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Synthesis and structural features of new calix[4]resorcinols with anthracene- and pyrene-ended isoxazole-containing fragments

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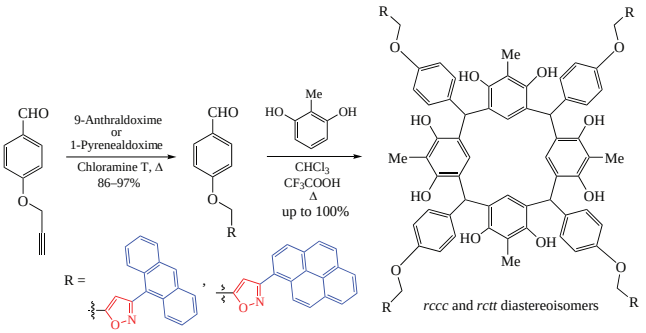
Reactions between 4-(propargyloxy)benzaldehyde with anthracene-9-carbaldehyde oxime or pyrene-1-carbaldehyde oxime in the presence of chloramine T in ethanol lead to new isoxazole-containing derivatives of benzaldehyde. The subsequent acid-catalyzed condensation of these compounds with 2-methylresorcinol in chloroform/trifluoroacetic acid mixtures affords novel calix[4]resorcinols with anthacene- and pyrene-ended isoxazole-containing fragments as all–*cis* (*rccc*) and *cis–trans–trans* (*rctt*) diastereoisomers, their ratios being dependent on the CF_3CO_2H percentage in the medium. The crystal structures of pyrene-ended isoxazole-containing benzaldehyde and corresponding calix[4]resorcinol *rctt* isomer have been established by single crystal X-ray diffraction.



Keywords: calix[4]resorcinols, condensation, isoxazole, anthracene, pyrene, diastereoisomer.

Calix[4]resorcinols are unique but accessible macrocyclic compounds which can be readily modified at multiple positions. The presence of macromolecular cavity in calix[4]resorcinols, a number of reaction centers, various substituents, and their pre-organization on a calixarene scaffold, in addition to the hydrogen bonding ability and conformational diversity of spatial structure of these molecules provide a challenge to the design of their new representatives.[1–6]

Functionalized derivatives of calix[4]resorcinols are prepared either *via* direct acid-catalyzed cyclocondensation of functional aldehydes or acetals[7–15] with resorcinols or through modification of the very calixarene scaffold. Calix[4]resorcinols may exist in various stereoisomeric forms such as all-*cis* (*rccc*), *cis–trans–trans* (*rctt*), *cis–cis–trans* (*rcct*), and *trans–cis–trans* (*rtct*) differing by the spatial arrangement of substituents at the methine bridges. The formation of a particular isomer depends on a number of factors, such as the structure of precursors, nature of solvents, catalysts, and their ratios as well as the relative solubility of produced macrocyclic isomers. Complexity of this approach involves separation of the mixture of isomers or optimization of the conditions for the selective preparation of a particular isomer.

An advantage of functionalization of the calix[4]resorcinol scaffold is that chemical transformations proceed with the retention of configuration of macromolecule; however, employment of pure starting diastereoisomer or subsequent separation of stereoisomer products are necessary.[1,3,4,14] To functionalize macrocyclic compounds including calixarenes, click reactions are widely used, in particular, Cu-catalyzed azide–alkyne cycloaddition toward triazole-containing calixarenes displaying sensing ability to various metal ions.[16–23] However, a copper-free click approach, namely, catalyst-free nitrile oxide–alkyne cycloaddition (NOAC) leading to isoxazoles was utilized in the chemistry of macrocyclic compounds quite rarely. In the course of this reaction, the corresponding nitrile oxide is generated *in situ* by exposure of chloramine T on starting oxime without catalyst. A few examples of such reactions of functionalized oximes with a classical calix[4]arene scaffold containing terminal triple bonds are known.[24–26] Isoxazole derivatives of calix[4]arenes with bulky pyrene or anthracene groups which may be obtained by these reactions look promising highly selective copper(II) ion chemosensors.[24]

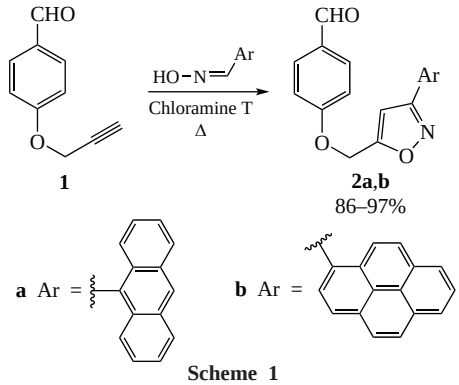
In this work, we studied the reactions of benzaldehyde derivatives and calix[4]resorcinol bearing terminal triple bonds with anthracene- and pyrene-containing oximes in the presence of chloramine T in order to synthesize new isoxazole-containing calix[4]resorcinol derivatives. We disclosed that pre-functionalization of the starting aromatic aldehyde prior to condensation with 2-methylresorcinol was the only synthetic pathway for target macrocyclic compounds.

We have previously synthesized *rccc* and *rctt* diastereoisomers of calix[4]resorcinols containing from 4 to 12 terminal acetylene moieties which seemed to be interesting multifunctional objects for the study of various click reactions and for the design of complex macrocyclic objects.[14,27] However, their reaction with anthracene-9-carbaldehyde oxime[28] or pyrene-1-carbaldehyde oxime[29] in the presence of chloramine T in ethanol upon heating did not afford the desired isoxazole-containing calix[4]resorcinols.

In fact, the reaction brought about much precipitate which did not dissolve neither at long-term heating of the reaction mixture nor at its dilution. IR spectrum of the precipitate showed the absorption bands intrinsic for terminal triple bond at 2125–2126 (C≡C) and 3290 cm^{-1} (C≡CH), as well as for C=N-bond at 1602–1605 cm^{-1}; that is, there was incomplete conversion of the precursor. Its MALDI mass spectrum did not show peaks for the desired products including partially substituted ones. Taking into account poor solubility of the formed substance, it looked unreal to prepare the target isoxazole-containing calix[4]resorcinols from calix[4]resorcinols bearing terminal acetylene moieties.

A more convenient route to the synthesis of isoxazole-containing calix[4]resorcinols is to perform the click reaction prior to condensation. For this purpose, modification of 4-(propargyloxy)benzaldehyde **1** with oximes of anthracene-9-carbaldehyde or pyrene-1-carbaldehyde in the presence of chloramine T in refluxing ethanol (12 h) was carried out to afford new isoxazole-containing anthracene- or pyrene-ended derivatives **2a**,**b** (Scheme 1). Products **2a**,**b** appear as light-yellow powders soluble in most organic solvents. Their structures were confirmed by ^{1}H, ^{13}C NMR, IR spectroscopy, mass spectrometry, elemental analysis; the crystal structure of compound **2b** was established by single crystal X-ray diffraction (Figure 1).† For the synthetic details and characteristics of compounds obtained, see Online Supplementary Materials.

Subsequent condensation of aldehydes **2a**,**b** with 2-methylresorcinol was studied in chloroform and trifluoroacetic acid at their various ratios. We recently discovered[14,15] that an increase in the trfluoroacetic acid (TFA) content in chloroform had an impact on the ratio of formed *rccc*/*rctt* diastereomers of calix[4]resorcinols upon condensation of 2-methylresorcinol and functionalized benzaldehydes. The equal volumes of chloroform and TFA were optimal for the preparation of *rccc* diastereomers in high yields; in this case, the yield of macrocyclic products also increases. With lower content of TFA, *rctt* diastereomers would preferably form.[14,15]



Scheme 1

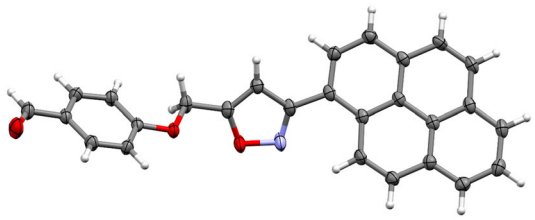


Figure 1 ORTEP view of the molecule in the crystal of **2b**. Displacement ellipsoids are drawn at the 50% probability level.

Herein, the reaction of equimolar amounts of 2-methylresorcinol with anthracene-containing aldehyde **2a** in chloroform in the presence of TFA at a 15 : 1 ratio (v/v) in argon atmosphere at reflux for 32 h gave a mixture of the *rccc* (**3a**) and *rctt* (**4a**) diastereomers in a 1:1.4 ratio, respectively, with a total yield of 70% (Scheme 2, method *a*). Upon increase in the amount of TFA up to the $CHCl_3$/TFA = 1 : 1, a mixture of these isomers in a 1.9 : 1 ratio with the *rccc* isomer **3a** as a major product was formed; the total yield of the products grew up to 76% (see Scheme 2, method *b*). During the condensation of pyrene-containing aldehyde **2b** with 2-methylresorcinol in $CHCl_3$/TFA = 15 : 1, *rctt* isomer **4b** precipitated from the reaction mixture after 5.5 h of processing; in this case, the corresponding *rccc* isomer **3b** remained in the solution. The total yield of the products amounted to 100% and their ratio was 1 : 2.2 with *rctt* isomer being major (method *a*). With an increase in the TFA content in the reaction mixture up to 1 : 1, the fraction of *rctt* isomer increased to the ratio of 3.5 : 1 relative to *rccc* isomer over the same time of reaction (5.5 h), and the total yield of the products also approached 100% (method *b*).

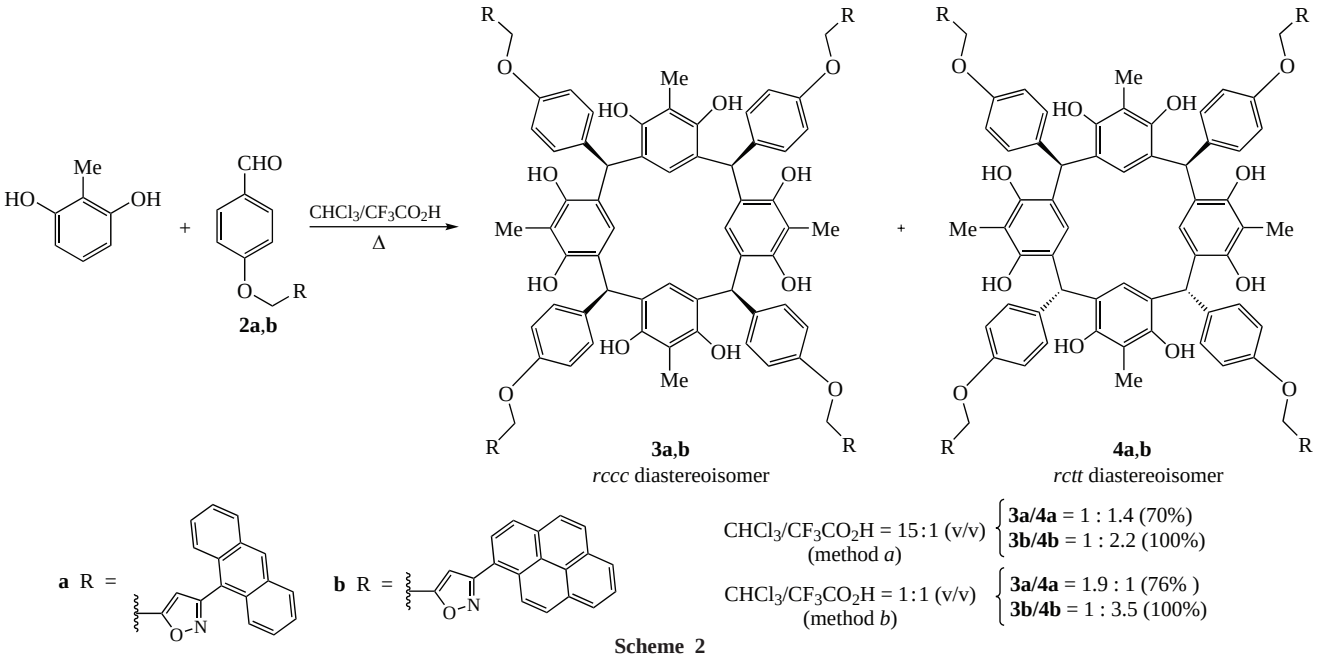
It should be noted that, in this case, an increase in the amount of TFA in the reaction mixture in chloroform did not increase the content of *rccc* isomer **3b**, as observed in our previous works.[14,15] Earlier we related this effect of the increased TFA content in chloroform on the ratio of formed *rccc*/*rctt* isomers to the relative solubility of the *rctt* isomer formed in the reaction. At a low content of TFA, that is, $CHCl_3$/TFA = 15 : 1, a less soluble *rctt* isomer, the kinetic product, precipitates from the reaction mixture, and the reaction does not further proceed. With an increase in the TFA content to the $CHCl_3$/TFA ratio of 1 : 1, the relative solubility of *rctt* isomer increases, equilibrium condensation continues, and the *rccc* isomer of corresponding calix[4]resorcinol, the thermodynamic product, is predominantly

† X-ray diffraction (XRD) study of the single crystal **2b** and **4b** were obtained on a Bruker D8 QUEST three-circle diffractometer with a PHOTON III area detector and an IμS DIAMOND microfocus X-ray tube at 150(2) K: λ(Mo $K\alpha$) = 0.71073 Å, ω/ϕ scanning mode with a step of 0.5°. Data collection and indexing, determination, and refinement of unit cell parameters were carried out using the APEX3 software package. Numerical absorption correction based on the crystal shape, additional spherical absorption correction, and systematic error correction were performed using the SADABS-2016/2 software.[30] The structures were solved by the intrinsic phasing method using the SHELXT-2018/2 program[31] and refined by full-matrix least-squares on F^2 using the SHELXL-2018/3 program.[32] Nonhydrogen atoms were refined anisotropically. Positions of H(O) hydrogen atoms were determined from difference electron density maps and refined isotropically. The positions of hydrogen atoms of methyl groups were inserted using the rotation of the group with idealized bond angles. The remaining hydrogen atoms were refined using a riding model. Most calculations were performed using the WinGX-2021.3 software package.[33]

Crystal data for **2b**. $C_{27}H_{17}NO_3$ (M = 403.42), colorless plate crystal, monoclinic, $P2_1/c$, a = 15.0205(6), b = 7.6051(3) and c = 16.7132(7) Å, β = 98.359(2)°, V = 1888.91(13) Å^3, Z' = 1, d_{calc} = 1.419 g cm^{-3}, μ(Mo $K\alpha$) = 0.093 mm^{-1}. F(000) = 840, reflections collected = 42312, unique = 4137, R_{int} = 0.0758, full-matrix least-squares on F^2, parameters = 280, restraints = 0. Final indices R_1 = 0.0683, wR_2 = 0.1647 for 3376 reflections with $I > 2\sigma(I)$, goodness-of-fit on F^2 = 1.160, largest difference in peak and hole (0.315 and –0.246 e Å^{-3}), data completeness 0.999.

Crystal data for **4b**. $C_{136}H_{92}N_4O_{16}\cdot 7(CH_3)_2SO$ (M = 2585.02), colorless prism crystal, triclinic, $P\bar{1}$, a = 12.2841(6), b = 20.1982(10) and c = 29.1846(13) Å, α = 80.748(2)°, β = 77.926(2)°, γ = 83.458(2)°, V = 6964.7(6) Å^3, Z' = 1, d_{calc} = 1.233 g cm^{-3}, μ(Mo $K\alpha$) = 0.183 mm^{-1}. F(000) = 2716, reflections collected = 386836, unique = 30438, R_{int} = 0.0959, full-matrix least-squares on F^2, parameters = 1683, restraints = 8. Final indices R_1 = 0.0864, wR_2 = 0.2257 for 21029 reflections with $I > 2\sigma(I)$, goodness-of-fit on F^2 = 1.030, largest difference in peak and hole (2.167 and –1.221 e Å^{-3}), data completeness 0.1.

CCDC 2252173 (**2b**) and 2252174 (**4b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.



Scheme 2

formed at a higher yield. The current result is presumably associated with the extremely low solubility of the formed *rctt* isomer **4b** under the employed reaction conditions. In this case, the role of excess of TFA is to accelerate the reaction, which also affects the ratio of formed isomers, but increases the fraction of *rctt* isomer, the kinetic product, which precipitates from the reaction mixture. The choice of more solubilizing reaction medium for this reaction could presumably provide better access to the corresponding *rccc* isomer.

The *rccc*-isomers **3a**,**b** appear as beige powders soluble in most organic solvents; the *rctt* isomers **4a**,**b** are white powders soluble only in DMSO and DMF. The difference in their solubility and chromatographic mobility provided obtaining these compounds in individual forms. Their structures were confirmed by NMR (^{1}H, ^{13}C) and IR spectroscopy; the composition was proved by mass spectrometry (MALDI-MS) and elemental analysis data. The assignment of signals in the NMR spectra of macrocyclic products was performed on the basis of ^{1}H, ^{13}C, HSQC, COSY, and HMBC experiments.

The structure and conformation of **4b** were unambiguously confirmed by single crystal X-ray diffraction.† Compound is crystallized in triclinic unit cell with seven DMSO molecules. The calix[4]resorcinol molecule in the unit cell is located in the *chair* conformation (Figure 2). All the DMSO molecules are located outside the pseudocavities of the calixarene molecule and form hydrogen bonds with three hydroxy groups of horizontally directed resorcinol moieties and three hydroxy groups of the vertically directed ones, the two remaining hydroxy groups of resorcinol moieties remain unsolvated.

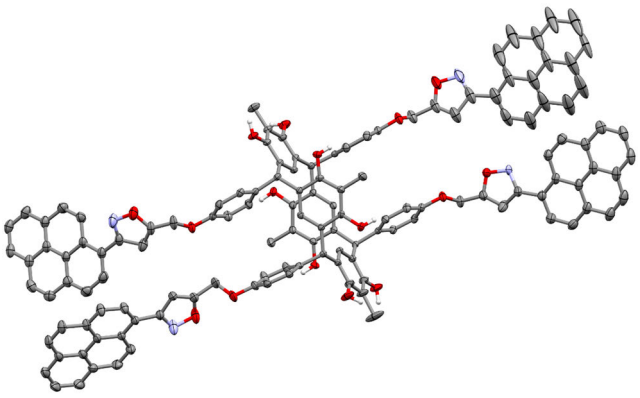


Figure 2 ORTEP view of the molecule in the crystal of **4b**. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms (excluding H-atoms of hydroxyl groups) and solvent molecules are omitted for clarity.

In summary, we have performed an effective synthesis of new isoxazole-containing calix[4]resorcinols with anthracene- and pyrene-ended organic fragments. Our approach involved preliminary functionalization of 4-(propargyloxy)benzaldehyde with the corresponding oximes in the presence of chloramine T in ethanol and subsequent condensation of modified benzaldehydes with 2-methylresorcinol in chloroform in the presence of trifluoroacetic acid. As a result, *rccc* and *rctt* isomers of the target calix[4]resorcinols were formed whose ratios and yields depended on the chloroform-to-trifluoroacetic acid ratio in the medium.

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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.2024.04.025.

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