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New calix[4]resorcinol *rccc* diastereoisomer with terminal triple bonds: synthesis, structural features and reactions

Irina R. Knyazeva,*[a] Victor V. Syakaev,[a] Wolf D. Habicher[b] and Alexander R. Burilov[a]

[a] *A. E. Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 843 273 4872; e-mail: ihazieva@mail.ru*

[b] *Institute of Organic Chemistry, Dresden University of Technology, D-01062 Dresden, Germany*

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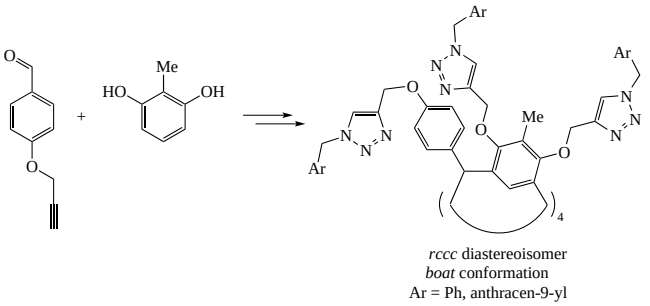
One-pot acid-catalyzed cyclocondensation of 2-methylresorcinol with 4-(propargyloxy)benzaldehyde in $CHCl_3$/CF_3CO_2H media affords all-*cis* (*rccc*) and/or *cis-trans-trans* (*rctt*) calix[4]resorcinol diastereomers bearing four terminal alkyne groups at aromatic substituents, the isomer ratio and yield being dependent on the $CHCl_3$/CF_3CO_2H ratio. The *rctt* isomer (kinetic control product) can be converted to thermodynamically more stable *rccc* isomer at prolonged refluxing in $CHCl_3$/CF_3CO_2H mixture. The *rccc* diastereomer was subjected to additional propargylation followed by the click reactions with benzylic azides to afford new highly triazolated calix[4]resorcinols.



rccc diastereoisomer
boat conformation
Ar = Ph, anthracen-9-yl

Keywords: calixresorcinols, condensation, diastereoisomers, conformation, click reaction, 1,2,3-triazoles.

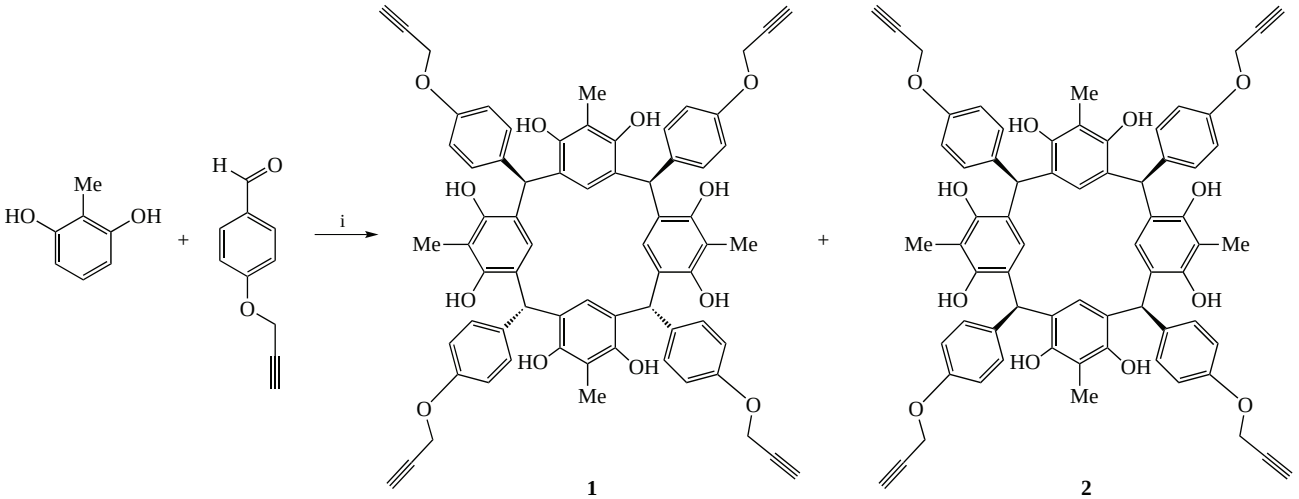
At present, macrocyclic compounds, calixarenes in particular, are of interest due to their broad opportunities and easiness of their structural transformations. The conformational diversity of calix[4]resorcinols, the presence of macromolecular cavity, a number of reaction centers and substituent diversity, as well as almost unlimited possibilities of modification make them promising for fundamental research.[1–10] The traditional method for obtaining calix[4]resorcinols is a one-pot mineral acid-catalyzed cyclocondensation of resorcinols with aldehydes or acetals in alcohol–aqueous environment.[11–17] The reaction of aliphatic aldehydes or acetals with resorcinols usually affords *rccc* (all-*cis*) diastereomers of calix[4]resorcinols whereas aromatic aldehydes normally produce the mixtures of *rccc* and *rctt* (*cis-trans-trans*) isomers. Under conditions different from those of the traditional way, for example, when employing organic acids, Brønsted and Lewis acids, in the presence of molecular iodine, lanthanide salts as catalysts, the *rccc* or *rctt* diastereomers can be accessed exclusively. In rare cases, other isomers could be isolated.[16,18–27] Different isomers exhibit nearly identical IR and mass spectra; however, their solubility in organic solvents, melting points, and R_f values are noticeably different, and structural features are highlighted in ^{1}H and ^{13}C NMR spectra.[11–16,18–27]

Preparation of individual diastereomers of calix[4]resorcinols is of importance since *rctt* diastereomers usually possess higher melting points while different solubility of *rctt* and *rccc* isomers would influence their reactivity. The conformationally fixed resorcinol fragments of *rctt* isomer along with appropriate substituents on the calixarene scaffold could provide different reactivity of hydroxy groups located horizontally or vertically relative to the macrocyclic cavity. This allows for the selective modification of OH-groups of *rctt* isomer, whereas for *rccc* isomers the reactivity of all hydroxy groups is identical.[28,29] Nickel complexes of *rccc* and *rctt* diastereomers of some thiophosphorylated calix[4]resorcinols show different catalytic activity in electrochemical hydrogen evolution.[30]

We have been recently investigating cyclocondensation of resorcinols with various functionalized benzaldehydes in aprotic solvent in the presence of organic acid, namely, chloroform/trifluoroacetic acid (TFA) system. Initially, under these conditions we performed the reactions of phosphorylated aromatic aldehydes poorly soluble in conventional water–alcohol media. Subsequently, we have revealed that chloroform/TFA system could be successfully applied to the synthesis of a wide range of new functionalized calix[4]resorcinols. The target macrocycles were mostly formed as mixtures of *rctt* and *rccc* diastereomers.[18–23,31]

In this work, we have discovered that the relative solubility of the formed diastereomers and, consequently, their ratio and yields can be tuned by variation of the composition of reaction medium through the TFA content, which makes the reaction mixture more solubilizing. Thus, one can guide the reaction towards the formation of *rccc* diastereomers which are better soluble in organic solvents. It is of note that we previously[20] synthesized new *rctt* diastereomers of calix[4]resorcinols in *chair* conformation bearing four terminal alkyne moieties;[20] however, these compounds possessed fairly low solubility in most organic solvents, which makes further studies of their synthetic capabilities difficult.

Here, 2-methylresorcinol was chosen as the starting compound since the difference in solubility of *rccc* and *rctt* calix[4]arene diastereomers derived from it is higher than that for the cases of resorcinol or pyrogallol. An additional advantage of 2-methylresorcinol is a simpler interpretation of NMR spectra of the formed calixarenes.[18–23,31] In our previous work[20] we found that the reaction of 2-methylresorcinol with



Scheme 1 *Reagents and conditions*: i, CF_3CO_2H, $CHCl_3$, reflux, 32 h.

4-(propargyloxy)benzaldehyde in $CHCl_3$ in the presence of TFA at a 15 : 1 ratio (v/v) in argon atmosphere gave exclusively *rctt* isomer in *chair* conformation **1** in 80% yield (Scheme 1). In this study, we found that employment of the $CHCl_3$/TFA = 1 : 1 (v/v) mixture for this reaction afforded the mixture of isomers **1** (*rctt*) and **2** (*rccc*) at a 1 : 10 ratio, respectively, in total yield of 87%, while full replacement of solvent by TFA gave the 2.5 : 1 ratio of the formed isomers, respectively, in total yield of 58% (see Scheme 1, for synthetic details see Online Supplementary Materials).

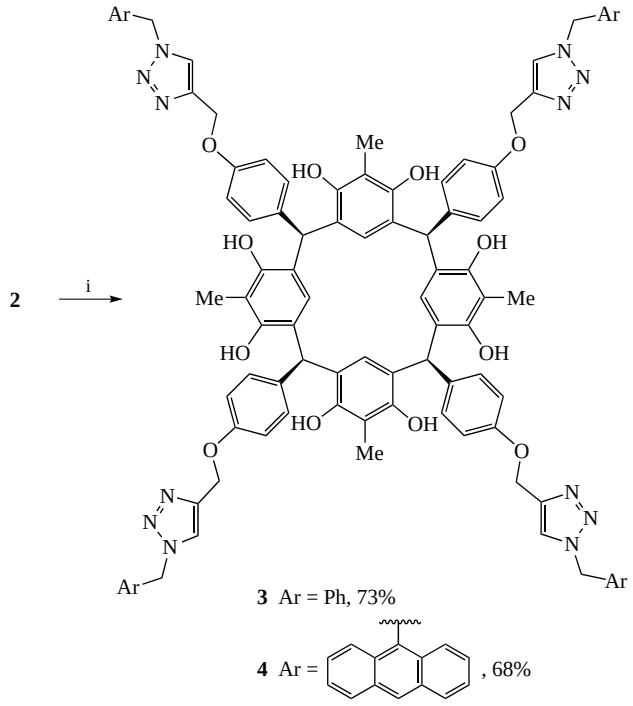
Apparently, the ratio between *rccc* and *rctt* diastereoisomers obtained strongly depends on their relative solubility in the reaction medium. Thus, the less soluble *rctt* isomer **1** would precipitate upon formation from $CHCl_3$/TFA mixture with a lower fraction of TFA (15 : 1, v/v). Since the condensation is a steady-state process, the reaction equilibrium shifts to the formation of product that is eliminated from the reaction zone (*e.g.*, by precipitation), so the *rctt* isomer **1** is formed in the maximum 80% yield. With an increase in the content of TFA in the reaction mixture [$CHCl_3$/TFA = 1 : 1 (v/v)], relative solubility of the formed *rctt* diastereomer increases, and its fraction in solution is involved in the equilibrium isomerization process. As a result, its precipitated fraction is lower and the main product is the soluble *rccc* isomer **2** (see Scheme 1). When the solvent is pure TFA, the relative solubility of the *rctt* isomer **1** is lower again and the *rctt*/*rccc* ratio would somewhat grow; however, in pure TFA medium resinification and decomposition are more pronounced, which drops the total yield of the products to 58%.

An increase in the yield of the *rccc* isomer with an increase in the content of TFA in the reaction medium may be rationalized in view of the fact that long-term heating under homogeneous conditions results in the transformation of the product of kinetic control (*rctt* isomer) into the product of thermodynamic control (*rccc* isomer), which is analogous to that described by Hogberg[14] for HCl/EtOH media. To confirm this suggestion, we refluxed individual *rctt* isomer **1** in a more solubilizing $CHCl_3$/TFA = 1 : 1 (v/v) mixture for 48 h and obtained *rccc* isomer **2** in 70% yield while the rest was the unreacted starting *rctt* isomer **1**. In this medium, no reverse transformation **2** → **1** occurred.

Due to the different solubility, diastereomers **1** and **2** were isolated in pure form. The *rctt* isomer **1** is a white powder soluble only in hot DMSO and hot DMF, whereas *rccc* isomer **2** is a light-brown powder soluble in most organic solvents. NMR data (^{1}H, ^{13}C) for compound **1** are totally identical to our previous data.[20] The structure of compound **2** was elucidated using ^{1}H and ^{13}C NMR spectroscopy and HSQC, HMBC, and 2D NOESY experiments. ^{1}H and ^{13}C NMR spectra show individual signals for each group of protons and carbon atoms, which indicates high symmetry of its structure and existence of only one isomer with C_{4v} (*cone* conformation) or D_{2d} symmetry (*1,3-alternate* conformation).[1,5,7,11] In the case of other isomers, at least two sets of peaks or signal broadening are usually observed at room temperature. 2D NOESY spectrum of compound **2** shows in-phase correlations between the peaks for aromatic protons at the lower rim and the methine proton and aromatic *ortho*-proton of the calixarene scaffold. At the same time, there are no cross-peaks for the protons of any fragment on the lower rim with the protons of methyl group of upper rim. This unambiguously indicates *cone* stereoisomeric form (C_{4v}) of the compound with corresponding *rccc* configuration of the substituents (see Online Supplementary Materials). The structure and composition of calix[4]resorcinol **2** were also confirmed by mass spectrometry (MALDI), IR spectroscopy, and elemental analysis data.

It should be noted that the previously synthesized *rctt* diastereomer **1** containing terminal triple bonds adopts *chair* conformation both in solution and crystal state.[20] It possesses extremely low solubility in organic solvents, which makes it difficult to explore its synthetic potential, as well as to perform physicochemical studies of these interesting macromolecules. At the same time, a new *rccc* diastereomer **2** seems promising for subsequent synthetic and other studies due to its good solubility in most organic solvents. Subsequent reactions could involve terminal triple bonds, whereas free hydroxy groups could be used for further modification to develop new types of highly functionalized macromolecular compounds.

The click reactions of tetrapropargyl calixarene **2** with benzyl azide or 9-(azidomethyl)anthracene furnish the corresponding products **3** and **4** with four 1,2,3-triazole fragments in 68–73% yields (Scheme 2). The reactions procced with the retention of the *rccc* spatial structure of initial macrocycles. Previously,[21,23] we obtained these compounds through alternative one-pot acid-catalyzed condensation of the corresponding triazole-containing benzaldehydes with 2-methylresorcinol. However, that synthesis was less efficient because it required separation of the mixture of



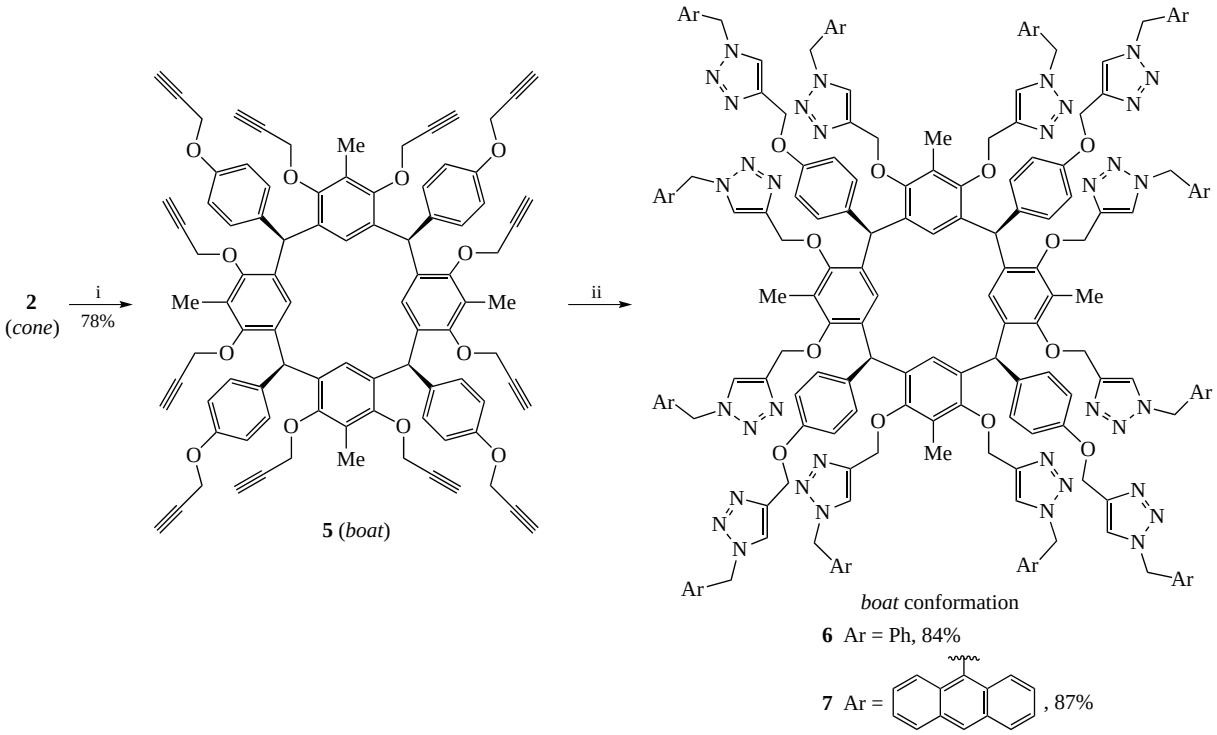
Scheme 2 *Reagents and conditions*: i, $ArCH_2N_3$, sodium ascorbate, $CuSO_4 \cdot 5H_2O$, THF/H_2O, room temperature, 24 h.

formed *rccc* and *rctt* isomers. It should be noted that *rctt* isomer **1** also undergoes analogous click reactions; however, elevated temperatures and longer reaction time are necessary.

The *O*-alkylation of phenolic groups of compound **2** with propargyl bromide in the presence of K_2CO_3 gave rise to novel calix[4]resorcinol **5** with multiple ethynyl fragments in 78% yield (Scheme 3). The process was monitored by MALDI mass spectrometry and terminated when it showed only one peak of the dodecapropargylated derivative **5** (~12 h). Note that *rctt* isomer **1** may be also involved in this reaction;[20] however, the target octapropargylated product is formed only after 24 h of processing. Dodecapropargylated calix[4]resorcinol **5** is a light-orange powder highly soluble in most organic solvents. Its IR spectrum shows the alkyne absorption bands. ^1H and ^{13}C NMR spectra of the calix[4]resorcinol **5** reveal a double set of hydrogen and carbon atoms of 2-methylresorcinol fragments of calix[4]-resorcinol core, which indicates conformational change from *cone* (C_{4v}) to *boat* (C_{2v}) with *rccc* configuration of substituents in solution of this compound (*cf*. refs. 32–35).

The click reaction of dodecapropargylated calixarene **5** with benzyl azide or 9-(azidomethyl)anthracene resulted in novel compounds **6**, **7** bearing twelve 1,2,3-triazole nuclei (see Scheme 3). The reactions were monitored by MALDI mass spectrometry. The structure of synthesized compounds was confirmed by NMR (^1H, ^{13}C) spectroscopy, MALDI mass spectrometry and elemental analysis. The IR spectra of products **6**, **7** do not contain absorption bands characteristic of triple bonds, which proves the completion of the reaction. The configuration features are retained, and the resulting macrocycles **6**, **7** adopt *boat* conformation. It is of note that analogous per-*O*-propargylated *rctt* isomer also undergoes similar click transformations; however, these products are almost insoluble and the subsequent structural and chemical investigations are practically impossible (in this case, the reaction progress may only be stated from IR spectra according to the disappearance of intrinsic bands of triple bonds).

In summary, we have synthesized the novel *rccc* diastereomer of calix[4]resorcinol derivative in *cone* conformation with terminal triple bonds in aromatic substituents, which is identical in composition and structure to the previously synthesized *rctt* diastereomer in *chair* conformation, but features excellent solubility in most organic solvents. This opens broad opportunities to the modification of this compound involving free hydroxy groups and terminal triple bonds with the aim to design and study the characteristics of new types of highly functionalized macromolecules including dendrimer-like structures. We have compared some characteristics and reactivity of the synthesized *rccc* or *rctt* isomers in *O*-alkylation and click reactions. As a result of these reactions, new highly functionalized



Scheme 3 *Reagents and conditions*: i, $BrCH_2C{\equiv}CH$, K_2CO_3, MeCN, reflux, 12 h; ii, $ArCH_2N_3$, sodium ascorbate, $CuSO_4 \cdot 5H_2O$, THF/H_2O, room temperature, 24 h.

triazole-linked calix[4]resorcinols were produced, which may be classified as zero-generation dendrimers having calix[4]-resorcinol core and triazole units in each of 4 or 12 branches.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.04.031.

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