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Synthesis of novel highly functionalized triazole-linked calix[4]resorcinols *via* click reaction

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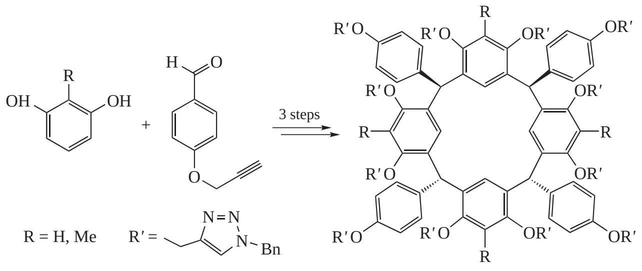
A single-step acid-catalyzed condensation of resorcinol or 2-methylresorcinol with 4-(prop-2-yn-1-yloxy)benzaldehyde stereoselectively gives exclusively *rctt*-isomers of new calix[4]resorcinols in chair conformation bearing four terminal alkyne groups at aromatic substituents. Further alkylation of free hydroxy groups with propargyl bromide affords new calix[4]resorcinols containing 12 terminal alkyne groups. Subsequent click reaction of these compounds with benzyl azide results in highly functionalized calix[4]resorcinols with 12 triazole-linked branches.

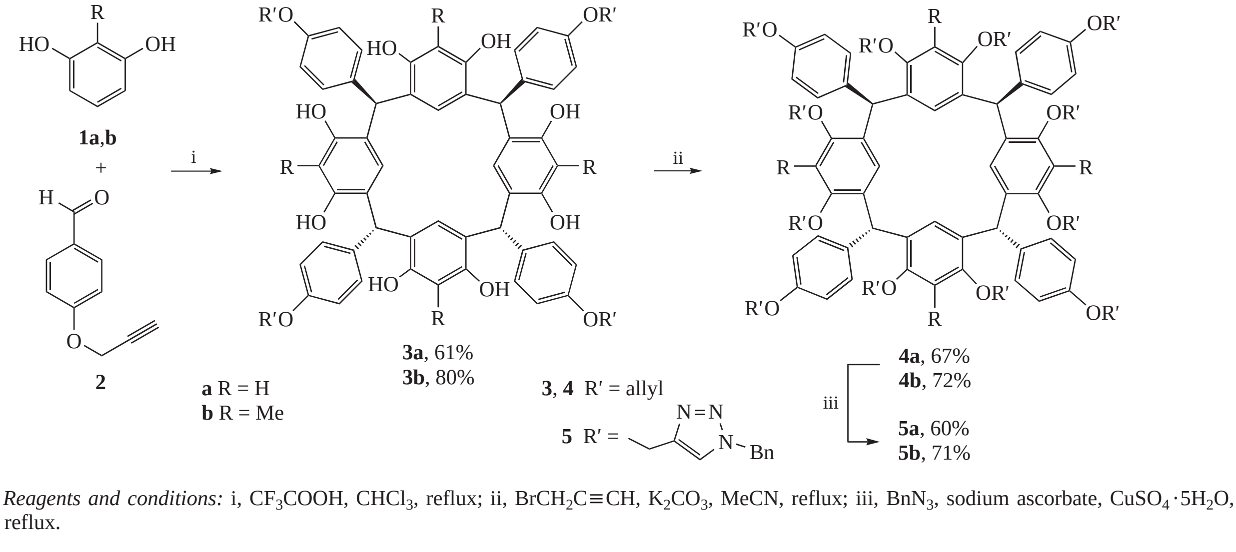


In recent years, Cu-catalyzed azide–alkyne cycloaddition (click reaction) has attracted an increasing attention as a simple and effective strategy for the formation of 1,2,3-triazole ring.[1–3] In the chemistry of macrocyclic compounds, in particular, calixarenes, the click reaction is used as a sufficiently easy approach to their modification and the design of more complex macromolecules. For example, functionalization of calixarenes with triazole-containing fragments using click reaction afforded their amphiphilic[4] and water-soluble derivatives,[5] cavitands and calix nanotubes,[6] multivalent glycoclusters,[7,8] calixarene-based chemosensors,[9–15] analogues of antitumor agents,[16] drug-solubilising agents,[17] effective dye sorbents,[18] and others.

Calix[4]resorcinols have significantly more diverse synthetic opportunities for subsequent modification as compared to classical calixarenes, which is determined by the conformational stability and a large number of phenyl hydroxyl groups. In addition, the availability of these macrocyclic compounds is related to the single-step acid-catalyzed condensation of resorcinol and its derivatives with functionalized aldehydes, which usually proceeds in sufficiently high yields.[19–26]

In this work, we synthesized new triazole-modified calix[4]resorcinols employing click reaction of calix[4]resorcinols containing 12 alkyne terminal groups with benzyl azide.

To access novel calix[4]resorcinols, we firstly carried out the condensation of equimolar amounts of resorcinol **1a** or 2-methylresorcinol **1b** with 4-(prop-2-yn-1-yloxy)benzaldehyde **2**[27] in $CHCl_3$ in the presence of trifluoroacetic acid under argon atmosphere (Scheme 1). The thus obtained calix[4]resorcinols **3a**,**b**



Scheme 1 *Reagents and conditions:* i, CF_3COOH, $CHCl_3$, reflux; ii, $BrCH_2C{\equiv}CH$, K_2CO_3, MeCN, reflux; iii, BnN_3, sodium ascorbate, $CuSO_4\cdot 5H_2O$, THF–H_2O, reflux.

contained four terminal alkyne groups in aromatic substituents. Note that the reaction proceeds strictly stereospecifically affording only *rctt*-isomer in chair conformation in moderate to high yields (from 61 to 80%).[†]

The structure of synthesized compounds **3a**,**b** was confirmed by NMR (^{1}H, ^{13}C) and IR spectroscopy; the composition was proved by mass spectrometry (MALDI) and elemental analysis data. The ^{1}H and ^{13}C NMR spectra of compound **3b** in the chair conformation display doubling of their proton and carbon signals for the resorcinol fragments; this attests to the different, vertical and horizontal, arrangements of opposite resorcinol rings with respect to the macrocyclic plane as was in the case of analogous thiophosphorylated calix[4]resorcinols[24,25] (for details, see Online Supplementary Materials).

The chair conformation of calixarene **3b** was confirmed by single crystal X-ray diffraction method.[‡] The crystals suitable for X-ray analysis were grown from DMSO solution. Two perspective views of the molecules are shown in Figure 1. Compound **3b** crystallized with DMSO molecules, macrocycle is situated at the special position, namely, in the centre of symmetry of triclinic unit cell (space group $P\bar{1}$), *i.e*. the calix[4]resorcinol : DMSO stoichiometry in the crystal is 1 : 4. Two symmetrically independent DMSO molecules are disordered over two positions in the crystal with relative occupancies 0.52 : 0.48 and 0.81 : 0.19. All DMSO molecules are located outside the pseudocavities of the calixarene molecule. The detail of the crystal packing for calix[4]resorcinol **3b** are shown in Figure 2.

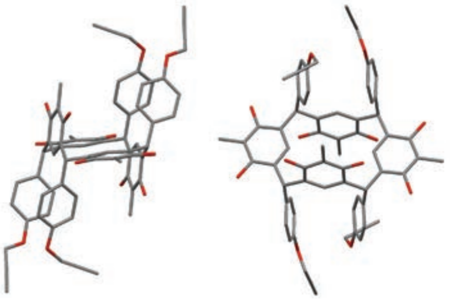


Figure 1 Two projections of the calix[4]resorcinol **3b** molecule in the crystals. Hydrogen atoms (excluding H-atoms of hydroxyl groups) and solvent molecules are omitted for clarity.

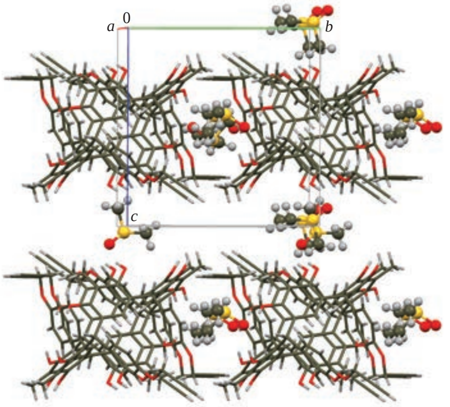


Figure 2 Crystal packing for **3b**: calix[4]resorcinol colons are shown in the ‘stick’ model style and solvent molecules, which localized in the channels along 0*a* axis, are shown in the ‘ball-stick’ style. View along 0*a* axis.

Bulky substituents of the calix[4]resorcinol **3b** hinder dense packing of the molecules in the crystal, so potential cavities for solvent exist in the crystal with overall volume of 512 Å^3 per unit cell, which amounts to 23.9% of unit cell volume. The characteristic feature of macrocycle **3b** is a parallel arrangement of opposite vertical resorcinol rings with respect to the macrocycle plane and co-planar arrangement of horizontal aromatic cycles. Despite the fact that the calixarene **3b** molecule contains eight hydroxyl groups, capable of forming classical hydrogen bonds, they are involved only in the hydrogen bonding with the solvent DMSO molecules. Therefore, they participate in the intermolecular interactions and constructing of the supramolecular structure in the crystal only indirectly, *via* solvate molecules. These DMSO molecules are involved both in the classical hydrogen bonds and in the π-electronic contacts with resorcinol moieties. Such a system of interactions leads to channel-type location of the solvent molecules in the crystal of **3b**, the direction of the channels coincides with the 0*a* axis.

O-alkylation of calix[4]resorcinols **3a**,**b** with propargyl bromide in the presence of K_2CO_3 under argon atmosphere affords products **4a**,**b** bearing 12 terminal alkyne groups in 67–72% yields (see Scheme 1). The reaction was monitored by MALDI mass spectrometry and was terminated as soon as the spectrum showed only one signal of the target **4a**,**b** (~24 h).

Subsequent click reaction of calixresorcinols **4a**,**b** with benzyl azide in THF–H_2O (1 : 1) in the presence of $CuSO_4$ / sodium ascorbate catalytic system (60–65 °C, 24 h) provided novel calix[4]resorcinols **5a**,**b** in chair conformation in 60 and 71% yields, respectively. The structure of synthesized compounds was confirmed by ^{1}H NMR spectroscopy, MALDI mass spectrometry and elemental analysis. The IR spectra of products **5a**,**b** do not exhibit intrinsic absorption bands of C≡C and C=C–H groups, which proves the completion of the reaction.

According to NMR spectral data, the chair conformation is preserved in all products. In analogy to macrocycles **3a**,**b**, ^{1}H NMR spectra of compounds **4a**,**b** and **5a**,**b** display the doubling of the signals of protons of resorcinol rings, which proves the different, horizontal and vertical, arrangements of the distal aromatic fragments with respect to the macrocycle plane. This shows that both calix[4]resorcinols **5a**,**b** and their precursors **3a**,**b** and **4a**,**b** exist in chair conformation with *rctt*-configuration of aromatic substituents.

In conclusion, novel calix[4]resorcinols equipped with twelve triazole moieties were obtained clearly from available reactants in three simple steps. The obtained compounds may be regarded as zero-generation dendrimers incorporating calix[4]resorcinol core and triazole units in each of 12 branches.

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[†] For synthesis and characteristics of compounds obtained, see Online Supplementary Materials.

[‡] The X-ray diffraction data for the crystal of **3b** were collected on a Bruker Smart Apex II CCD diffractometer in the ω- and φ-scan modes using graphite monochromated MoKα radiation [λ(MoKα) = 0.71073 Å] at 296(2) K. The crystal of **3b** is air sensitive and weakly diffracts, two solvent molecules are disordered over two positions with relative occupancies 0.59 : 0.41 and 0.81 : 0.19.

Crystal data for **3b**: $C_{68}H_{56}O_{12}\cdot 4(C_2H_6OS)$, colourless prism, M = = 1377.64, triclinic, space group $P\bar{1}$, a = 12.001(6), b = 13.699(7) and c = 13.809(7) Å, α = 87.507(7)°, β = 79.646(7)°, γ = 78.022(7)°, V = 2184.5(18) Å^3, Z = 1, d_{calc} = 1.047 g cm^{-3}, μ(MoKα) = 0.164 mm^{-1}. F(000) = 728. A total of 18964 reflections were collected, 7851 unique, R_{int} = 0.0787, 495 parameters with 78 restraints. The structure was solved using full-matrix least-squares method on F^2. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were inserted at calculated positions and refined as riding atoms except the hydrogen atoms of NH and OH groups, which were located from difference maps and refined isotropically. Final indices: R_1 = 0.0618, wR_2 = 0.1571 for 7851 reflections with $I > 2\sigma(I)$, GOF on F^2 = 0.985, largest difference peak/hole 0.210/–0.317 eA^{-3}.

CCDC 1515436 contains 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.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.11.005.

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