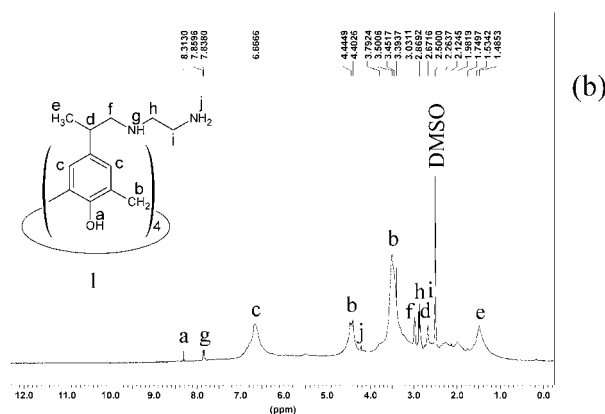
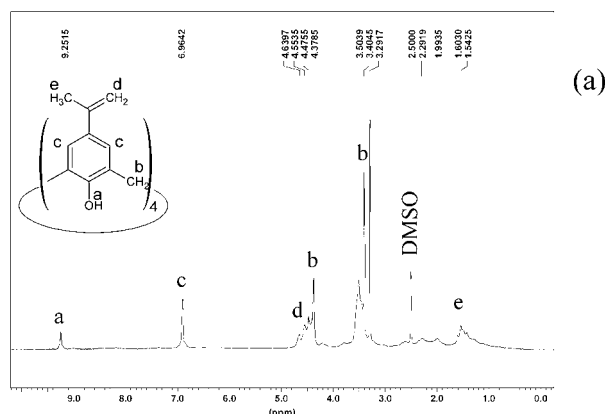


Fig.4. ^1H NMR spectra of: a) p-isopropenylcalix[4]arene; modified p-isopropenyl-calix[4]arene with: b) ethylene diamine; c) cysteamine hydrochloride.

chloride. In this instance it was found that BP and ABIN are more effective to initiate the reaction at the double bond than PTSA.

In the IR spectra of the products obtained characteristic bands at 3368 (OH, NH_2), 2927 ($\text{ArC}-\text{H}$, OH-

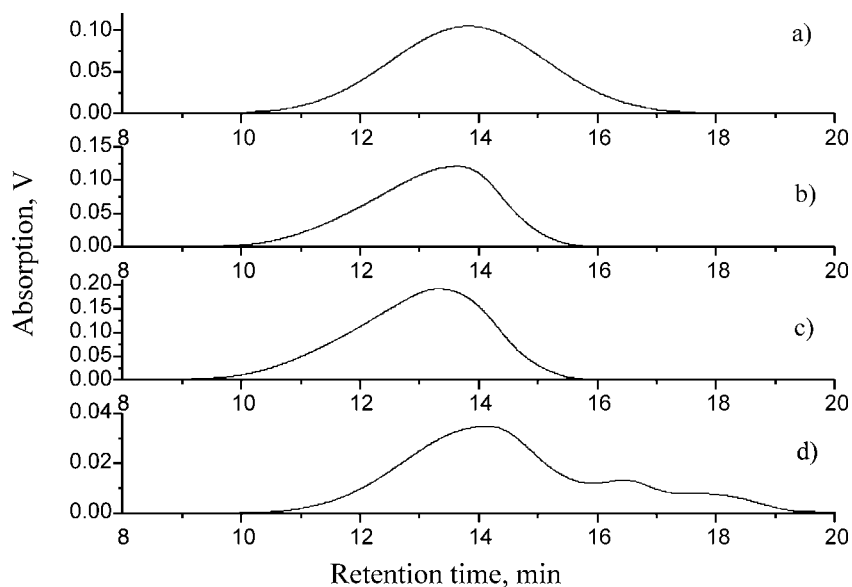


Fig. 5. Gel permeation chromatograms of: a) p-isopropenylcalix[4]arene; p-isopropenylcalix[4]arene modified with cysteamine hydrochloride obtained in the presence of: b) 1 mol % BP; c) 1 mol % ABIN; d) 4 mol % PTSA.

C-H), 2346 (-SH-), 1611 (ArC=C), 1496-1477 cm^{-1} (-CH₂-, -CH₃) were observed. The band at 1656 cm^{-1} (>C=CH₂) is not observed. In the UV spectra of the products obtained in the presence of initiator, analogically to the spectra discussed above lacks the absorption band at $\lambda = 256$ nm, typical of the >C=CH₂ double bond. In confirmation of that UV and ¹H NMR spectra of 5,11,17,23-tetra-p-{2'-(2"-aminoethyl)thio}-1'-methylethyl}-25,26,27,28-tetrahydroxy-calix[4a]rene (2), obtained with an initiator BP, are presented on the Fig.3c and Fig. 4c. The main absorption bands of 2 at $\lambda = 238$ and 282 nm are similar to 1. They are distinguished from these of the initial p-isopropenylcalix[4]arene (Fig.3). The lack of the pronounced multiplet from the protons of >C=CH₂ group at δ 4.38 - 4.47 ppm, as well as the presence of signals at δ 2.69, 2.97-3.01, 3.11 ppm arising from the methylene protons of -CH₂-NH₂-, -CH₂-S-, -S-CH₂-, -CH- groups in the ¹H NMR spectrum of 2 (Fig. 4c) demonstrate that all p-isopropenyl groups are fully modified.

Thus modified p-isopropenylcalix[4]arenes (1 and 2) containing four terminal reactive amino groups could be used in future experiments as a "platform" for binding of amino acids or for construction of a spatial branched structure.

CONCLUSIONS

The possibility for modification of p-isopropenylcalix[4]arene at the upper rim with ethylenediamine and cysteamine hydrochloride in the presence of different initiating agents has been investigated. It was established that a fully modified p-isopropenylcalix[4]arene is obtained when an initiator was used.

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