The Jan Kochanowski University
in Kielce
Institute of Chemistry
Świętokrzyska 15G
25-406 Kielce

Professional Accomplishments

(Appendix 2)

Mariusz Urbaniak

1) Name and Surname: Mariusz Urbaniak

2) Diplomas, degrees in science – including name of a degree, data and place of issue and title of PhD dissertation

1996 - Master of Science in Chemistry, Pedagogical University in Kielce

2002 - Doctor of Philosophy in Chemistry, thesis in physical chemistry of supramolecular connections, Jagiellonian University, title of dissertation
"Complexion Properties of Selected Calixresorc[4]arenes".

3) Information on employment in scientific institutes:

1997 - assistant, Institute of Chemistry, Pedagogical University in Kielce

1998 - PhD student, Faculty of Chemistry, Jagiellonian University, Krakow.

2002 - assistant, Institute of Chemistry, Świętokrzyska Academy in Kielce

2002- to the present - adiunkt, Institute of Chemistry, Świętokrzyska Academy
(currently the Jan Kochanowski University)

4) Indicated achievements pursuant to art. 16.2 of the 14 March 2003 law on academic degrees and title and degrees and title in art (Journal od Laws, No 65, item 595 with amendments):

a) Title of achievement in science:

New derivatives of resorcinarenes obtained by the catalyzed Mannich reaction

b) Authors, title of the publication, year of publication, name of the publication:

H1 M. Urbaniak, W. Iwanek, "Synthesis of Alkoxymethyl Derivatives of Resorcinarene via the Mannich Reaction Catalysed with Iminodiacetic Acid", *Tetrahedron*, 2006, 62, 1508-1511.

(**IF** = 2.817, 30 pkt MNiSW)

H2 M. Urbaniak, J. Mattay, W. Iwanek, "Synthesis of Resorcinarene Derivatives by the Catalyzed Mannich Reaction, Part 2: Resorcinarene Derivatives with Unsaturated Bonds", *Synthetic Communications*, 2008, 38, 4345-4351.

(**IF** = 0.981, 20 pkt MNiSW)

H3 M. Urbaniak, J. Mattay, W. Iwanek, "Synthesis of Resorcinarene Derivatives by the Catalyzed Mannich Reaction, Part 3: Glycol Derivatives of Resorcinarene", *Synthetic Communications*, 2011, 41, 670-676.

(**IF** = 1.062, 20 pkt MNiSW)

H4 M. Urbaniak, A. Pedrycz, B. Gawdzik, A. Wzorek, "Preparation of Partially Functionalised Resorcinarene Derivatives", *Supramolecular Chemistry*, 2013, 25, 12, 777-781.

(**IF** = 2.132, 30 pkt MNiSW)

H5 M. Urbaniak, B. Gawdzik, A. Wzorek, W. Kaca, Ł. Lechowicz, "Synthesis and Complexing Properties of Diglycol Resorcinarene Podands", *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 2015, 81, 3-4, 357-365.

(**IF** = 1.426, 25 pkt MNiSW)

H6 B. Gawdzik, A. Wzorek, Ł. Lechowicz, M. Urbaniak, "Synthesis of New Arylmethylene Derivatives of Resorcinarene via the Catalyzed Mannich Reaction", SynLett, 2016, 27, 249-253.

(**IF** = 2.419, 25 pkt MNiSW)

H7 M. Urbaniak, W. Iwanek "Rezorcareny jako Receptory Molekularne", Syntetyczne receptory molekularne, Praca zbiorowa pod redakcja Grzegorza Schroedera, Poznań 2007, 71-119.

Sum of IF (as for the year of publication) - 10.837
Sum of points received for a series of scientific articles (as for the year of publication) - 150 MNiSW points

c) Description of scientific objective of the above-mentioned research, the result achieved and their potential application.

Introduction

Resorcinarenes are a group of macrocyclic compounds obtained by reaction of with aldehydes. [1,2] They can exists in several isomeric forms differing in arrangement of aromatic rings in the macrocycle and configuration of the substituents R at the methylene bridges. The combination of these elements gives six different stereoisomers and efficiency of the synthesis depends on kind of substituents R and the synthesis conditions.

Properties and cavity structure of resorcinarenes makes them interesting for supramolecular chemistry. [3] They are also compounds widely used as building blocks for constructing various supramolecular structures (Figure 1). The covalently linked hydroxyl groups of the adjacent resorcinol rings give the cavitands which can be used for preparation of a carcerands. Resorcinarene molecules can also self-assemble themselves into a larger supramolecular systems and form eg. tetramers or hexamers. [4,5,6]

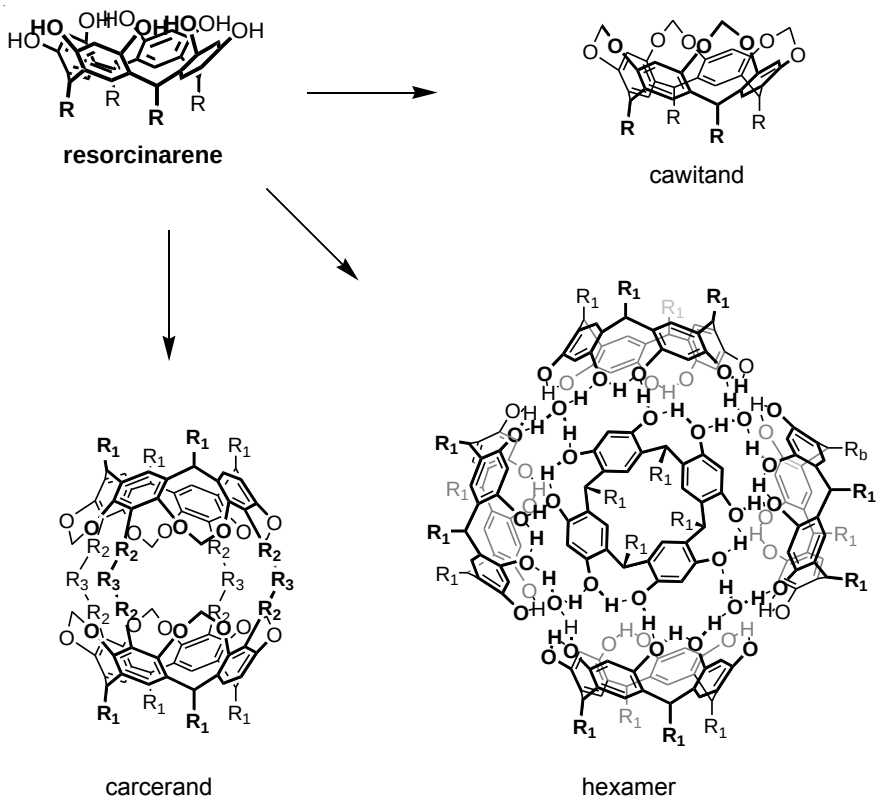


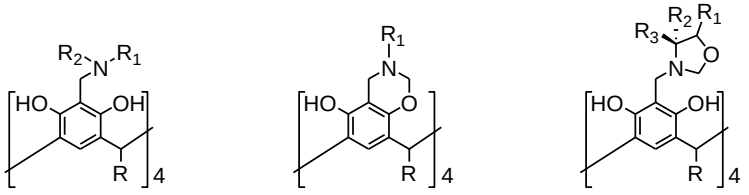
Figure 1

However, the most important feature of resorcinarenes is that they can be modified in various ways. Groups at the lower rim are usually modified at the resorcinarene synthesis stage by appropriate choice of aldehydes. The only limitation is the steric hindrance of bulky substituents directly attached to a carbonyl carbon.

If groups at the lower rim have suitable moiety such as an terminal unsaturated bonds, resorcinarene can further easily undergo other modifications. The hydroxyl groups on the aromatic rings can react in a typical manner e.g. with alkyl halides or acids. In this way can be obtained e.g. ethers, esters, siloxanes or phosphorus derivatives.

Electrophilic aromatic substitution of resorcinarene upper rim protons is also possible. The Mannich reaction is most commonly used for this purpose. [7] This is reaction between a primary or secondary amine, formaldehyde and an active hydrogen substrate e.g. ketones, aldehydes, nitriles, phenols. The resulting product is called the Mannich base. Many from such obtained aminoalkyl derivatives exhibit pharmacological properties and importance of the Mannich reaction has also increased when it turned out that stereochemistry of the reaction could be controlled and received products with high enantiomeric excess. [8] Mannich bases are generally very reactive and undergo deaminomethylaton, deamination, substitution of the amino group, reduction, reaction with organometallic compounds and cyclization.

Resorcinarenes also undergo the Mannich reaction and give different products depending on the amine used (Figure 2). Aminomethylene derivatives are obtained by reaction of resorcinarene with secondary amines while aminomethylene derivatives obtained from primary amines react further to give the oxazine derivatives. [9,10,11] Similarly, 1,3-oxazolidine derivatives are obtained by reaction of resorcinarene with primary amino alcohols. [12,13] The oxazine rings can be opened by hydrolysis to produce aminomethylene derivatives. This process is reversible and the oxazine derivatives can be obtained again by reaction with formaldehyde.



aminomethylene derivative | oxsazin derivatives | 1,3-oxazolidin derivatives

Figure 2

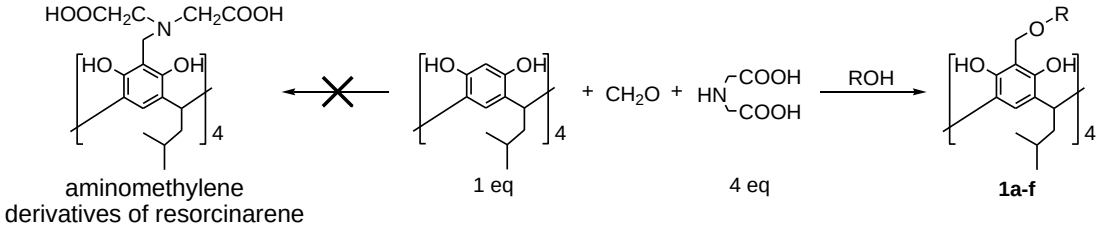
However, despite the fact that aminoalkyl derivatives of resorcinarene are easily formed, only a few examples of their use in synthesis have been described so far. The first paper about substitution of methylene resorcinarene derivatives was published in 1996. [14] It describes the synthesis of thiomethyl resorcinarene derivatives in the presence of triethylamine. The synthesis of alkoxymethylene derivatives in the reaction of resorcinarene with alcohols in the presence of trihydroxymethyl methylamine was described in 2004. [15] The authors suggested that aminomethylation of resorcinarene could be the first stage of this reaction.

The main objective of all presented research works was to confirm the formation of the aminomethylene derivatives of resorcinarene in the first step of the catalysed Mannich reaction and to use its reactivity in chemistry of resorcinarenes.

Description of the research results presented in the scientific articles included in the scientific achievement

Synthesis of alkoxymethyl derivatives of resorcinarene via the Mannich reaction catalysed with iminodiacetic acid (H1)

Studies on the Mannich reaction catalysed with iminodiacetic acid started with a preparation of tetra(ethoxymethyl) derivative of resorcinarene. The reaction was performed as follows: resorcinarene formaldehyde (4 eq) and iminodiacetic acid (4eq) was refluxed for 16 h. The mixture of ethanol and water was used as the solvent, in which resorcinarene and iminodiacetic acid are soluble at reaction temperature. Unreacted iminodiacetic acid was removed by extraction with chloroform and the crude product was purified by column chromatography (silica gel, hexane/ethyl acetate).
The NMR and MS analysis showed that this product was tetra(ethoxymethyl) derivative **1b** of resorcinarene (Scheme 1). Product of aminomethylation expected for the Mannich reactions was not observed. Replacement of the ethanol by other simple alcohols resulted in a series of new tetra(alkoxymethyl) derivatives **1a-f**.



Scheme 1

The yield of reaction with simple short chain alcohols is very high. However, the yield of products significantly decreased, while the length of the carbon chain of the alcohols increased (Table 1).

Table 1. Yields of formation of the tetra(alkoxymethyl) derivatives **1a-f** of various alcohols in the presence of stoichiometric and catalytic amounts of iminodiacetic acid.

Product	**R**	Yields of reaction with stoichiometric amounts of iminodiacetic acid	Yields of reaction with catalytic amounts of iminodiacetic acid
1a	CH_3	88.2%	79.3%
1b	C_2H_5	75.4%	65.8%
1c	C_3H_7	72.6%	64.1%
1d	C_4H_9	56.6%	45.8%
1e	C_5H_{11}	49.9%	40.2%
1f	C_6H_{13}	36.5%	27.6%

The alkoxymethylation of resorcinarenes with formaldehyde and alcohols does not occur without iminodiacetic acid. However, if products of aminomethylation are not observed, the iminodiacetic acid has a different function and the stoichiometric ratio is not necessary. It showed that only 7%-10% by weight of iminodiacetic acid (i.e. 0.1 eq.) with respect to resorcinarene is enough to maintain high reaction yield (Table 1).
The reaction is characteristic of resorcinarenes. When all or part of resorcinarene hydroxyl groups are substituted with methoxy groups, products of O-alkylation are not observed. This shows the importance of the hydroxyl groups on the upper rim of the resorcinarene in the reaction mechanism. The lower rim of a resorcinarene does not have effect on the reaction. The analogous reactions gave products **2** and **3** in which the lower rim is functionalized with methyl and undecyl groups. The yields of the reactions were 65 and 42% respectively (Figure 3).

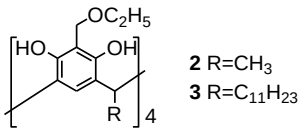
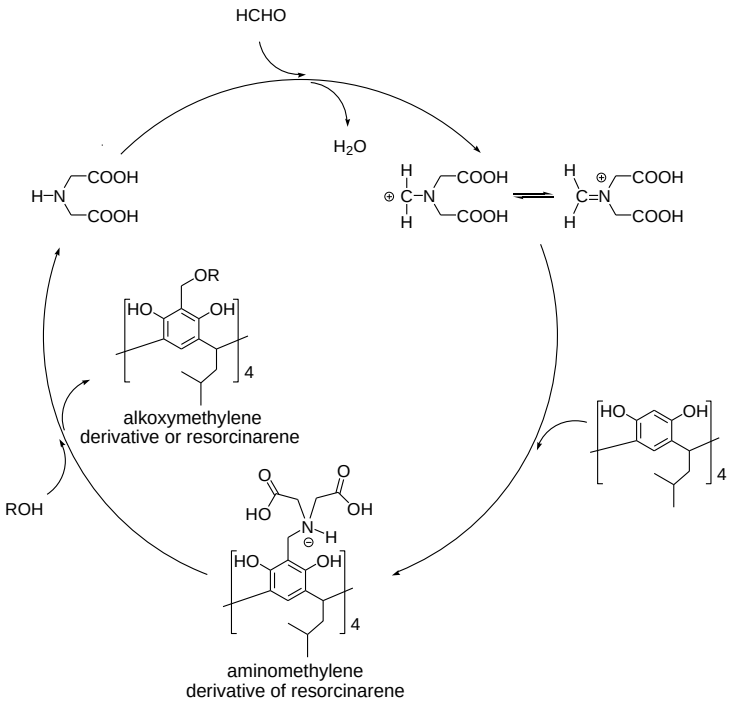


Figure 3

The possible mechanism of formation of the alkoxymethyl derivatives **1a-f** in the presence of iminodiacetic acid is shown in Scheme 2.

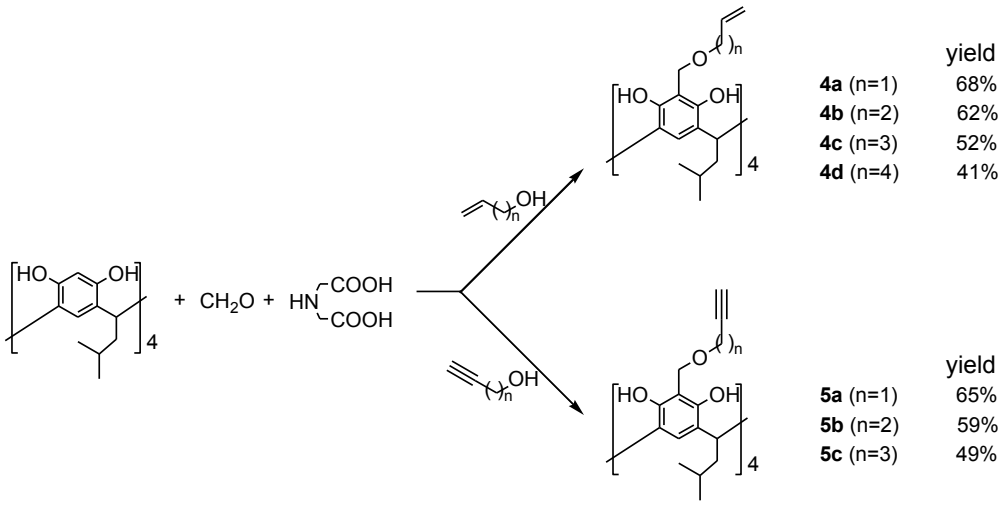


Scheme 2

First, the formaldehyde and iminodiacetic acid molecules form the iminium cation, which then adds at the 2-position to the resorcinarene. This aminomethylene derivative of resorcinarene is appropriate product of the Mannich reaction also known as a Mannich base. The presence of two carboxyl groups in the the aminomethyl derivatives of resorcinarene favours an intermolecular transfer of a proton to the amino group. The thus-formed quaternary aminomethyl salt of resorcinarene is susceptible to elimination followed by addition of the alcohol or other nucleophiles. The displacement of tertiary and quaternary nitrogen atoms by nucleophilic reagents is known reaction. [16] As a result, the 2-position of resorcinarene is substituted with a simultaneous elimination of iminodiacetic acid. Then, the latter molecule can form the next reactive iminium cation with formaldehyde, and the reaction cycle repeats, to form finally the tetra(alkoxymethyl) derivative of resorcinarene.

Synthesis of resorcinarene derivatives by the catalyzed Mannich Reaction Part 2: Resorcinarene derivatives with unsaturated bonds (H2)

The previously described method is general and useful for the synthesis of new resorcinarene derivatives by the use of suitable nucleophiles. By heating resorcinarene with formaldehyde, iminodiacetic acid in acetonitrile, and with alcohols containing terminal double bonds, we obtained resorcinarene derivatives **4a-d**. When we used the same reaction method with alcohols containing terminal triple bonds, we obtained resorcinarene derivatives **5a-c** (Scheme 3). The presence of such functional groups opens new possibilities for complexation with heavy metal cations and additional modifications for larger supramolecular assemblies.



Scheme 3

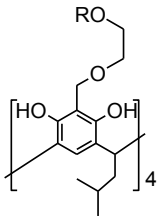
This reaction is so efficient that alcohols with terminally unsaturated bonds must not be used in large excess (e.g., as a solvent). All reactions were conducted in acetonitrile with 32molar ratio of the appropriate alcohol.

The reaction yield for resorcinarene derivatives **4a** is 68%. For comparison, when this reaction was conducted in pure alcohol, the yield increased only up to 76%. As already observed for simple alcohols, the yields of products decreased with increased alcohol chain length.
The branched alcohols, such as *t*-butanol or *iso*-propanol also undergo this catalyzed Mannich reaction in good yields. They may also contain other functional groups. In this manner, the 2-chloroethoxy derivative was obtained. However, if the alcohols contains another nucleophilic group, reaction results in a complex mixture of products mostly polymeric. If the reaction is carried out in the absence of a nucleophilic alcohol by heating resorcinarene with formaldehyde, iminodiacetic acid in acetonitrile, distinctly crystalline, substantially insoluble product was obtained.

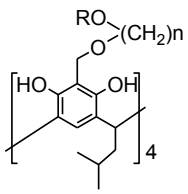
Synthesis of resorcinarene derivatives via the catalyzed Mannich reaction
Part 3: Glycol derivatives of resorcinarene (H3)

Acyclic ligands obtained from ethylene glycol, called podands, are interesting and useful compounds [17,18]. In comparison with the macrocyclic analogs, podands are usually regarded as poor ligands because opened structures are flexible and easily undergo deformations. However, this feature allows adjustment to guest molecules and makes podands more universal ligands. The rigid macrocyclic cavity significantly increases the selectivity; applications of these ionophores are limited to molecules of suitable size. The flexible pendant groups attached to macrocyclic ligands, like crown ethers, cryptands, and cyclodextrins, appear to be a useful complement to closed macrocycles and effect new ionophores. Podands not lost its importance today. The excellent properties of biological receptors are still assigned to self-assembly, molecular recognition and multivalency. Multiple-interaction ligands are useful both for cation binding and protein surface recognition, cell transfection or crystal engineering [19,20,21,22,23].

The new resorcinarene podands **6a-e** with good yields obtained in reaction with ethylene glycol derivatives. In a similar manner propylene glycol derivatives **7** and butylene glycol derivatives of resorcinarene **8** were obtained (Figure 4).



	yield
6a R=H	73%
6b R=CH_3	68%
6c R=C_2H_5	70%
6d R=C_3H_7	67%
6e R=C_4H_9	69%



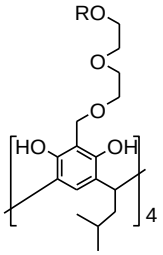
	yield
7 n=3	50%
8 n=4	33%

Figure 4

The ^{1}H-NMR spectra of podand 6a with terminal hydroxyl groups show the broad signal of the resorcinol hydroxyl protons and the very broad signal of terminal pendant hydroxyl groups. This indicate on a strong intramolecular interaction through hydrogen bonds.
The broad signals of the resorcinol hydroxyl protons and terminal glycol hydroxyl protons also are observed for resorcinarene podands **7** obtained from propylene glycol. Both these signals for resorcinarene podands **8** obtained from butylene glycol are sharp and well defined similarly as for derivatives **6b-e** with terminal alkyl chain. The glycol arms in this resorcinarene podand probably formed a structure similar to that of crown ethers, but this interaction does not destroy the intramolecular framework of hydrogen bonds keeping the resorcinarene in the crown conformation with C_{4v} symmetry. These interactions are not observed for resorcinarene derivatives obtained from long-chain glycols.
A significant decrease in yield was observed from ethylene to butylene glycol derivatives, whereas the terminal alkyl chain length of ethylene glycol derivatives **6b-e** does not influence the yield. These data indicate that stable intramolecular hydrogen bonds are strongly dependent on the length of the glycol chain and the exact position of the oxygen atom.

Synthesis and complexing properties of diglycol resorcinarene podands (H5)

In the paper (H5) we reported synthesis of some new podands from resorcinarene and diethylene glycols. The synthesis were performed by Mannich reaction under previously described conditions with one modification. Resorcinarene with formaldehyde and iminodiacetic acid were heated in a mixture of equal volume of ethylene diglycol derivatives and acetonitrile. This large excess of ethylene diglycol derivatives significantly improves yields and, in the case of diglycol ethers causes precipitation of some product from the reaction mixture. Recrystallization from acetonitrile gave pure products **9b-e** in 75-81 % yields (Figure 5). Product **9a** was purified by chromatography on silica but yields did not exceed 36%.



	yield
9a R=H	36
9b R=CH_3	75
9c R=C_2H_5	77
9d R=C_3H_7	84
9e R=C_4H_9	81

Figure 5

The ^{1}H-NMR spectra of podand **9a** with terminal hydroxyl groups on the pendant diethylene glycol arms is shown in Figure 6. Compared to the previously obtained from ethylene glycol podand **6a**, the spectra show the very broad signal of the resorcinol hydroxyl protons at 8.53 ppm and signal of terminal pendant hydroxyl groups completely disappears.

This indicates that diethyl glycol moiety with three oxygen atoms is appropriate length of the pendant polyether arm of resorcinarene podands to form cyclic hydrogen-bonded structure similar to crown ethers.

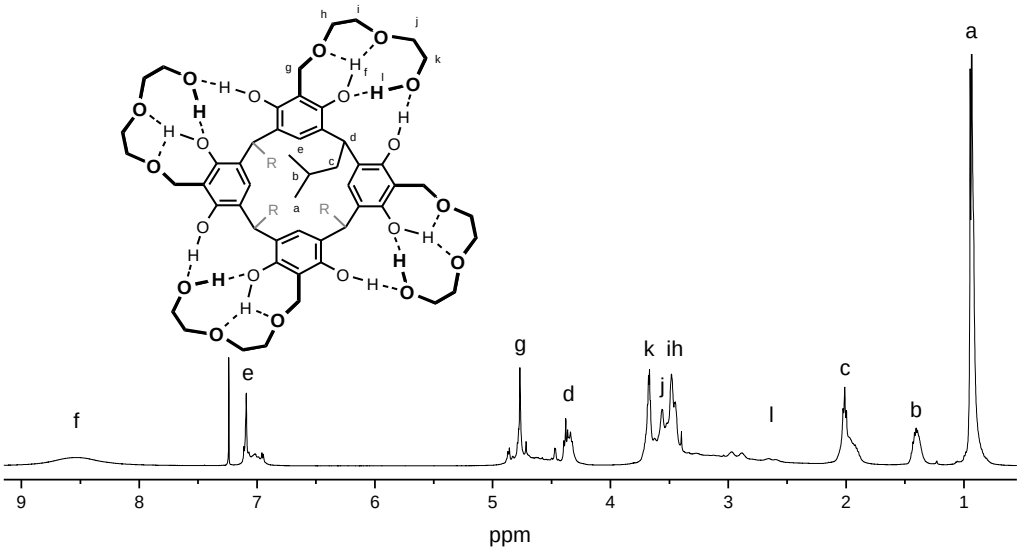


Figure 6. ^{1}H NMR spectrum of diglycol resorcinarene podands **9a** in $CDCl_3$ at 25°C

The ^{1}H-NMR spectra of the podands **9b-e** with terminal alkoxy groups on the diethylene glycol arms are sharp (Figure 7), as in the case of shorter podands **6b-e** synthesized from glycol ethers. All podands obtained from resorcinarene and diglycols or their ether derivatives are thus in the crown conformation with C_{4v} symmetry. The high symmetry of the podands **9a** and **9b** is retained also in the presence of alkali cations during the titration experiments with potassium and cesium ions.

This shows that the long diethylene glycol arms of podands does not interact independently with alkali metal cations through adjacent or opposite arms. All pendant diethylene glycol arms interact together and form a sufficiently long cavity to accommodate more than one metal ion inside without disturbance of the axial symmetry and a crown conformation of the resorcinarene moiety. The podands **9b-e** with terminal alkoxy groups on the diethyl glycol arms under appropriate conditions can thus form an ion channel [24].

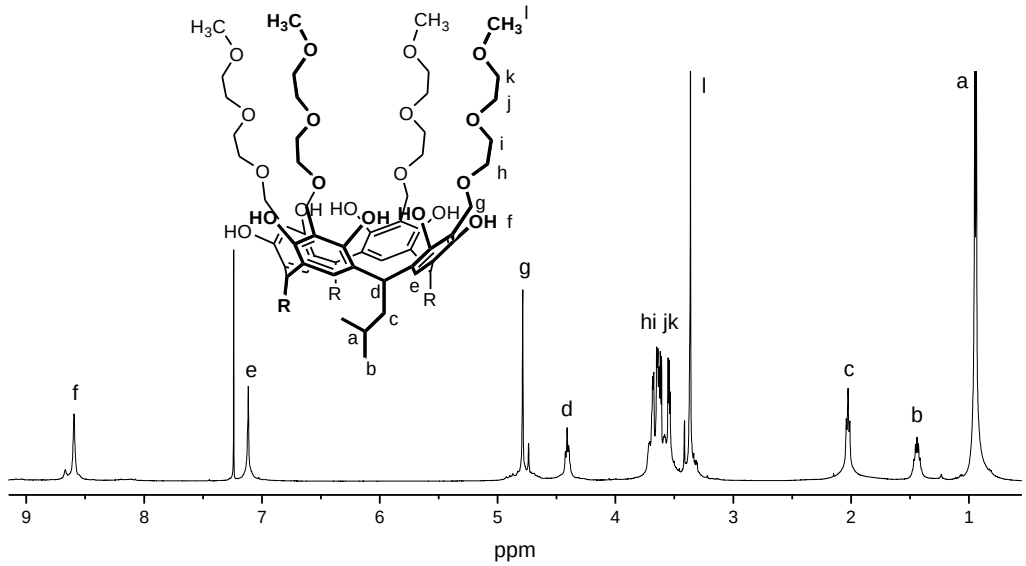


Figure 7. ^{1}H NMR spectrum of diglycol resorcinarene podands **9b** in $CDCl_3$ at 25**°**C.

The formation of complexes with two metal ions are confirmed by ESI–MS analysis. The spectrum of podand **9e** in acetonitrile/water (1:1, v/v) (Figure 8a) shows mainly adducts with a single ion of metal at m/z 1431.889 $[M+Na]^+$ and 1447.892 $[M+K]^+$ (contamination of solvent is the only source of sodium and potassium). The intensity of signals corresponding to adducts at m/z 735.427 $[M+Na+K]^{2+}$ and 2841.799 $[2M+Na]^+$ are relatively low. The ESI-MS spectrum of podand **9e**, significantly changes in the presence of equimolar amounts of potassium chloride (Figure 8b). The peaks derived from sodium and potassium adduct ions of the podand dimmers $[2M+Na]^+$ and $[2M+K]^+$ completely disappearing. The main peaks at m/z 716.962 $[M+H+Na]^{2+}$ and 724.447 $[M+H+K]^{2+}$ corresponding to doubly charged adducts with a proton and cations. The signal intensity of the adducts with one metal cation at 1447.892 $[M+K]^+$ and two metal cations at 743.430 $[M+2K]^{2+}$ is comparable. The addition of a second equivalent of potassium chloride (Figure 8c) shifts the equilibrium towards the adduct with two metal cations, at m/z 735.442 $[M+Na+K]^{2+}$ and 743.430 $[M+2K]^{2+}$ and other signals almost disappeared.

Similar analyses were performed also for other alkali metal cations. In each case, addition of equimolar amounts of ions resulted in the disappearance of the dimeric adduct signals and the base peak is the signal at m/z 724.448 $[M+H+K]^{2+}$. In the doubly charged group, adducts with the same two-metal ion $[M+\mathbf{9c}]^{2+}$ (c = Li, Na, K, Rb and Cs) are always formed but the relative abundance decreases with increase of the ion size. At this concentrations, mixed adducts, containing e.g., sodium and potassium ions also were observed. The most intense signals of adducts with one metal cation was always observed for adduct with added cation and next for the sodium adduct at m/z 1431.889 $[M+Na]^+$.

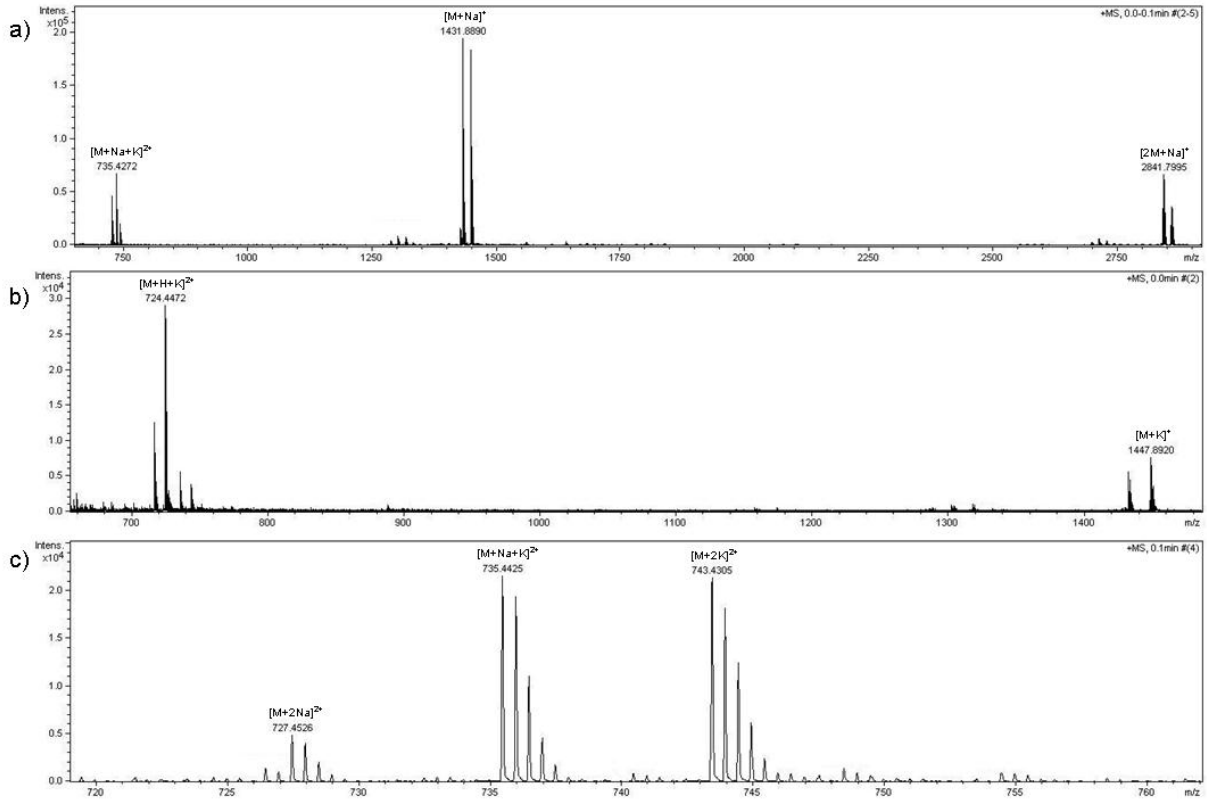


Figure 8. ESI-MS mass spectrum of the podand **9e** a) in acetonitrile-water mixture, b) in the presence of equimolar amounts of potassium chloride, c) in the presence of twofold excess of potassium chloride.

Quite different results were obtained for podand **6a** with terminal pendant hydroxyl groups and shorter arms, obtained from ethylene glycol. In the mass spectrum of pure podand **6a** are present only signals of the monomeric at m/z 1047.513 and dimeric at m/z 2041.099 adducts (Figure 9a). Addition of any alkali metal ions resulted in appearance at 524.249 strong signal of $[M+H+K]^{2+}$ adduct. This is the only signal in this doubly charged group and addition of the next equivalent of metal ion does not change the spectrum in this area. This is a significant difference compared to podands **9b-e**, which means that the cavity formed by the podand **6a** with ethyl glycol arms, is too small for simultaneous complexation of two metal ions. The addition of metal ions also does not prevent formation of the dimers. The intensities of these peaks strongly depends on the size of the added ion and for the dimeric lithium adduct intensity of peak at m/z 2025.107 $[2M+Li]^{+}$ is 39 % and for dimeric adduct cesium adduct at m/z 2150.987 $[2M+Cs]^{+}$ only 3 %. Furthermore clear signals of doubly charged trimeric complex also are observed. The signal at m/z 1533.293 $[3M+H+K]^{2+}$ is present independently of the added metal ions while signals for the trimeric adducts with cesium and rubidium are not observed even if these ions were tested. The most intense peaks in the spectra was always observed for adduct formed with added cation $[M+c]^{+}$ (c = Li, Na, K, Rb and Cs). In case of cesium, podand **6a** selectively form the $[M+Cs]^{+}$ adduct at m/z 1141.442. The other adducts, are observed with very low abundance. The competitive binding experiment in the presence of equimolar alkali metal chlorides also confirmed that Cs^{+} is the preferred guest for the podand **6a**.

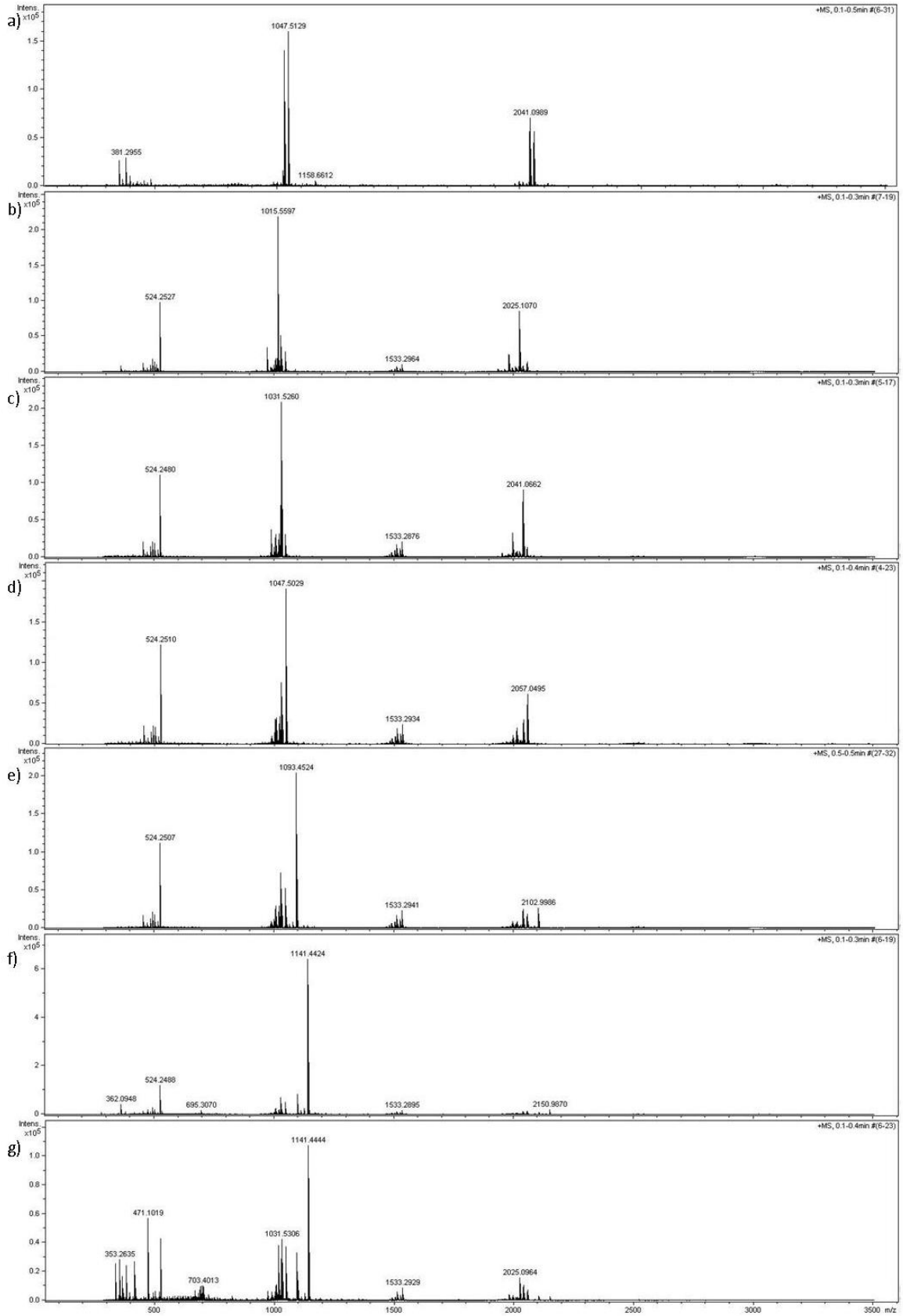


Figure 9. ESI–MS mass spectrum of the podand **6** a) in MeCN/H_2O mixture, in the presence of equimolar amounts of b) LiCl, c) NaCl, d) KCl, e) RbCl, f) CsCl and g) competitive experiment with equimolar amounts of all of these chlorides.

The significant affinity of synthesized podands for the biologically important alkali metal ions inclined us to determine their effects on living organisms. The ability to form the including complexes with two ions, allows to assume that the glycol resorcinarene podands can acts as an artificial ion channels that may resulted in antibacterial activities. Resorcinarene podands antibacterial activities were tested with series of Gram-positive and Gram-negative bacteria (Table 2).

Table 2. The measurement of grow inhibition zone (mm) on Mueller–Hinton agar and tryptic soy agar (The average results of three replicates.)

	Mueller-Hinton Agar			TrypticSoy Agar	
Bacterial strain	**podand 9a**	**podand 9e**	**podand 6a**	**podand 9a**	**podand 6a**
S. aureus	0,0,0	0,0,0	1,1,0	0,0,0	0,0,0
S. epidermidis	1,1,0	1,2,0	3,1,0	0,0,0	1,0,0
B. subtilis	0,0,0	0,0,0	0,0,0	0,0,0	0,0,0
P. aeruginosa PAO1	0,0,0	0,0,0	0,0,0	0,0,0	1,1,1
E. coli ISO	0,0,0	0,0,0	0,0,0	0,0,0	1,1,0
E. coli B	0,0,0	0,0,0	0,0,0	0,0,0	1,1,0
P. mirabilis R110	0,0,0	0,0,0	1,0,0	0,0,0	3,2,1
P. mirabilis R45	0,0,0	0,0,0	1,0,0	0,0,0	9,7,7
P. mirabilis S1959	1,0,0	2,0,0	2,0,0	0,0,0	0,0,0

Tested podands exhibited antibacterial activity against some Gram-positive (*S. epidemidis*, *S. aureus*) as well as Gram-negative (*P. mirabilis*) strains at dose 680 μg/ml. However comparison of podands **9a** and **9e** indicates that terminal groups on the pendant diether arms do not play a significant role in the interactions between podands and bacterial cells. More important, it seems, is length of the pendant arms. The podand **6a**, with ethylene glycol arms exhibit somewhat enhanced antibacterial activity than the podand **9e** with longer diethylene glycol arms. This effect is even more evident when antibacterial tests are performed on Tryptic soy agar. When bacteria were cultivated in this medium, podand **6a** have significant antibacterial properties, especially against *P. mirabilis* R45(Re). The differences on antibacterial activities of two R mutants - Ra and Re and smooth S 1959 strain may suggests that presence of hydrophilic polysaccharides on bacterial cells surface may prevent anti-bacterial activities of podand **6a**. The complexation of more than one alkali ion in the podand cavity observed in MS spectra does not significantly effect on bacteria.

Preparation of partially functionalised resorcinarene derivatives (H4)

Resorcinarenes are often used as supramolecular ligands or building blocks for novel supramolecular assemblies. This is caused by various functionalization of their upper rim. So far, as the cavity platforms they have been solely functionalised with identical groups. The articles on synthesis of resorcinarene monoderivatives, mainly as by-products of reactions, have also recently appeared [25,26].

In manuscript H4 the synthesis and purification of a series of mono-, di- and trisubstituted resorcinarenes is described (Figure 10). The goal was to elaborate methods of introduction of different groups in the upper rim, which would allow to design of new selective ligands with cavities showing axial chirality.
These homosubstituted derivatives were synthesised in good yields by heating resorcinarene with an excess of formaldehyde and alcohols in the presence of iminodiacetic acid as the catalyst. It is also possible to obtain partially functionalised resorcinarenes **10a-h** under the same experimental conditions (Figure 11).

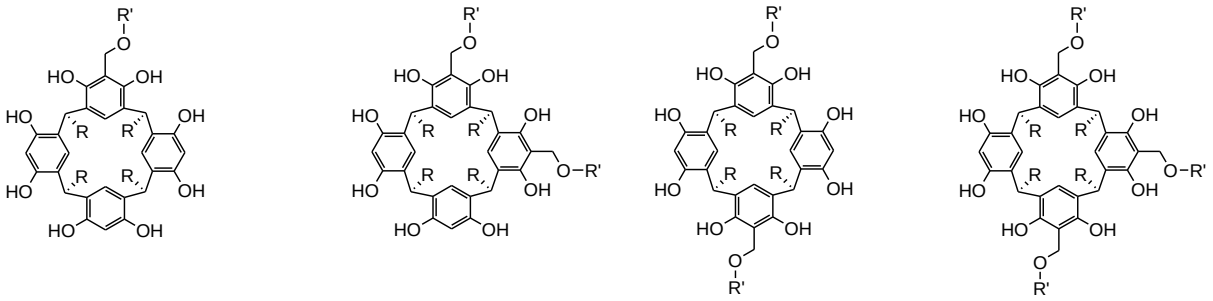
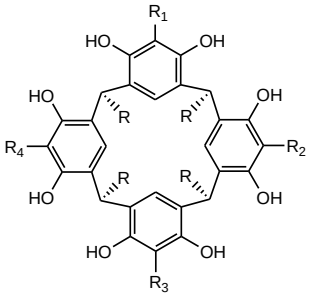


Figure 10

The reaction conditions were optimised with respect to molar ratio of reagents and the time of heating. Reaction between resorcinarene, formaldehyde (1 eq) and with excess of propanol, in the presence of catalytic amount of iminodiacetic acid gave low yields of monosubstituted product **10c** regardless of heating time and temperature.



10a $R_1 = CH_2OCH_3$, $R_2 = R_3 = R_4 = H$
10b $R_1 = CH_2OC_2H_5$, $R_2 = R_3 = R_4 = H$
10c $R_1 = CH_2OC_3H_7$, $R_2 = R_3 = R_4 = H$
10d $R_1 = CH_2OCH_2CH{=}CH_2$, $R_2 = R_3 = R_4 = H$
10e $R_1 = CH_2OCH_2CH_2OH$, $R_2 = R_3 = R_4 = H$
10f $R_1 = R_2 = CH_2OC_3H_7$, $R_3 = R_4 = H$
10g $R_1 = R_3 = CH_2OC_3H_7$, $R_2 = R_4 = H$
10h $R_1 = R_2 = R_3 = CH_2OC_3H_7$, $R_4 = H$
10i $R_1 = R_2 = R_3 = CH_2OCH_2CH{=}CH_2$, $R_4 = H$

Figure 11

When the molar ratio of resorcinarene to formaldehyde was 1:2, the yields of the products increased. Figure 12 shows the relative concentration of partially functionalised propoxyresorcinarenes over the reaction time.

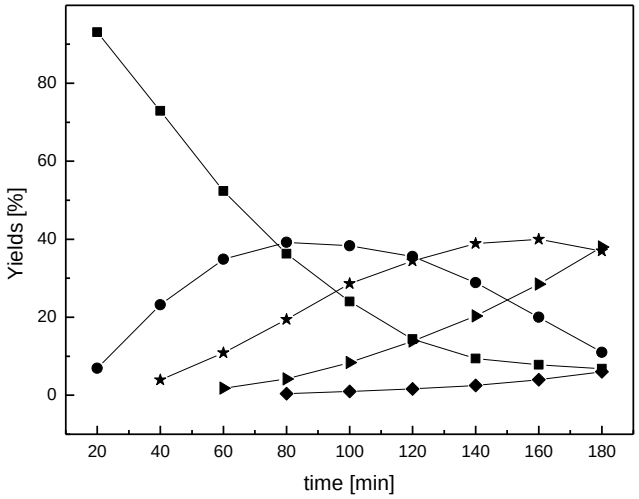


Figure 12. Relative concentration of partially functionalised resorcinarenes: ■ resorcinarene, ● monopropoxy, ★ dipropoxy, ▲ tripropoxy, ♦ tetrapropoxy.

The maximum yield (39%) for the monopropoxysubstituted derivative was achieved after 90 min of heating at 82°C. If the molar ratio of resorcinarene to formaldehyde was increased to 1:3 or higher, yields for monosubstituted derivatives increased only slightly (43%), but conversion of resorcinarene is more efficient in the concomitantly higher yields of the di- and trisubstituted derivatives. The yields after chromatographic separation and optimal heating times for particular monosubstituted derivatives **10a-e** are given in Table 3.

Table 3. Time of heating and yields for partially functionalised derivatives **10a-i**.

Compound	Derivative of Alcohol	Yield (%)	Time of heating (min.)
10a	CH_3OH	34	240
10b	CH_3CH_2OH	39	135
10c	$CH_3CH_2CH_2OH$	39	90
10d	$CH_2=CHCH_2OH$	43	90
10e	$HOCH_2CH_2OH$	37	30
10f	$CH_3CH_2CH_2OH$	14	160
10g	$CH_3CH_2CH_2OH$	24	160
10h	$CH_3CH_2CH_2OH$	29	180
10i	$CH_2=CHCH_2OH$	30	180

This method is also useful for the synthesis of new di- and trisubstituted resorcinarene derivatives. If the reaction is carried out for 160 min, a mixture of diastereomers **10f** and **10g** obtained in 24% and 14% yields.

This result may be explained by a larger steric hindrance of two alkyl groups on adjacent aromatic rings of 1,2-dipropoxy derivative **10f**. This selectivity decreased for diethoxy- and dimethoxy- diastereomers. Heating the reaction mixture for 3 h led to tripropoxy derivative **10h**, as the main product in 29% yield.

Analysis of chemical shifts for monopropoxy resorcinarene **10c** showed that substitution of one resorcinol ring causes distortion of C_{4v} symmetry of crown conformation of the macrocycle. The comparison of the chemical shifts and patterns for hydroxyl and aromatic protons of partially substituted derivatives is shown in Figure 13. Two signals for aromatic protons on the lower rim at δ 7.35 and 7.28 reflect the boat conformation (C_{2v}) of derivatives **10c**. Dipropoxy isomers **10f** and **10g** exist in different conformations. Only two signals for the hydroxyl protons at δ 10.28 and 8.03 and two well-separated signals for lower rim aromatic protons of 1,3-dipropoxy derivative **11g** at δ 7.37 and 7.27 suggests a boat conformation. The presence of two very close signals at δ 7.35 and 7.33 for the lower rim aromatic protons suggests that the 1,2-dipropoxy derivative **10f** adopted distorted crown conformation. The tripropoxy resorcinarene **10h** showed three well-separated aromatic signals in the ratio 2:1:1 on the lower rim. Two signals at δ 7.35 and 7.40 correspond to protons attached to the unsubstituted resorcinol ring and to the opposite resorcinol ring of the macrocycle. The differential shielding effect is caused by the distortion of C_{2v} symmetry of boat conformation.

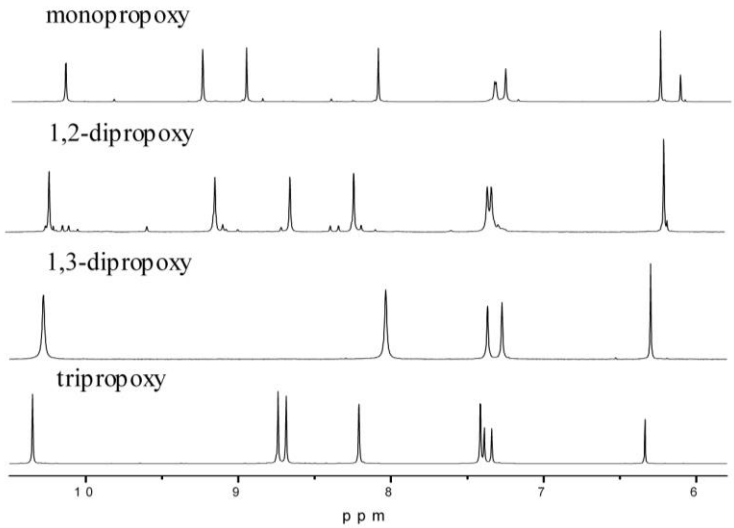
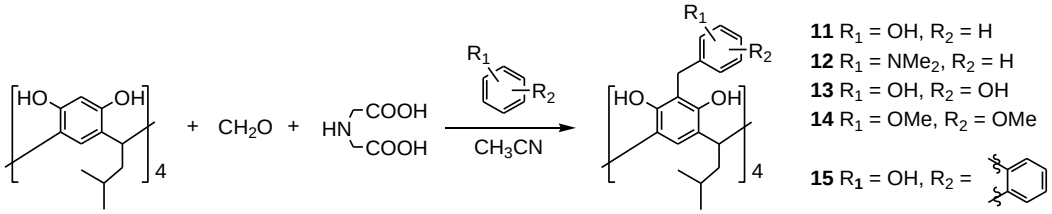


Figure 13. The comparison of chemical shifts and patterns for hydroxyl and aromatic protons of mono-, di- and tripropoxy functionalised resorcinarenes.

The preparation of resorcinarene monosubstituted derivatives provides the possibility to access selectively functionalised resorcinarenes and will be useful in the design of molecular receptors with cavities showing axial chirality.

Synthesis of New Arylmethylene Derivatives of Resorcinarene *via* the Catalyzed Mannich Reaction (H6)

The Mannich reaction is well known and useful reaction in the synthesis of aminoalkyl derivatives. The Mannich bases are generally very reactive and provide more possibilities for the synthesis of numerous other compounds. However, for the resorcinarenes the nucleophilic substitution of aminomethyl derivatives is only known. [15,27]
In paper H6 shown that activated aromatic rings can also act as a nucleophiles in the reaction with Mannich-base of resorcinarene and allows to obtain a series of new derivatives functionalized with arylmethylene groups which are not reported in the literature.
The reaction of resorcinarene with formaldehyde and catalytic amount of iminodiacetic acid requires a suitable aryl nucleophiles. Simple benzene derivatives were tested and the reaction proceeds with sufficient yield only for the aromatic ring substituted with OH, OR or NR_2 groups (Scheme 4). A series of new arylmethylene resorcinarene derivatives 11-14 have been synthesized but for mono-substituted phenyl rings the mixture of isomeric products is obtained.



Scheme 4.

In the reaction with phenol mixture, the three main products are obtained. LC-ESI/MS analysis showed that all products have the same mass, which corresponds to tetra(methylene phenol) derivatives of resorcinarenes **11**. One of the reaction products proved to be tetra(methylene 2-phenol) resorcinarene derivative **11a**. The ^{1}H NMR spectra in DMSO of this derivative (Figure 14a) show signals of compound with symmetry C_{4v}. All four phenolic substituents are attached to upper rim of the resorcinarene in the same way.
The two other products of this reaction proved to be derivatives in which, respectively, one (**11b**) and two (**11c**) phenolic groups are attached to methylene bridges in positions 4.Three signals for resorcinarene aromatic protons on the lower rim at 7.41, 7.39 and 7.36 ppm indicates that this derivative adopts a scoop conformation, an intermediate of the crown and the boat conformations. [28] The characteristic pattern of aromatic protons on the lower rim in derivative **11c** suggest that molecule tends to adopt a boat conformation and methylene 4-phenolic moieties are attached to opposite resorcinol rings in the resorcinarene.
In an analogous reaction with *N*,*N*-dimethylaniline obtained only two products **12a** and **12b** of the same mass. Analysis of ^{1}H-NMR spectra showed that one of the product **12a** is tetra(methylene 4-aniline) derivative while in other product (**12b**) three substituents are connected to the methylene group by 4-position and one by 2-position.

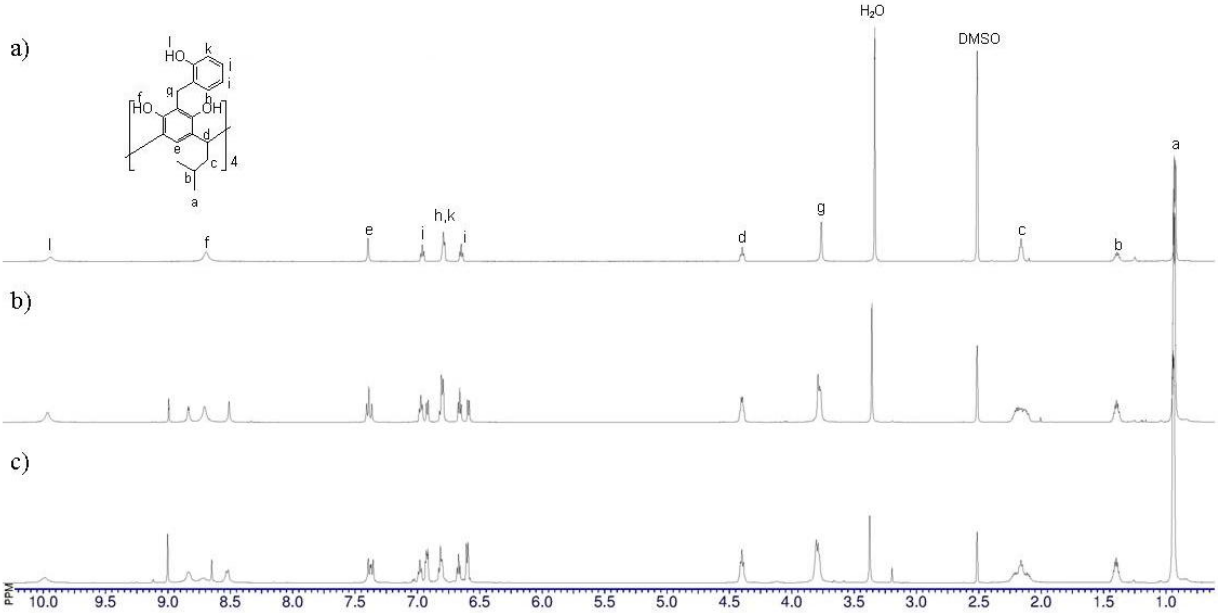
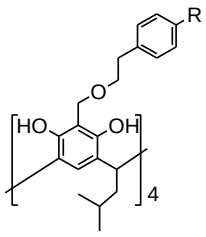


Figure 14. The comparison of 1H NMR spectra of tetra(methylene phenol) derivatives of resorcinarene a) tetra(methylene 2-phenol) derivatives **11a** b) tri(methylene 2-phenol) mono(methylene 4-phenol) derivatives **11b** and c) di(methylene 2-phenol) di(methylene 4-phenol) **11c**.

This observation suggests that type of activating substituents of the aromatic ring plays an important role in this type of reactions. Small substituents, especially capable of forming hydrogen bonds, causes the aromatic ring is attached to methylene bridge in the position 2. The substitutions at the position 4 to methylene groups are more frequent in case of bulky groups.

The number of conformational products can be reduced to only one by the use of suitable nucleophiles. Reaction of resorcinarene with 1,3-disubstituted phenyl gives derivatives of resorcinarene as one main product. In this way new compounds **13** and **14** are obtained from 1,3-dihydroxybenzene and 1,3-dimethoxybenzene. The NMR spectra indicate the structure of the derivatives in which all disubstituted phenyl rings are connected to methylene bridges in positions 4. Similar results were obtained in the reaction of the resorcinarene with 2-naphthol. The reaction also takes place in high yield with a small excess of aromatic nucleophile and results in formation of resorcinarene derivative **15**.



16 R = H
17 R = OMe

Figure 15

We were unable to obtain any products of C-arylation reaction when nucleophilic aromatic ring was substituted with electron-withdrawing groups or unsubstituted. Such aromatic rings are a weaker nucleophile compared to activated aromatic rings and these in turn are a weaker nucleophile compared to the previously used in this reaction alcohols. This confirms the fact that in the reaction of resorcinarene with 2-phenylethanol or 2-(4-methoxyphenyl)-ethanol products of resorcinarene O-alkylation **16** and **17** were obtained (Figure 15). The same reaction carried out with 2-(4-hydroxyphenyl)-ethanol results in a complex mixture of products. This indicates that the aromatic ring activated with a hydroxyl group is under these conditions so effective nucleophile that it can compete with ethanol moiety in the reaction.
These results show that activated aromatic rings can act as a nucleophile in the catalyzed Mannich reaction with resorcinarenes. Unsubstituted aromatic ring or substituted by deactivating groups are not reactive enough and do not participate in this reaction. The monosubstituted phenyl ring can be connected to the methylene bridge in positions 2 or 4 and forms several substituent isomers with different conformations. For the 1,3-disubstituet benzene ring, steric hindrance causes that only position 4 is available for reaction and all arylmethylene moieties are arranged outside the resorcinarene cavity.

Resorcinarenes as supramolecular receptors (H7)

Article H7 is a brief outline of the complexion properties of resorcinarenes. It focuses on their noncovalent interactions, typical of supramolecular systems. A large variety of compounds makes it impossible to indicate a common complexing property. Each of these compounds has an individual affinity for different molecules and reactivity is usually the result of several different structural features
However, typical places of interaction may be indicated for different derivatives of resorcinarenes. These are:

- cavity formed by aromatic rings and functional groups of individual isomers
- cavity formed by groups of the lower rim
- outer surface of functional groups at upper or lower rim
- outer surfaces of the aromatic skeleton
- large supramolecular cavity created by resorcinarene hexamers.

Another class of interaction are inclusion complexes of carcerands. "Molecules within molecules" can not leave the host molecule without breaking its covalent bonds.

Summary

The results in H1-H6 have confirmed that the first step in the reaction of resorcinarene with iminodiacetic acid and formaldehyde is the formation of the aminomethylene Mannich base. It may, under certain conditions, formed quaternary aminomethyl salt, which readily undergo substitution. Alcohols and aromatic compounds can be used as nucleophiles in this reaction. The reactivity of the aminomethylene derivative opens up new possibilities for resorcinarene Mannich base which have not yet been used as substrates for further modifications. The result of this work is 41 new derivatives of resorcinarene and development of a general method of modifying resorcinarenes. It allows the introduction in the upper rim of resorcinarene functional groups such as alkyls, aklenyls, alkyl halides, ethers and aromatic rings.

Moreover, the method of selective functionalization of the resorcinarene macrocycle has been proposed (H4). This is the first work dedicated entirely to synthesis of mono-, di- and trisubstituted derivatives of resorcinarene. These results allow us to design a new supramolecular systems based on resorcinarenes and to obtains them with higher yields. This work opens up a new route for the synthesis of hetero substituted resorcinarenes for example with axial chirality. Such structural analogs are also arylmethylene derivatives of resorcinarene (H6) in which the identical substituents are attached in different ways to the aromatic rings of resorcinarene macrocycle.

The new supramolecules obtained during the study (H3 and H5) are podandoresorcinarenes. Already, preliminary analysis have shown their outstanding complexing properties. These compounds have been found to be selective receptors for metal cations and other molecules which can be used, for example, in microbiology or crystal engineering.

Description of other scientific research achievements

My research interests have been closely related to supramolecular chemistry Resorcinarenes were excellent for this and the first works focused on spectroscopic studies of chiral resorcinarenes with amines and amino alcohols and the phenomenon of chiral discrimination. I was also interested in other types of supramolecular resorcinarene complexes; a charge-transfer complexes with strong electron acceptors and a host-guest complex with fullerenes. I also conducted research on interactions of the resorcinarene derivatives with organic acids. These studies included, among others; determination of complex composition, stability constants and quantum modeling of complexes.

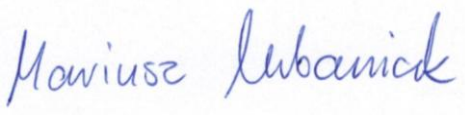
During postdoctoral fellowship at University of Bielefeld supervised by prof. Jochen Mattay I also focused on synthesis of methoxypyrogalloarene and enantiomerically and diastereomerically pure oxazoborininone derivatives of resorcinarene from L-proline. I also participate in research on biologically active compounds, such as iodolactones and others.

My recent work has focused on biochemical studies therefore the synthesis of new compounds are conducted with a view to properties and applications especially

in microbiology. I also deal with application of spectroscopic methods in biomedical diagnostics e.g. use of IR spectroscopy for detection of pathogenic strains of bacteria (eg. *Escherichia Coli).*

List of scientific works

Original creative works published in journals that have IF	22
Original creative works published in journals that have not IF	1
Chapters in textbooks	1
Original creative works published in journals after PhD	19
Sum of IF	40,5
Sum of MNiSW points	521
Sum of time cited without self citations	137
h- index	7
Patents	2
Patent applications	2
Lectures and oral communications	3
Posters and presentations at national and international conferences	29



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