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Optimization of reaction conditions for synthesis C-tetramethylcalix[4]resorcinarene

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A new alternative method for the synthesis of calix[4]resorcinarenes has been shown. The optimal parameters for obtaining a C-tetramethylcalix[4]resorcinarene as a representative of the class of calix[4]resorcinarenes have been determined by varying the reaction conditions. It has been demonstrated that cyclic products can be prepared under certain conditions using catalytic amounts of mineral acid. It has been found that *cis-cis (rccc)* and *trans-trans* (rttt) isomers of C-tetramethylcalix[4]resorcinarene can be synthesized selectively by changing the ratio of water-organic phase, i.e. by changing the polarity of the medium. The reaction products have been separated using semi preparative liquid chromatography and characterized by gel permeation chromatography (GPC), nuclear magnetic resonance (^{1}H NMR), ultraviolet (UV) and fourier transform infrared (FTIR) spectroscopy.

Key words: C-tetramethylcalix[4]resorcinarene, polycondensation, resorcinol, acetaldehyde

INTRODUCTION

Resorcinarenes, the cyclic compounds belonging to calixarenes group are products of a polycondensation reaction between resorcinol and acetaldehyde (Figure 1) [1–9]. The presence of two hydroxide groups in the benzene rings, forming the macro cycle determines their relatively easy participation into large number of chemical interactions. Recently there has been a growing interest in the use of resorcinol based calixarenes and especially the calix[4]resorcinarene that have proved to be valuable for many applications in chemistry, biology and medicine [10–12].

Usually the synthesis of calix[4]resorcinarene is carried out by acid activated polycondensation in the presence of mineral acids and various alcohols. Concentrated hydrochloric acid in equimolar quantities to other reagents is the most used catalyst. Isolation of final cyclic products has been done through different approaches ranging a practical yield. Some authors reported for preparation of isolated products of relatively high yields in the presence of acid as a catalyst and in the presence of adequate solvents (methanol, ethanol) [13–15]. Reported reaction conditions (temperature, reaction time, sequence of reagents addition, etc.) have been varied widely, which leads to contradictory conclusions.

Therefore the aim of the present work is to investigate and optimize the route to the synthesis of C-tetramethylcalix [4]resorcinarene.

The effect that the catalyst amount has on polycondensation and subsequent cyclization of oligomeric products has been traced in the course our research. The influence of the polarity of the medium on product composition has been also investigated. A procedure for optimization the isolation of cyclic products has been worked out as well.

EXPERIMENTAL

Materials

The reagents were purchased from Fluka (resorcinol and acetaldehyde), Merck (hydrochloric acid (37%)) and Lab-Scan (ethanol (96%), methanol, tetrahydrofurane (THF)).

Syntheses

Syntesis of calix[4]resorcinarene in ethanol medium using different amount of catalyst. The synthesis was performed according to methodology analogous to the one suggested by Ito and coworkers [16].

Resorcinol 15,46mmol (1,71g) and 20ml of ethanol were placed into a two-necked flask fitted with a reflux condenser and stirrer. The mixture was homogenized till complete dissolving of the resorcinol. The solution was placed into an ice bath and 15.46mmol (0,86ml) of acetaldehyde in 10ml of ethanol were added in a separating funnel for 10min. Then the required amount of hydrochloric

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acid (0.01 – 30.15 mmol) was added taking care that the temperature of the reaction medium did not increase highly. Having added the catalyst the reaction solution was heated at 75ºC for 5 to 24h. Then the resulting mixture was cooled to room temperature. The precipitate formed was filtered, washed with hot water (to neutral pH of washing water fractions) and dried under vacuum at 40ºC.

Synthesis of calix[4]resorcinarene in ethanol/water medium using catalytic amount of hydrochloric acid. A series of syntheses was conducted using the optimal catalytic amounts of hydrochloric acid found experimentally and varying the ratio of ethanol/water in the reaction medium.

Resorcinol 0,3 mol (33,03g), 0,3mol (13,23ml) acetaldehyde and 120 ml ethanol/water mixture of different ratios were placed into a two-necked flask fitted with reflux condenser and stirrer. Acid catalyst (4 mol % compared to the other reagents concentrated hydrochloric acid) was added to the homogenized solution. The reaction solution was heated at 75ºC under stirring for at least 1h. Then the resulting mixture was cooled to room temperature. The precipitate formed was filtered and recrystallized from methanol/water (v/v=50/50) solution. The reaction products were isolated using semi preparative liquid chromatography and characterized by GPC and ^{1}H NMR.

Instrumentation

Gel permeation chromatography (GPC). GPC experiments were performed on a chromatography line consisting of a tunable absorbance detector M 484, a differential refractive index detector M 410 (all Millipore Co., Waters Chromatography Division), a U6K universal injector and a set of three UltraStyragel gel columns (Waters) with nominal pore sizes of 100Å, 500Å and linear. THF was used as an eluent at 45^{o}C and a flow rate of 1.0 ml.min^{-1}. Molecular weight characteristics were calculated using a calibration curve constructed with monodisperse poly(vinylpyridine) standards on a station for collection and processing of data through Clarity software. 1,3-dihydroxybenzene was used as an internal standard.

High-performance liquid chromatography (HPLC). The chromatograms were taken on a HP 1100 chromatography line (Agilent Technologies) equipped with a diode array UV detector, and a Kinetex C18 column with 2.6 pore size. Acetonitrile/water (68/32 v/v) mixture was used an eluent at 30^{o}C and a flow rate of 0,7 ml.min^{-1}.

Semi preparative liquid chromatography. The chromatographic separation was achieved on a chromatography line consisting of M501 pump, a tunable absorbance detector M 490 (all Millipore Co., Waters Chromatography Division), a U6K universal injector and a semi preparative chromatographic column "µBondapak"C18 with a nominal pore size of 10 µm. A mixture of acetonitrile (A)/methanol (B)/phosphoric acid (0.5% water solution) (C) was used as an eluent. The samples were separated by running a linear gradient scheme as shown in Table 1.

Table 1. Gradient elution scheme

Time, (min)	Solvent mixture, %		
	A (%)	B (%)	C (%)
0	20	20	60
6	30	30	40
10	60	10	30
20	60	40	0
30	20	20	60

Ultraviolet spectroscopy (UV). UV spectra of the samples were recorded on a HP 1100 chromatography line (Agilent Technologies) equipped with a diode array UV detector in the course of chromatographic studies.

Fourier transform infrared spectroscopy (FTIR) Infrared spectra of the samples were recorded on a Bruker Vector 22 FT-IR spectrometer using potassium bromide pellet technique.

Nuclear magnetic resonance spectroscopy (^{1}H NMR). ^{1}H NMR spectrs were recorded on a Bruker Avance DRX 250 (250 mHz) instrument. The samples were dissolved in deuterated solvent (dimethyl sulfoxide-d$_6$). Trimethylsilane was used as an internal NMR standard.

RESULTS AND DISCUSSION

Influence of catalyst amount on the yield of the reaction products

The reaction of polycondensation of resorcinol and acetaldehyde was carried out with different amounts of hydrochloric acid as a catalyst (0,01 to 1,00 mol per mol phenolic compound). It was found that reaction products of different composition and amount are obtained depending on the amount of hydrochloric acid used as shown on Figure 1. Increasing the acid amount (up to equimolar) led to a higher content of higher molecular weight linear oligomeric products (Figure 1a). That became an obstacle to obtaining cyclic products in the next stage of the process. Using a catalytic amount of catalyst resulted into the formation of predominantly cyclic product (Figure 1b).

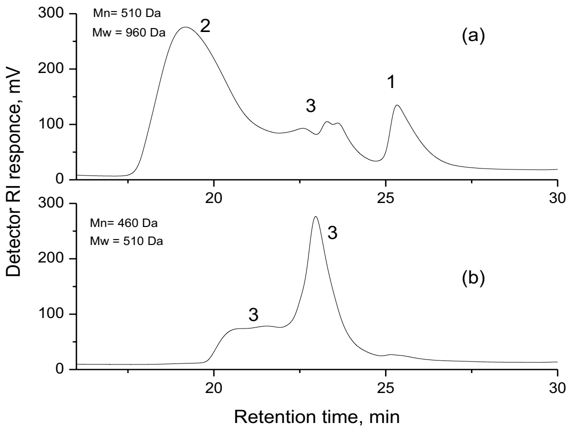


Fig. 1. GPC chromatograms of products obtained at 24h reaction time of polycondensation process catalyzed by hydrochloric acid: a) 1.0 mol per mol phenolic compound; b) 0.04 mol per mol phenolic compound (1- low molecular weight oligomers; 2- high molecular weight oligomers; 3- cyclic products.

Therefore, it was interesting to determine the minimum effective catalyst amount whereupon the reaction of polycondensation and oligocyclization proceeded at a comparable rate. Under the selected reaction conditions (see experimental section) a maximum yield of cyclic product was obtained with about 0,04 mol hydrochloric acid per mol phenolic compound as illustrated in Figure 1b. Further studies were preformed with that ratio.

Influence of medium polarity on the yield and composition of the reaction products

Our previous investigations as well as data in the literature demonstrated the influence that polarity of reaction medium had on the composition of the polycondensation products obtained [10].

To determine the effectiveness of influence of medium polarity on the yield and composition of the reaction products the ethanol/water ratio was varied in a wide range – from pure ethanol to neat water solutions. Dielectric constant was used as an effective feature for the polarity of the medium. According to the literature [16–21] the dependence changes linearly with a change of ethanol or water in their mixtures. This dependence can be illustrated with the average values varying in the range of 3–5 units as shown in Figure 2. The reduction of the amount of ethanol in the reaction medium increases its polarity.

The polycondensation process performed in the span of 24 h was monitored by GPC technique. Due to the strong reactivity of resorcinol the polycondensation process begins almost immediately upon reaching 75ºC. Reaching this temperature is considered to be conditional zero of the reaction. At this moment the products of different molecular weight are already formed as seen in Figure 3a. Their fractional composition changes with increasing the reaction time.

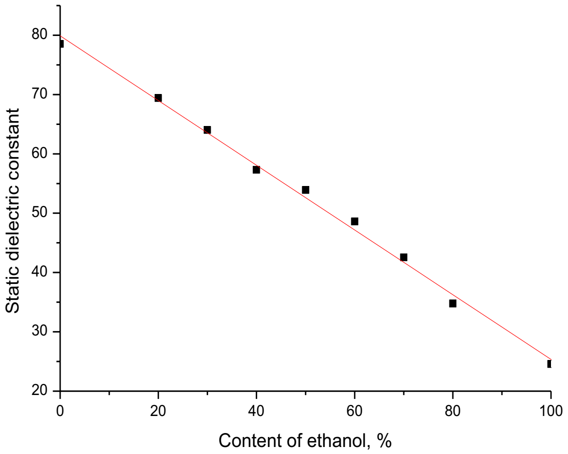


Fig. 2. Plot of the dielectric constant versus ethanol content in ethanol / water mixture (constructed on data cited in [16-21]).

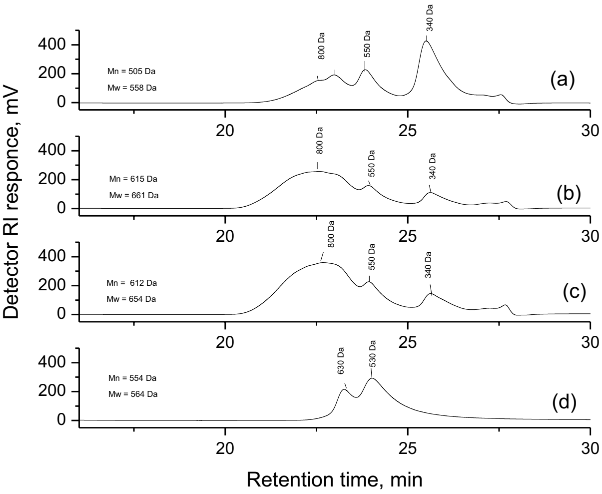


Fig. 3. GPC traces of reaction products obtained with hydrochloric acid (0.04 mol/mol phenolic compound) in ethanol/water mixture (20/80 v/v) at temperature 75°C for reaction time as follows: a) 0h; b) 2h; c) 5h; d) 24

Semi preparative liquid chromatography of reaction mixtures is used to clarify the mechanism of the polycondensation process as well as to define the products obtained. The fractionation of the products obtained at conditional zero and at 24 h reaction time was carried out. The fractions collected were analyzed by GPC chromatography and ^{1}H NMR spectroscopy as shown in Figure 4 and Figure 5, respectively.

It was found fractions of molecular weight of about 200, 340, 550 Da and those within range 800-

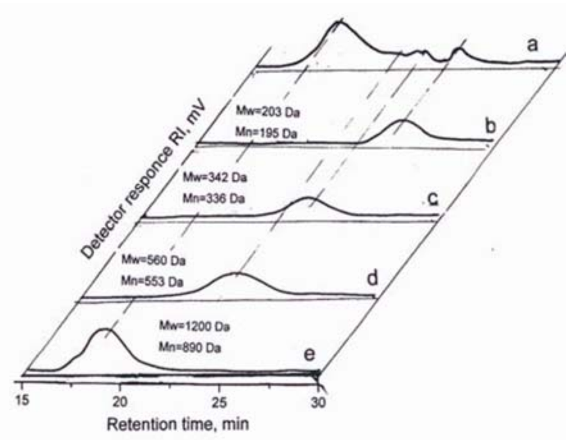


Fig. 4. GPC traces of reaction products obtained with hydrochloric acid (0.04 mol/mol phenolic compound) in ethanol/water mixture (30/70 v/v) at 75°C for 20h reaction time (a) and of fractioned products (b), (c), (d), (e) separated and isolated by semi preparative liquid chromatography.

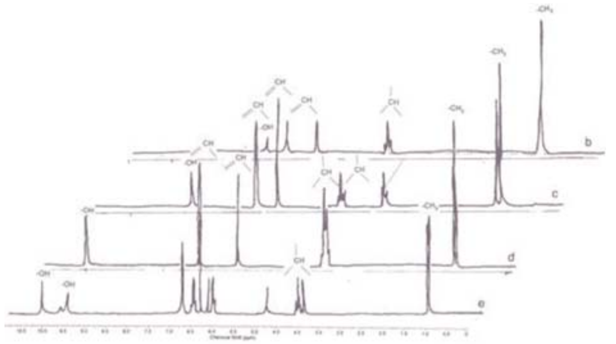


Fig.5. ^{1}H NMR spectra of fractionated by semi preparative liquid chromatography reaction products (b), (c), (d), (e) (see Fig. 4 caption).

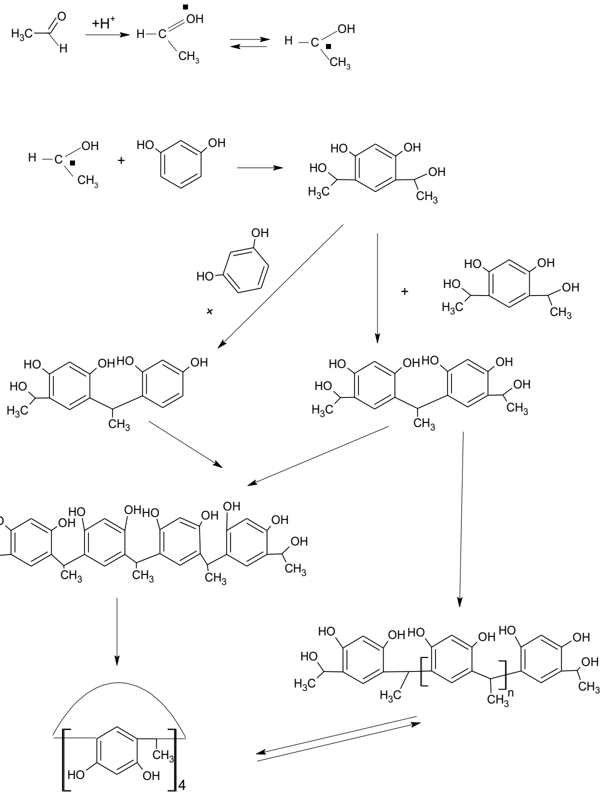
1300 Da regardless of the ratio of ethanol/water reaction mixtures to be the dominant (Figure 4). In the ^{1}H NMR spectrum of fraction 4 (Figure 5e) with experimentally determined average number molecular mass (Mn) is 890 Da (Figure 4e) multiple signals within the ranges of 1.32 – 1.39 (36H), 4.11- 4.30 (8H) and 4.69 (4H) ppm were observed. They can be attributed to protons of methyl and methine groups connecting aromatic rings, respectively. The total number of experimentally determined protons does not exactly correspond to the theoretically calculated ratio of protons in the elementary unit of the polymers obtained. Taking into account that finding as well as the high polydispersity index of the fraction (D=1.348) one can conclude that it consists of oligomeric chains with different numbers of elementary units. Furthermore, the observed resonance signals at 9.40 and 10.01 ppm in NMR spectra (Figure 5e) are attributable to the protons of hydroxyl groups. Most probably the signal at 9.40 ppm corresponds to dihydroxyalkyl oligomeric product while the signal at 10.01 ppm is attributed to the corresponding cyclic oligomeric product.

The ^{1}H NMR spectrum of fraction 1 (Figure 5b) having a molecular mass of about 200 Da as determined by GPC (Figure 4b) signals at 6.57 and 7.27 ppm which can be attributed to protons of the aromatic rings. The chemical shift at 7.78 ppm is estimated as a signal corresponding to four protons of hydroxyl groups. The presence of these signals and others at 4.94 ppm (2H) and 1.41 ppm (6H) attributed to the protons of methine and methyl groups in alkyl subsitute suggest that the product obtained is a dihydroxyalkyl derivative of resorcinol. Besides, the experimentally found molecular mass of 195 Da corresponds well to the theoretically calculated one of 198 Da.

In the ^{1}H NMR spectrum of fraction 2 (Figure 4c and 5c) multiple signals at 1,37 – 1,43 (9H), 4,05 (1H) and 5,05 (2H) ppm, respectively, were observed which can be attributed also as protons of methine and methyl groups. The resonance signals at 6,54 (2H) and 7,01(2H) ppm are referred to protons in the aromatic ring. Taking into account their number as well as other signal at 8,52 (6H) ppm corresponding to protons in hydroxyl groups it is presumed that the product obtained comprise dimers of dihydroxyalkyl derivative of resorcinol as main component. The theoretically calculated molecular mass of 334 Da matches the experimentally found one (336 Da) which also supports the supposed structure of the product obtained.

The multiple resonance signals at 1,28 – 1,30 (12H) and at 4,43 – 4,47 (4H) ppm observed in ^{1}H NMR spectrum of fraction 3 (Figure 5d) are attributed to protons of methine and methyl groups. The other signals observed at 6,43 (4H) and at 7,30 (4H) ppm corresponds to protons of the aromatic ring while that one at 10,00 (8H) ppm – to protons of hydroxyl groups. The experimentally found molecular mass of 553 Da is in good agreement with the theoretically calculated one of 544 Da which implies the C–tetramethylcalix [4] resorcinarene as a reaction product formed.

All separated fractions obtained at different stages of process of C-tetra-methylcalix [4] resorcinarene isolation were characterized by GPC chromatography and ^{1}H NMR spectroscopy. Well-established structures of the products obtained give grounds to suggest the most likely mechanism of the polycondensation and oligocyclization processes presented in Scheme 1.



Scheme 1. Proposed mechanism of the process of polycondensation and oligocyclization.

The proposed mechanism of propagation of oligomeric chains occurs mainly through dihydroxyalkyl derivative of resorcinol and its dimer product. A similar pattern is typical for polycondensation of p-substituted phenols [22] which ensures the formation of linear oligomers.

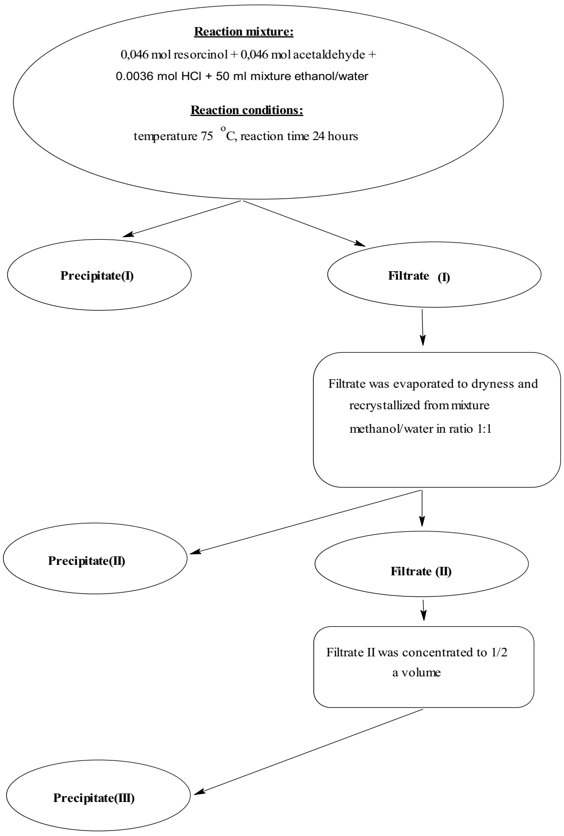
Considering the composition dependency of fractionation products allow the following conclusions:

1) Increasing the polarity of the reaction medium leads to an increase of oligocyclization which yields predominantly C-tetramethylcalix [4]arene products, respectively;

2) In contrast, decreasing the polarity, i.e. more ethanol in ethanol/water mixture, the longer reaction time is needed for the process of hydrolysis to proceed with hence for formation of “high molecular” weight oligomeric products.

Optimization of C-tetramethylcalix[4]arene isolation obtained by varying polarity of the medium

It is found from the above studies that the reaction mixtures after 24 hours time contain mainly cyclic products but in a quantity less than expected one. In order to optimize the procedure of isolation of C-tetramethylcalix[4]arene in a maximum quantity the following scheme was used (Scheme 2).



Scheme 2. A route to separation and isolation of C-tetramethylcalix[4]arene

Initially, the precipitate (I) was separated from the reaction mixture. The filtrate was evaporated to dryness and recrystalized from methanol/water mixture. A new residue (II) and filtrate (II) were collected. The methanol was evaporated from the filtrate (II) and additional precipitate (III) was collected. Following this procedure, the cyclic product obtained was almost completely isolated. The products yielded from the process run at different polarity of the medium ranged from 42% to almost quantitative (99%).

All products obtained at different stages of the procedure for the isolation of C-tetramethylcalix [4] arene are subjected to fractionation using semi preparative liquid chromatography. The fractions collected were characterised by HPLC, GPC, IR and ^{1}H NMR techniques to define the structure of products obtained. The summarized data are presented in Table 2.

As seen from Table 2 the increased medium polarity (at minimum ethanol content in ethanol/water mixtures) increases the formation of cyclic products. Their maximum yield is reached at

Table 2. Composition of separated and isolated products obtained upon various polarity of the reaction medium

	Ethanol/water solvent composition ratio								
	0:100	20:80	30:70	40:60	50:50	60:40	70:30	80:20	100:0
Fractionated products content in precipitate 1 (%)									
L1*	58,83	-	-	-	-	-	-	6,81	30,60
L2**	-	17,43	-	-	-	-	-	-	-
C1***	18,80	48,34	58,69	33,95	25,83	21,21	31,26	5,58	-
C2****	-	-	19,78	4,25	-	-	-	-	-
Fractionated products content in precipitate 2 (%)									
L1*	-	-	-	1,45	0,65	-	5,47	-	1,33
L2**	-	-	-	-	-	-	-	-	2,62
C1***	14,74	25,45	18,20	19,93	18,36	17,88	32,56	44,93	22,05
C2****	-	-	-	4,05	1,23	1,17	7,84	9,23	4,43
Fractionated products content in precipitate 3 (%)									
L1*	-	-	-	-	-	-	-	-	-
L2**	-	-	-	-	-	-	-	-	-
C1***	-	3,18	-	-	-	-	-	-	-
C2****	5,18	4,70	1,19	2,70	2,07	1,36	3,20	1,43	2,30
Total content of fractionated products (%)									
Total:	97,35	99,10	97,86	64,88	48,12	41,62	75,57	68,05	63,83
Content of oligocyclic isomers (%):									
C1***	33,54	76,97	76,89	53,88	44,19	39,09	63,82	50,51	22,05
C2****	5,18	4,70	20,97	11,00	3,30	2,53	11,04	10,66	6,73
Total:	38,72	81,67	**97,86**	64,88	47,49	41,62	74,86	61,17	28,78

*L1-Linear hydroxyl- and dihydroxyl derivatives of molecular mass up to 400 Da; **L2- Linear oligomers of molecular mass over 800 Da; *** C1 – rccc-isomer of C- tetramethylcalix[4]arene; **** C2- rttt-isomer of C-tetramethylcalix[4]arene

30 % ethanol content. Generally, an increase in medium polarity increases twice the content of linear low molecular weight hydroxyl and dihydroxyl derivatives which facilitates the subsequent cyclization. It should be noted that the comparable amount of cyclic product is obtained in both extreme cases (pure ethanol or water solution)

The existence of fractions of comparable molecular masses in some of precipitated products was found (for example C1 (553 Da) and C2 (556 Da) fractions). In addition, the existence of two peaks at different elution volumes but with identical UV spectra in HPLC eluograms (similar to those shown in Figure 4) are observed. Moreover, the IR spectra of these products were in a good agreement with each other.

A triplet signal at 1.28 – 1.32ppm in ^{1}H NMR spectrum of C1 fraction was observed (analogous to Figure 5). The spectrum of C2 fraction showed the existence of triplet signal at 1.54 ppm. In both cases, these peaks correspond to 12 protons and can be attributed to the signals characteristic for the protons of methyl groups. The observed signals at 4.48 ppm (C1 fraction) and at 4.54 ppm (C2 fraction) correspond to 4 protons assigned for the protons of methine groups. Singlet signals observed at about 10.0 ppm (C1 fraction, Figure 5e) as well as those at 9.8ppm and 8.9 ppm (C2 fraction, Figure 5d) both corresponding to 8 protons were assigned to the protons of hydroxyl groups of resorcinol since their disappearance in spectrum upon addition of deuterated water. Therefore, these products can be referred to rccc– and rttt-isomers of C-tetramethylcalix[4]arene, respectively. Regardless of their equal theoretical molecular weight (544 Da) due to the difference in hydrodynamic volumes a shift in elution volumes was observed on chromatogram.

The growing interest in the optimization of the reaction conditions for the synthesis of C-tetramethycalix[4]resorcinarene is not accidental. These products may serve as receptors of ionic and neutral species [23] and as building blocks of supramolecular chemistry structures of, i.e. as components of capsules [24], cavitand [24,25],and nanotubes [26,27]. The C-tetramethylcalix[4] resorcinarene isomers and their derivatives are applicable in the molecular recognition reactions [28], separation procedures [29] and as mimetics of biological processes [30].

CONCLUSIONS

The influence of the acid catalyst (hydrochloric acid) on the yield and structure of the products obtained in the course of polycondensation of resorcinol and acetaldehyde was studied. It has been shown that cyclic oligomeric products of quantitative yields are obtained under certain reaction conditions and catalytic amounts of hydrochloric acid.

The influence of the polarity of the medium on the composition of the obtained products has been investigated. It has been found that by altering of polarity of the reaction medium the formation of cis- or trans-isomers of cyclic oligomeric products can be controlled selectively. A possible mechanism of the polycondensation and oligocyclization processes is proposed. The structure of the products obtained has been defined.

An optimized procedure for the separation and isolation of the cyclic C-tetramethylcalix[4]arene products has been proposed. It has been shown that the cyclic product of quantitative yield is formed by running the synthesis in alcohol - water reaction mixture containing 30% ethanol.

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ОПТИМИЗАЦИЯ НА РЕАКЦИОННИТЕ УСЛОВИЯ ЗА СИНТЕЗ НА С-ТЕТРАМЕТИЛКАЛИКС[4]РЕЗОРЦИНАРЕНИ

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(Резюме)

Показан е нов алтернативен метод за синтез на каликс[4]резорцинарени. Определени са оптималните параметри за получаване на С-тетраметилкаликс[4]резорцинарени, като представител на класа на каликс[4]резорцинарените, чрез вариране на реакционните условия.. Показано е, че тези циклични продукти могат да бъдат получени при определени условия, използвайки каталитично количество минетарна киселина. Установено е, че цис-цис (rccc) и транс-транс (rttt) изомери на С-тетраметил-каликс[4]резорцинарени може да бъдат синтезирани селективно чрез промяна на съотношението на водно-органичната фаза, т.е. чрез промяна полярността на средата. Реакционните продукти са разделени чрез полупрепаративна течна хроматография и охарактеризирани чрез гел-протикваща хроматография (GPC), ядрено магнитен резонанс (^{1}H NMR), ултравиолетова (UV) и Фурие преобразуваща инфрачервена (FTIR) спектроскопия.