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Synthesis and structure of new chlorine containing calix[4]resorcinols

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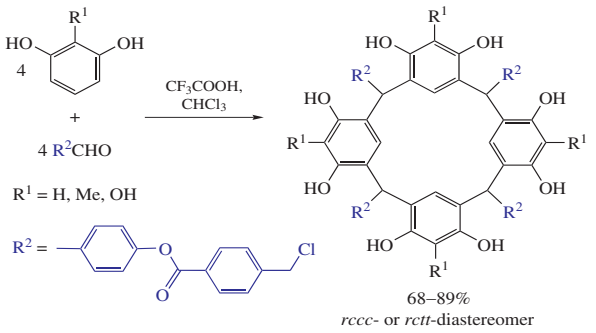
New calix[4]resorcinols containing four organochlorine moieties have been synthesized in high yields *via* one-step condensation of resorcinol, 2-methylresorcinol or pyrogallol with 4′-formylphenyl 4-(chloromethyl)benzoate. It has been found that the diastereomeric ratio of the products depends substantially on the starting polyphenol. The *rctt*- and/or *rccc*-diastereomers have been isolated and their structure and composition have been determined by ^{1}H, ^{13}C NMR and IR spectroscopy, MALDI mass spectrometry and elemental analysis, the crystal structure of one *rctt*-product has been established by single crystal X-ray diffraction.



Halogen containing calixarenes are typically functionalized at the upper rim and find an application in the design of new macrocyclic receptors, in particular phosphorus containing ones, using various methods of their structural modification.[1,2] For example, water-soluble calix[*n*]arenes bearing *para*-phosphonic acid moieties,[3] used as receptors for organic molecules like benzene derivatives and isobutanol,[4] or amphiphilic calix[4]arenes with phosphonyl groups, which found an application as effective binders for biorelevant uracil derivatives,[5] were synthesized by introduction of organophosphorus groups into the upper rim of halogen containing calix[*n*]arenes through the Ni^{II}-catalyzed Arbuzov reaction.

Calix[4]resorcinols are cyclic products of acid-catalyzed condensation of resorcinol or its derivatives, like 2-methylresorcinol and pyrogallol, with aliphatic or aromatic aldehydes, and these products are known to have four possible diastereoisomers with *rccc*-, *rcct*-, *rctt*- and *rtct*-configurations of substituents relative to the macrocycle plane.[6] The ratio of diastereoisomers formed under particular reaction conditions depends on factors like the structure of starting aldehyde and the resorcinol derivative as well as on the catalysts and solvents used. For example, the reaction of long chain aliphatic aldehydes with resorcinol results in predominant formation of *rccc*-isomer,[7] while aromatic aldehydes usually afford a mixture of *rccc*- and *rctt*-isomers.[8–11] Besides, calix[4]-resorcinols can exist in *1,2-alternate*, *1,3-alternate*, *cone* and *chair* conformations, differing in the arrangement of aromatic rings relative to each other and to the macrocycle plane. The preferred conformation and configuration depend on reaction conditions and nature of substituents in the calixarene matrix.[6]

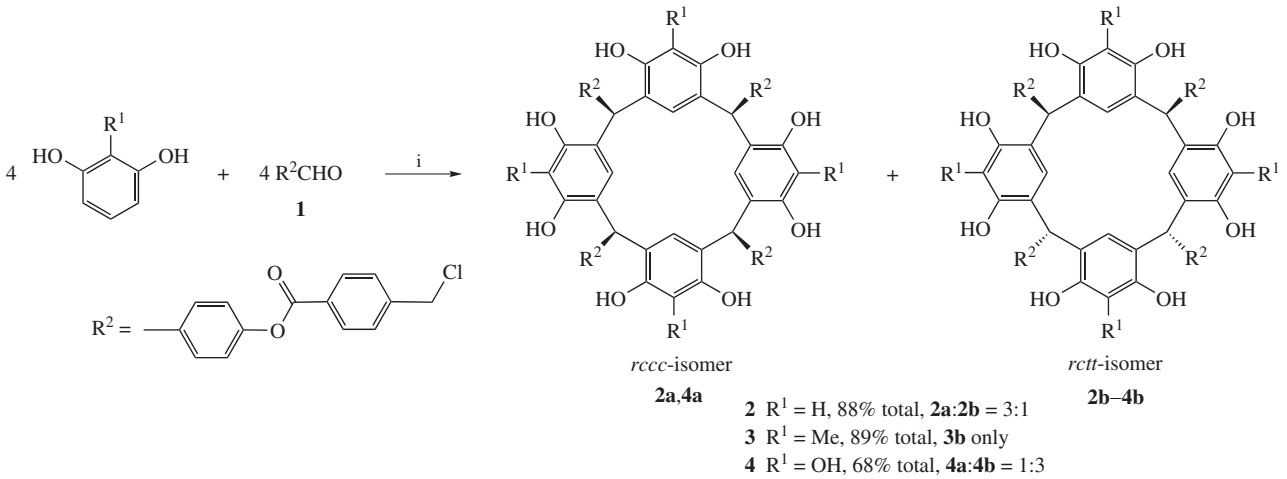
To develop a synthesis of new calix[4]resorcinols with four organochlorine moieties at the lower rim of the macromolecule, contrary to the typical functionalization at the upper rim, in this work we used 4′-formylphenyl 4-(chloromethyl)benzoate **1** for the condensation with resorcinol and its derivatives. Compound **1** was obtained by the reaction of 4-hydroxybenzaldehyde with 4-(chloromethyl)benzoyl chloride in the presence of triethylamine in 89% yield (for the synthesis and characteristics of the compounds obtained, see Online Supplementary Materials).

In our hands, the diastereomeric ratio of calix[4]resorcinols formed significantly depended on the starting polyphenol (Scheme 1). Thus, equimolar amounts of resorcinol and aldehyde **1** in chloroform in the presence of trifluoroacetic acid under reflux for 24 h resulted in the mixture of *rccc*- and *rctt*-diastereoisomers **2a** and **2b**, respectively, in the corresponding *cone* and *chair* conformations, in a 3 : 1 ratio and a total yield of 88%. Compounds **2a** and **2b** were separated and isolated by flash chromatography. Similar reaction of 2-methylresorcinol and aldehyde **1** led to single *rctt*-diastereomer **3b** in the *chair* conformation in 89% yield. Condensation of pyrogallol and aldehyde **1** under similar conditions afforded a mixture of two diastereomers **4a** and **4b** (1 : 3) in 68% total yield, and the *rctt*-isomer **4b** was isolated in pure form, due to the difference in solubility, by consecutive recrystallizations from acetone and ethanol, while we failed to isolate compound **4a** in a pure form.

The structures of the macrocyclic products **2**–**4** were confirmed by ^{1}H, ^{13}C NMR and IR spectroscopy, their composition was confirmed as well by MALDI mass spectrometry and elemental analysis. The assignment of NMR signals was carried out using COSY, HSQC and HMBC experiments.

In the NMR spectra of compound **2a**, only one signal corresponds to each group of atoms, which indicates the highly symmetric *cone* conformation in solution. For calixarenes **2b**–**4b** in the *chair* conformation, the doubling of ^{1}H and ^{13}C signals for resorcinol moieties is observed, because the opposite aromatic rings are arranged vertically or horizontally with respect to the macrocycle plane, corresponding to our earlier results.[11,12]

The structure and conformation of compound **3b** were unambiguously confirmed by the single crystal X-ray diffraction (Figure 1).[†] The crystals suitable for X-ray analysis were grown from DMSO solution. Compound **3b** is crystallized in triclinic unit cell with six DMSO molecules, five of which are disordered. All the DMSO molecules are located outside the pseudocavities of the calixarene molecule and form hydrogen bonds with four hydroxyl groups of horizontally directed resorcinol moieties and two hydroxyl groups of the vertically directed ones, the two



Scheme 1 *Reagents and conditions*: i, CF_3COOH, $CHCl_3$, 60–65°C, 24 h.

remaining hydroxyl groups of vertically directed resorcinol moieties remain unsolvated. The terminal chloromethyl groups of the macromolecule are disordered in two positions. The feature of the *chair* conformation for compound **3b** is the parallel arrangement of the opposite resorcinol rings in the vertical position relative to the macrocycle plane and coplanar arrangement of the horizontal rings.

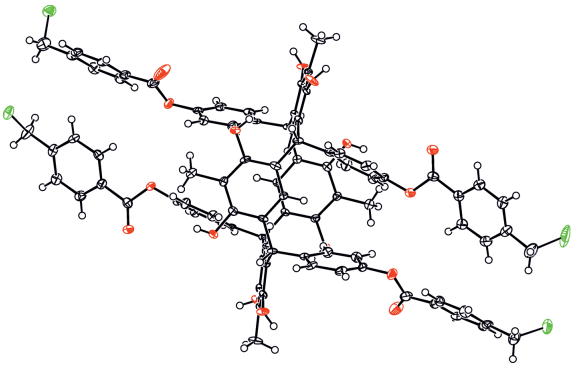


Figure 1 ORTEP view of chloro-substituted calix[4]resorcinol molecule in the crystal of **3b**. Displacement ellipsoids are drawn at the 50% probability level. Solvent molecules are omitted for clarity.

† The X-ray diffraction data for the single crystal of compound **3b** were collected on a Bruker Kappa Apex II CCD diffractometer, equipped with an Oxford Cryostream LT device, in ω-scan mode using graphite monochromated MoKα (λ = 0.71073 Å) radiation at 100 K. The operation mode of the sealed X-ray tube was 50 kV and 30 mA. For the data collection, the images were indexed and integrated using APEX2 data editing package (v.2014.11-0, Bruker AXS). The structure was solved by direct methods using SHELXT-2014/5 and refined by the full-matrix least-squares on F^2 using SHELXL-2017/1. Calculations were mainly performed using WinGX-2014.1 program suite. Non-hydrogen atoms were refined anisotropically. The H(C) hydrogen atoms were inserted at the calculated positions and refined as riding atoms. The H(O) hydrogen atoms were inserted at the calculated positions and refined with AFIX 147.

Crystal data for **3b**·6DMSO. $C_{100}H_{104}C_{14}O_{22}S_6$ (M = 1992.00), yellow plates, triclinic, space group $P\bar{1}$, a = 15.1625(12), b = 18.4880(14) and c = = 19.2124(15) Å, α = 85.691(4)°, β = 74.048(4)°, γ = 66.192(3)°, V = = 4733.7(7) Å^3, Z = 2, d_{calc} = 1.398 g cm^{-3}, μ(MoKα) = 0.331 mm^{-1}. F(000) = 2088, total of 119196 reflections were collected, from which 18484 unique (R_{int} = 0.113), 1301 parameters and 1 restraint were used for refinement. Final indices R_1 = 0.0804, wR_2 = 0.2013 for 9884 reflections with $I > 2\sigma(I)$, GOF = 1.02, largest difference peak/hole −1.16/1.20 e A^{-3}.

CCDC 1903867 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.

In summary, the one step acid-catalyzed condensation of resorcinol, 2-methylresorcinol and pyrogallol with 4′-formylphenyl 4-(chloromethyl)benzoate results in new calix[4]resorcinols with four organochlorine moieties in aromatic substituents of the calixarene matrix. It has been demonstrated that, depending on the starting polyphenol, *rccc*- and/or *rctt*-diastereoisomers are formed in high yields and can be isolated. The macrocyclic products with synthetically promising chlorine substitution can be further modified through the reactions with phosphorus(III) derivatives into new P-containing ligands for subsequent investigation of complex formation with metal ions and for application in catalysis.

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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.2019.11.034.

References

1 D. Sémeril and D. Matt, *Coord. Chem. Rev.*, 2014, **279**, 58.
2 I. R. Knyazeva, A. R. Burilov, M. A. Pudovik and W. D. Habicher, *Russ. Chem. Rev.*, 2013, **82**, 150.
3 T. E. Clark, M. Makha, A. N. Sobolev, D. Su, H. Rohrs, M. L. Gross, J. L. Atwood and C. L. Raston, *New J. Chem.*, 2008, **32**, 1478.
4 A. V. Solovyov, S. O. Cherenok, O. I. Kalchenko, L. I. Atamas, Z. I. Kazantseva, I. A. Koshets, I. F. Tsymbal and V. I. Kalchenko, *J. Mol. Liq.*, 2011, **159**, 117.
5 O. Kalchenko, A. Marcinowicz, J. Poznanski, S. Cherenok, A. Solovyov, W. Zielenkiewicz and V. Kalchenko, *J. Phys. Org. Chem.*, 2005, **18**, 578.
6 A. G. S. Högberg, *J. Org. Chem.*, 1980, **45**, 4498.
7 L. M. Tunstad, J. A. Tucker, E. Dalcanale, J. Weiser, J. A. Bryant, J. C. Sherman, R. C. Helgeson, C. B. Knobler and D. J. Cram, *J. Org. Chem.*, 1989, **54**, 1305.
8 Y. Yamakawa, M. Ueda, R. Nagahata, T. Takeuchi and M. Asai, *J. Chem. Soc., Perkin Trans. 1*, 1998, 4135.
9 A. V. Prosvirkin, E. Kh. Kazakova, A. T. Gubaidullin, I. A. Litvinov, M. Gruner, W. D. Habicher and A. I. Konovalov, *Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 2550 (*Izv. Akad. Nauk, Ser. Khim.*, 2005, 2470).
10 I. R. Knyazeva, V. I. Sokolova, M. Gruner, W. D. Habicher, V. V. Syakaev, V. V. Khrizanforova, B. M. Gabidullin, A. T. Gubaidullin, Yu. H. Budnikova, A. R. Burilov and M. A. Pudovik, *Tetrahedron Lett.*, 2013, **54**, 3538.
11 I. R. Knyazeva, K. M. Mukhamedyanova, V. V. Syakaev, A. T. Gubaidullin, W. D. Habicher and A. R. Burilov, *Tetrahedron Lett.*, 2018, **59**, 1683.

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