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SHORT COMMUNICATION

Single step preparation and conformational analysis of novel thiophosphorylated ligands based on calix[4]resorcinol matrix

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Abstract We have synthesized novel calix[4]resorcinols with four 2-thioxo-1,3,2-dioxaphospholane groups introduced in aromatic substituents in the methylidene bridges of macromolecules by the condensation of new thiophosphorylated benzaldehyde with resorcinol and its derivatives in acidic media with high yields. The formation of only one *rctt* isomer with corresponding *chair* conformation is observed, which was determined by 2D NMR-experiments.

Keywords Thiophosphorylated calix[4]resorcinol · Condensation · Resorcinol · Aldehyde · Conformation

Introduction

The great interest of many chemists to the calixarene compounds, in particular, calix[4]resorcinols does not weaken over the last decade. Special attention is devoted to their synthesis, conformational behaviour, modification of their upper and lower rims, and ability to form cavitands, capsules, monolayers, and host–guest complexes [1].

Calix[4]resorcinols are known to be readily available by acid-catalyzed condensation of resorcinol and its derivatives with various aliphatic and aromatic aldehydes [2–7] and can exist as four diastereomers. According to Högberg [4], when all four substituents in the calixarene matrix are *cis*-oriented, this compound is considered *rccc* isomer. Three other isomers possess *rcct*, *rctt* and *rtct* configurations of substituents (Fig. 1). The ratio of diastereomers usually depends on the structure of the starting aldehyde. The use of long-chain aliphatic aldehydes in the condensation leads predominantly to the *rccc* isomer [2]. The condensation with aromatic aldehydes usually gives a mixture of the *rccc* and *rctt* isomers [2, 5–7].

Earlier we obtained novel calix[4]resorcinols bearing phosphonate and phosphonium fragments on the lower rim of the molecule by the condensation of phosphorylated derivatives of benzaldehyde with resorcinol [7]. The substitution of oxygen atom of phosphoryl group for sulfur atom is found to enhance remarkably the binding ability of thiophosphate derivatives compared to the "soft" metal ions like Ag^{+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Cu^{+}, Pt^{2+}, Pd^{2+}, and so on [8–10]. Assuming the macrocyclic effect, the binding ability of the calixarene containing a few thiophosphoryl groups can be anticipated to increase by several times with respect to the linear thiophosphates.

Recently we have successfully synthesized novel calix[4]-resorcinols with four diethylthiophosphate groups with the use of 3- and 4-thiophosphorylated benzaldehydes as starting materials in the condensation with resorcinol and its derivatives [11]. Reaction proceeds strictly stereoselectively affording *rctt* isomer in *chair* conformation with moderate yield (from 60 to 65 %). It should be noted that the introduction of thiophosphoryl groups in calixarene framework was so far labor-consuming process and involved predominantly the addition of sulfur atom to trivalent phosphorus atoms, which were primarily introduced on the upper rim of calix[4]resorcinols or cavitands via *O*-phosphorylation [12, 13].

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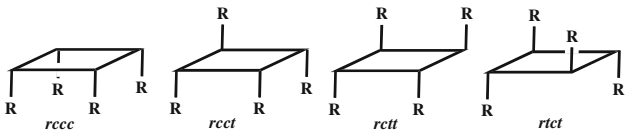


Fig. 1 Configurational isomers of calix[4]resorcinols

In this work, we demonstrated that new thiophosphorylated benzaldehyde **3** is a useful starting material for the single-step stereoselective preparation of *rctt* isomers of novel calix[4]resorcinols in *chair* conformation having four 2-thioxo-1,3,2-dioxaphospholane-containing aromatic substituents with high yields (up to 90 %).

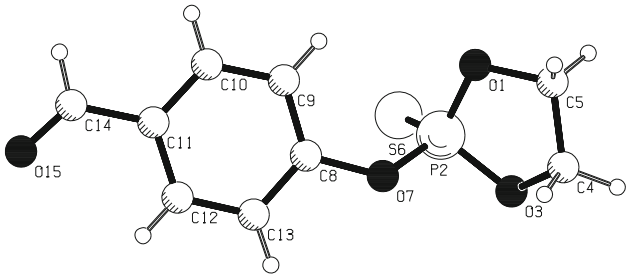


Fig. 2 View of **3** in the crystal. The selected bond lengths (Å) and angles (°) are: P2 O1 1.5667(16), P2 O3 1.5715(16), P2 O7 1.5908(16), P2 S6 1.8897(12), O1 P2 O3 99.37(9), O1 P2 O7 105.94(9), O3 P2 O7 100.64(9), O1 P2 S6 117.05(7), O3 P2 S6 117.34(8), O7 P2 S6 114.20(7)

Results and discussion

A new reactant **3** for calixarene design was obtained as white solid in 58 % yield by the reaction of 2-chloro-2-thioxo-1,3,2-dioxaphospholane with 4-hydroxybenzaldehyde and sodium hydride in anhydrous THF (Scheme 1).

The compound **3** crystallized from the acetone–water mixture in the monoclinic crystal system and $P2_1/c$ space group. Four-coordinated phosphorus atom is a part of a five-membered cycle, which has an *envelope* conformation with the deviation of C4 atom from plane at 0.396(2) Å. The selected bond lengths and angles around the phosphorus atom are in the range of the typical values for thiophosphates and are given in the description of Fig. 2.

Molecules of **3** form chains along *0b* axis by CH…O interactions, benzene rings participate in the $\pi\ldots\pi$ interactions; and, as a result, the layers are formed in *b0c* plane. The layers are linked into a 3D structure by van der Waals forces.

The condensation of thiophosphorylated benzaldehyde **3** with resorcinol and its derivatives (2-methylresorcinol and pyrogallol) **4a–c** resulted in the formation of novel calix[4]resorcinols **5a–c** with four 2-thioxo-1,3,2-dioxaphospholane groups introduced in aromatic substituents of the calixarene matrix (Scheme 2). It should be noted that the reactions under study were accompanied by the side processes, presumably decomposition of the starting aldehyde, under general conditions for this type of interaction (mixture of protic polar solvents like alcohol and water and mineral acid catalyst like concentrated hydrochloric acid) [11]. High yields (up to 90 %) of desired products were attained using chloroform as solvent and trifluoroacetic acid as catalyst.

The ^{31}P, ^{1}H, and ^{13}C NMR data; ESI mass spectra; and elemental analysis are in a good agreement with the structure proposed. The existence of only one signal in the ^{31}P NMR spectrum at approx. 78–79 ppm for each compound is a good evidence for the equivalence of four phosphorus atoms in the molecule.

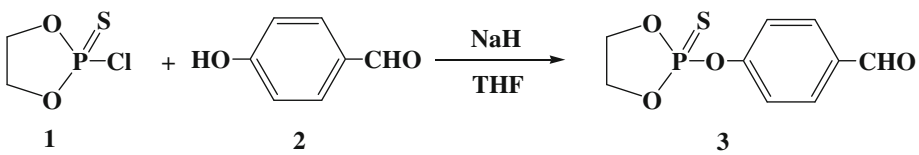
^{1}H and ^{13}C NMR spectra of **5a–c** display a doubling of their proton and carbon signals for the resorcinol fragments as for analogous thiophosphorylated calix[4]resorcinols in our previous publication [11]. This gives reason for the exact elucidation of structures using 2D NMR-experiments, namely, COSY, HSQC, HMBC and ROESY, and the assignment of ^{1}H and ^{13}C signals according to the designation of atoms (see Scheme 2).

Starting with HSQC correlations for C,H-3 and C,H-3′ atoms, the NMR signals for calixarene rings and side chain groups were determined step by step from the HSQC and HMBC spectra. As was shown for compound **5a** (Fig. 3), the well-established HMBC correlations like C_i-4,4′/H-3,3′, as well as C_i-4,4′/5,5′ and C_i-2,2′/5,5′, giving rise to the elucidation of neighboring resorcinol C(H) and C-*ipso* atoms.

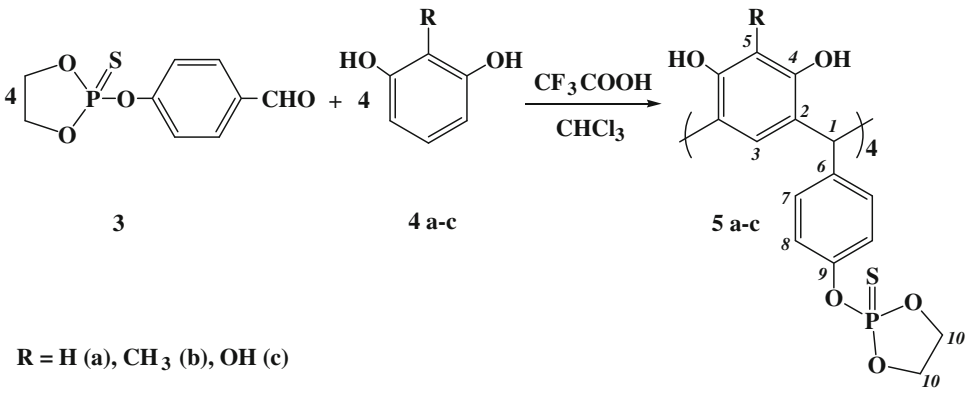
Further correlations between signals of H-1 bridge protons with those of surrounding carbon atoms, namely, C_i-2,2′/H-1, C-3,3′/H-1, as well as C_i-6,C-7/H-1, indicate the symmetric arrangement of calixarene rings and their neighboring side chain groups.

In order to gain an insight into the configuration of the calixarene ring, in particular, for *rcct* or *rctt,* we checked the ROESY spectrum of **5a** (Fig. 4). Owing to the positive cross-peak for calixarene ring protons H-3/H-3′, the *rctt* isomer in *chair* conformation is preferred. Finally, both different types of resorcinol rings in the calixarene structure can be

Scheme 1 Synthetic procedure for preparation of compound **3**



Scheme 2 Synthesis of thiophosphorylated calix[4]resorcinols **5a–c**



distinguished by the means of different ROE intensities for correlations between calixarene ring protons and side chain protons like H-3/H-7 > H-3′/H-7 and H-3/H-1 > H-3′/H-1. Consequently, the orientation of opposite resorcinol rings of calixarene platform in solution is clearly evident—two vertical (*v*) rings with C-1–C-4′ and two horizontal (*h*) rings with C-1–C-4 relative to the macrocycle plane.

Experimental

General procedures

^{1}H and ^{13}C NMR spectra as well as the 2D NMR spectra of COSY, HSQC, HMBC, NOESY and ROESY type were recorded on a Bruker AVANCE-600 spectrometer (600 and 150 MHz, respectively) in d6-DMSO or CDCl3; 31P NMR spectra were recorded on a Bruker MSL-400 NMR-Fourier spectrometer (166.93 MHz). NMR-experiments were carried out in solutions (10 mmol·L^{-1}) at 303 K. The IR spectra of the compounds as emulsions in vaseline were recorded on a Vector 22 FTIR Spectrometer (Bruker) in the 4,000–400 cm^{-1} range at a resolution of 1 cm^{-1}. ESI mass-spectra were recorded on an Esquire-LC 00084 instrument. Microelemental analyses data were obtained on a CHN-3 analyzer and they were within ±0.3 % of the theoretical values for C, H, P, and S. The uncorrected melting points were measured on a Boetius hot-stage apparatus. Thin layer chromatography was performed on Silufol-254 plates; visualization was carried out with UV light. For column chromatography silica gel of 60 mesh from Fluka was used. All solvents were dried according to standard protocols.

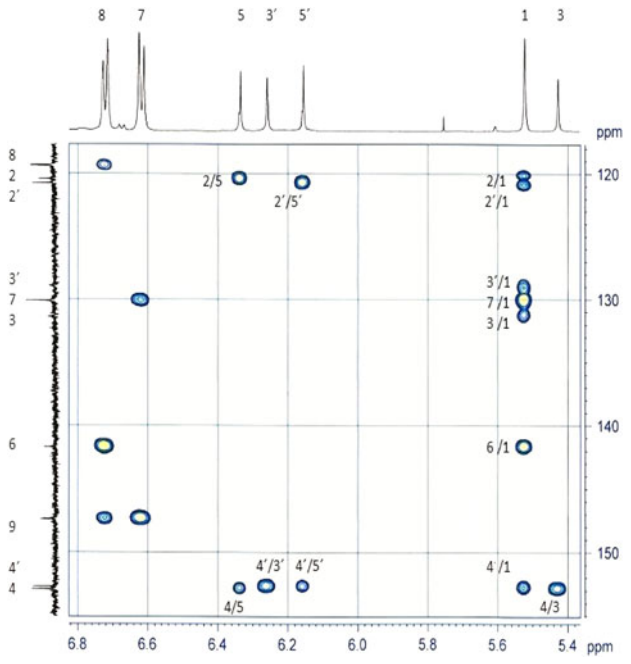


Fig. 3 ^{1}H/^{13}C-HMBC spectrum of **5a** for the aromatic region

X-ray crystallography

Suitable single crystals were obtained from a solution of **3** in mixture of acetone and water at ambient temperature. The X-ray diffraction data for crystal of compound **3**, $C_9H_9O_4PS$, was collected at 296 K on a Bruker AXS Smart Apex II CCD diffractometer in the ω and φ-scan modes using graphite monochromated MoK$_\alpha$ (λ 0.71073Å) radiation. Crystallographic data for compound **3** are given in Table 1. The structure was solved by direct method and refined by the full matrix least-squares using SHELXTL [14] and WinGX [15] programs. All non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were located from the Fourier electron density synthesis and were included in the refinement in the isotropic riding model approximation. Figure was made using PLATON [16].

Crystallographic data (excluding structure factors) for **3** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 832280. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

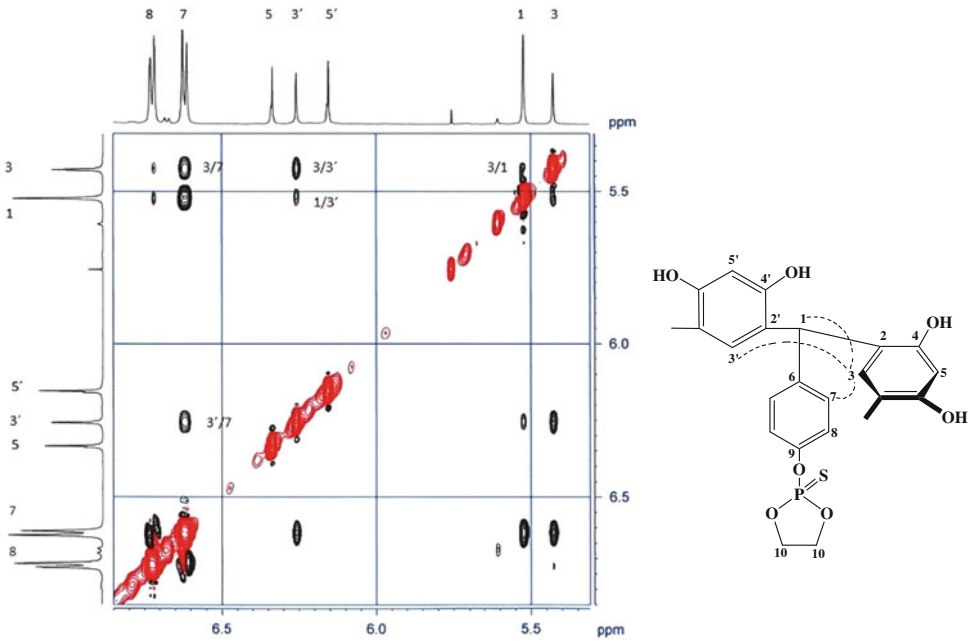


Fig. 4 $^{1}H/^{13}C$-HMBC spectrum of **5a** for the aromatic region

2-(4-Formylphenoxy)-2-thioxo-1,3,2-dioxaphospholane 3

A solution of 4-hydroxybenzaldehyde **2** (6.50 g, 0.0532 mol) in THF (80 mL) was added dropwise to the suspension of NaH (1.28 g, 0.0532 mol) in THF (80 mL) at 10 °C and reaction mixture was stirred at room temperature for 60 min. Then, the solution of 2-chloro-2-thioxo-1,3,2-dioxaphospholane **1** (8.44 g, 0.0532 mol), synthesized according to a known procedure [17], in THF (80 mL) was added and resulted suspension was stirred at heating (~45 °C) in the nitrogen atmosphere. The progress of the reaction was monitored by TLC. After 2 h the precipitate was filtered, washed with benzene. Then solvent from filtrate was evaporated and the crude product was purified by column chromatography using mixture dichloromethane/methanol (20:0.5) as eluent. The pure compound **3** was obtained as white solid (7.54 g, yield 58 %, $R_f = 0.82$). Mp 68–69 °C. ^{31}P NMR (166.93 MHz, $CDCl_3$) δ 76.8 ppm. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.51 (m, 4H, OCH_2), 7.32 (d, $^{3}J_{HH} = 8.69$, 2H, CH_{ar}), 7.90 (d, $^{3}J_{HH} = 8.69$, 2H, CH_{ar}), 9.97 (s, 1H, CHO) ppm. IR ν_{max}: 824 cm^{-1} ($P = S$). ESI–MS: $m/z = 245$ $[M + H]^+$ (calcd. $M = 244$). Anal. calcd. for $C_9H_9O_4PS$: C, 44.26; H, 3.69; P, 12.70; S, 13.11. Found: C, 44.17; H, 3.91; P, 12.76; S, 13.16.

Table 1 Crystallographic data for compound **3**

Chemical formula	$C_9H_9O_4PS$
Formula mass	244.19
Temperature (K)	296 (2)
Crystal system	Monoclinic
Space group	$P2_1/c$
a (Å)	5.772(3)
b (Å)	22.147(11)
c (Å)	8.470(4)
β (°)	97.500(6)
V (Å^3)	1073.4(10)
Z	4
ρ_{calc} (g cm^{-3})	1.511
μ (cm^{-1})	0.440
Reflections collected	8,049
Reflections observed ($I > 2\sigma$)	1,078
Reflections unique	2,108 ($R_{int} = 0.0628$)
R_1, wR_2 (2σ data)	0.0360, 0.0489
R_1, wR_2 (all data)	0.0852, 0.0489
GooF on F^2	0.822

Calix[4]resorcinol 5a

To the solution of resorcinol **4a** (0.45 g, 4.10 mmol) in the mixture of $CHCl_3$ (5 mL) and CF_3COOH (2 mL) the solution of thiophosphorylated aldehyde **3** (1.00 g, 4.10 mmol) in $CHCl_3$ (7 mL) was added dropwise. The reaction mixture was stirred under argon atmosphere at 70 °C for 5 h. The precipitate formed was filtered, washed with diethyl ether and acetone. After drying *in vacuo* (40 °C, 0.06 Torr) the product was obtained (1.20 g, yield 87 %) as white powder. Mp > 240 °C (dec.). ^{31}P NMR (166.93 MHz, DMSO-d_6) δ 78.8 ppm. ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.51 (m, 16H, H10), 5.43 (s, 2H, $H3^h$), 5.52 (s, 4H, H1), 6.16 (s, 2H, $H5^v$), 6.26 (s, 2H, $H3^v$), 6.33 (s, 2H, $H5^h$), 6.62 (d, $^{3}J_{HH} = 8.52$, 8H, H7), 6.72 (d, $^{3}J_{HH} = 8.52$, 8H,

H8), 8.60 (s, 4H, OH^v), 8.70 (s, 4H, OH^h) ppm. NMR ^{13}C (150 MHz, DMSO-d_6) δ 41.5 (s, C1), 67.6 (s, C10), 67.6 (s, C10), 101.8 (s, $C5^h$), 101.9 (s, $C5^v$), 119.3 (s, C8), 120.4 (s, $C2^h$), 120.8 (s, $C2^v$), 128.9 (s, $C3^v$), 130.1 (s, C7), 131.4 (s, $C3^h$), 141.7 (s, C6), 147.4 (s, C9), 152.7 (s, $C4^v$), 152.9 (s, $C4^h$). IR ν_{max}: 831 (P = S); 924, 1028 (P-O-C); 3,100–3,600 (OH) cm^{-1}. ESI–MS: m/z = 1345 $[M + H]^+$ (calcd. M = 1344). Anal. calcd. for $C_{60}H_{52}O_{20}P_4S_4$: C, 53.57; H, 3.87; P, 9.23; S, 9.52. Found: C, 53.59; H, 3.60; P, 8.98; S, 9.31.

Calix[4]resorcinol 5b

was obtained as light-pink powder by a method analogous to that used to prepare **5a** by the treatment of 2-methylresorcinol **4b** (0.57 g of 90 % purity, 4.10 mmol) with aldehyde **3** (1.00 g, 4.10 mmol). Yield 1.42 g (89 %). Mp > 300 °C (dec.). ^{31}P NMR (166.93 MHz, DMSO-d_6) δ 78.9 ppm. ^1H NMR (600 MHz, DMSO-d_6) δ 1.93 (s, 6H, CH_3^h), 2.07 (s, 6H, CH_3^v), 4.54 (m, 16H, H10), 5.23 (s, 2H, $H3^h$), 5.65 (s, 4H, H1), 6.11 (s, 2H, $H3^v$), 6.65 (d, $^3J_{HH}$ = 8.4, 8H, H7), 6.72 (d, $^3J_{HH}$ = 8.4, 8H, H8), 7.45 (s, 4H, OH^v), 7.64 (s, 4H, OH^h) ppm. IR ν_{max}: 830 (P = S); 960, 1025 (P-O-C); 3,200–3,600 (OH) cm^{-1}. ESI–MS: m/z = 1401 $[M + H]^+$ (calcd. M = 1400). Anal. calcd. for $C_{64}H_{60}O_{20}P_4S_4$: C, 54.86; H, 4.29; P, 8.86; S, 9.14. Found: C, 54.73; H, 4.11; P, 8.61; S, 8.96.

Calix[4]resorcinol 5c

was obtained as light-pink powder by a method analogous to that used to prepare **5a** by the treatment of pyrogallol **4c** (0.26 g, 2.06 mmol) with aldehyde **3** (0.5 g, 2.06 mmol). Yield 0.58 g (80 %), Mp > 196 °C (dec.). ^{31}P NMR (166.93 MHz, DMSO-d_6): δ = 78.8 ppm. ^1H NMR (600 MHz, DMSO-d_6) δ 4.51 (m, 16H, H10), 5.07 (s, 2H, $H3^h$), 5.66 (s, 4H, H1), 5.93 (s, 2H, $H3^v$), 6.62 (d, $^3J_{HH}$ = 8.4, 8H, H7), 6.73 (d, $^3J_{HH}$ = 8.4, 8H, H8), 7.61 (s, 6H, OH^v), 7.71 (s, 6H, OH^h) ppm. IR ν_{max}: 831 (P = S); 924, 1026 (P-O-C); 3,100–3,600 (OH) cm^{-1}. ESI–MS: m/z = 1409 $[M + H]^+$ (calcd. M = 1408). Anal. calcd. for $C_{60}H_{52}O_{24}P_4S_4$: C, 51.14; H, 3.69; P, 8.81; S, 9.09. Found: C, 51.11; H, 3.30; P, 8.53; S, 8.98.

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