Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2017, **27**, 287–289
Mendeleev Communications

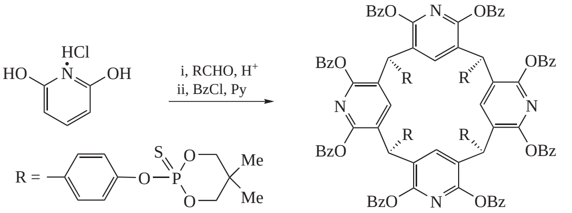
New phosphorus-containing calix[4]pyridine based on *para*-thiophosphorylated derivative of benzaldehyde

Irina R. Knyazeva,*[a] Victoria I. Matveeva,[a] Wolf D. Habicher,[b] Victor V. Syakaev,[a] Bulat M. Gabidullin,[a] Aidar T. Gubaidullin,[a] Alexander R. Burilov[a] and Michael A. Pudovik[a]

[a] *A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, 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*

DOI: 10.1016/j.mencom.2017.05.024

Novel calix[4]pyridine with four 2-thioxido-1,3,2-dioxaphosphorinane fragments attached to aromatic substituents was prepared by one-step condensation of 2,6-dihydroxypyridine hydrochloride with *para*-thiophosphorylated benzaldehyde. To improve the solubility of the obtained compound, O-benzoylation of its hydroxyl groups was implemented.



The design of phosphorus-containing macrocyclic compounds is one of the priority directions of organoelement chemistry.[1] We have recently suggested new precursors for the design of phosphorus-containing calix[4]resorcinols, such as thiophosphorylated derivatives of 2-, 3-, and 4-hydroxybenzaldehydes,[2,3] by their condensation with resorcinol, 2-methylresorcinol, and pyrogallol in acidic media. In this case, macrocyclic products were formed as *rccc*- and/or *rctt*-diastereomers whose ratio depended on the structure of reactants and experimental conditions.

Nickel complexes of the obtained thiophosphorylated calix[4]resorcinols mimicked hydrogenases, thus serving as natural catalysts of hydrogen electroreduction. The design of their synthetic counterparts opens the way to the generation of cheap hydrogen for hydrogen energetics.[4]

Following studies in this field, we attempted to synthesize calixarenes containing pyridine fragments instead of benzene units by employing 2,6-dihydroxypyridine hydrochloride. Note that there are only few examples of the synthesis of calix[4]pyridines, including the reactions of 2,6-dihydroxypyridine with some aliphatic aldehydes.[5,6] The synthesized macrocycles demonstrated interesting complexation behavior towards 2-aminonaphthyridine; these compounds form stable gel-like viscous liquids in nonpolar solvents in a 1 : 4 ratio.[7] Calix[4]pyridines would also form capsules capable of encapsulating various guest molecules such as carboxylic acids and amides,[8,9] as well as gold nanoparticles.[10] Earlier we have synthesized the first representative of phosphorus-containing calix[4]pyridines by the condensation of 2,6-dihydroxypyridine hydrochloride with (2-ethoxyvinyl)phosphonic dichloride or diethyl (2,2-diethoxy)phosphonate.[11]

In this work, we carried out the trifluoroacetic acid-catalyzed condensation of 2-(4-formylphenoxy)-5,5-dimethyl-2-thioxido-1,3,2-dioxaphosphorinane **1**[2] with 2,6-dihydroxypyridine hydrochloride **2** in chloroform at long-term reflux for 205 h (Scheme 1). Such severe reaction conditions were necessary due to the low reactivity of **2**. As the result, new calix[4]pyridine **3** bearing four 2-thioxido-1,3,2-dioxaphosphorinane fragments at aromatic substituents of calixarene scaffold was obtaned in 53% yield. It should be noted that prolongation of the reaction affects remarkably the yield of macrocycle; the yield was only 26% after heating the reaction mixture for 105 h.[†]

Product **3** is poorly soluble in water and organic solvents. Therefore, with the aim to improve this parameter, as well as to obtain reliable spectral data, we carried out O-acylation of hydroxyl groups using benzoyl chloride. As the result, new O-benzoylated calix[4]pyridine **4** containing thiophosphoryl groups at aromatic substituents was isolated in 65% yield (see Scheme 1). Indeed, compound **4** exhibits improved solubility (acetone, chloroform, alcohols) as compared to its precursor **3**.

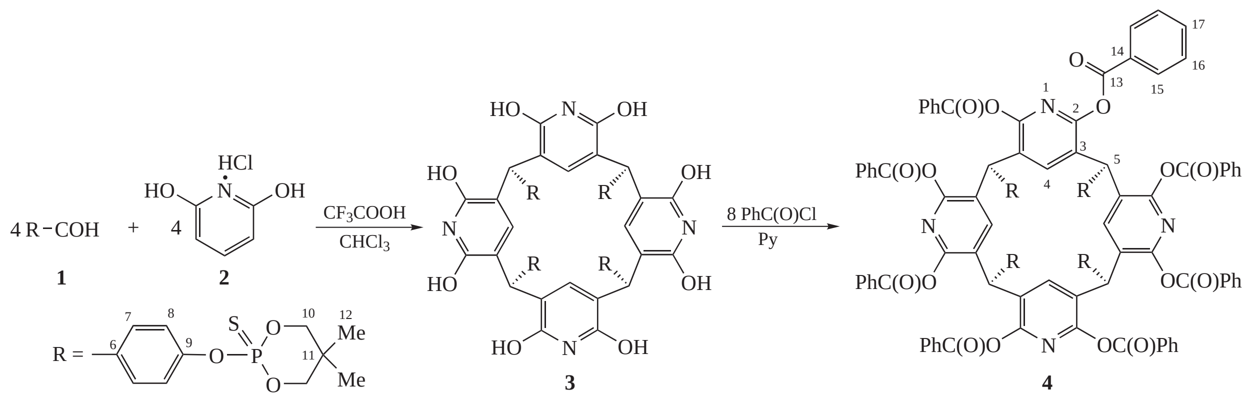
The assignment of signals in the NMR spectra of synthesized compounds was made on the basis of ^{1}H, ^{13}P, COSY, NOESY, ^{1}H-^{13}C HSQC, and ^{1}H-^{13}C HMBC experiments. The ^{1}H NMR spectra in DMSO-d_6 are represented by the broad signals of pyridine fragments. This is particularly clear in comparison with

---

[†] The ^{1}H NMR spectra were recorded on a Bruker AVANCE-600 instrument. The ^{31}P NMR spectra were obtained on a Bruker MSL-400 NMR-Fourier spectrometer. Microelemental analyses data were obtained on a CHN-3 analyzer and they were within ±0.3% of the theoretical values for C, H, Br, N, and P. The uncorrected melting points were measured on a Boetius hot-stage apparatus. The MALDI-TOF mass spectra were obtained on a ULTRAFLEX III mass spectrometer (Bruker Daltonik). Recording was performed with the use of plastic and metal plates. 2,5-Dihydroxybenzoic acid (2,5-DHB) was used as a matrix. The solvents in use were of chemically pure grade.

Calix[4]pyridine **3**. The mixture of 2,6-dihydroxypyridine hydrochloride **2** (1.03 g, 6.98 mmol) and 2-(4-formylphenoxy)-5,5-dimethyl-2-thioxido-1,3,2-dioxaphosphorinane **1** (2.00 g, 6.98 mmol) in chloroform (55 ml) and trifluoroacetic acid (10 ml) was stirred at 70–75 °C for 205 h under argon atmosphere. The precipitate formed was filtered, washed sequentially with chloroform and diethyl ether. The procedure was repeated until only colourless filtrate was observed. After recrystallization from ethanol and drying *in vacuo* (40 °C, 0.06 Torr) the pure product **3** was obtained (1.35 g, 53%) as slightly grey powder, which was poorly soluble in DMSO and DMF. Mp > 170 °C (decomp.). ^{31}P NMR (242.9 MHz, DMSO-d_6, 30 °C) δ: 54.2. IR (KBr, ν/cm^{-1}): 830 (P=S); 970, 1004 (P–O–C); 3100–3600 (OH). MS (MALDI), *m/z*: 1539.0 [M+Na]$^+$ (calc. for [M]$^+$, *m/z*: 1516). Found (%): C, 53.90; H, 4.79; N, 3.75; P, 8.16; S, 8.42. Calc. for $C_{68}H_{72}N_4O_{20}P_4S_4$ (%): C, 53.82; H, 4.75; N, 3.69; P, 8.18; S, 8.45.

© 2017 Mendeleev Communications. Published by ELSEVIER B.V. on behalf of the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences.



Scheme 1

narrow signals for the protons of aromatic substituents of the upper and lower rims. That is, the intermediate rate of *boat* 1–*cone*–*boat* 2 interconversion is observed on the NMR time scale, which is presumably related to the introduction of bulky substituents to the upper rim of calixarene.

Ultimately, the structure of calix[4]pyridine **4** was confirmed by X-ray diffraction analysis of single crystal, which was grown from chloroform–ethanol solution.‡ Compound **4** crystallized with two different solvents molecules, ethanol and chloroform, in a ratio of 1 : 2, respectively. Two perspective ORTEP views of the molecules are shown in Figure 1. The characteristic feature of the distorted *boat* conformation of compound **4** is a parallel arrangement of opposite vertical (with respect to the macrocycle main reference plane) resorcinol rings and close to coplanar arrangement of horizontal aromatic cycles. Ethanol molecule is located in the pseudocavity formed by four phosphorus-containing substituents, whereas two chloroform molecules are arranged between calix[4]pyridine **4** molecules. Bulky substituents of calix[4]pyridine **4** hinder dense packing of the molecules in the crystal, so that there are solvent-accessible cavities in the crystal with overall volume of 255 Å^3 per unit cell, and the calculated value of the packing index is at the lower limit of the values, characteristic of the crystals of the organic compounds (65–75%), and equal to 63.4%.[12]

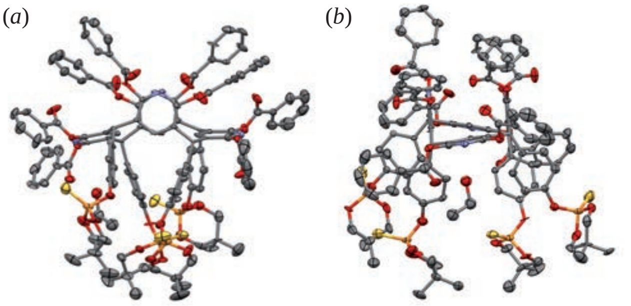


Figure 1 ORTEP view of calix[4]pyridine and ethanol molecules in the crystal of **4**. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms and two chloroform molecules are omitted for clarity. View along (*a*) 0*c* and (*b*) 0*a* axes.

In conclusion, novel calix[4]pyridines with 2-thioxido-1,3,2-dioxaphosphorinane groups attached to aromatic units were synthesized by condensation of *para*-thiophosphorylated benzaldehyde with 2,6-dihydroxypyridine hydrochloride providing a single *boat* stereoisomer of the macrocycle, with *rccc*-configuration of thiophosphoryl-containing aromatic substituents. To improve the solubility of the prepared calix[4]pyridine, O-benzoylation of hydroxyl groups was carried out. Due to the preorganization of four thiophosphoryl groups along with macrocyclic effect the compound obtained is expected to possess interesting complexation properties and act as an effective ligand for transition metal ions. This feature would be promising in the catalysis of hydrogen electroreduction, which has been previously demonstrated by thiophosphorylated calix[4]resorcinols.[4]

Calix[4]pyridine **4**. The mixture of calix[4]pyridine **3** (0.11 g, 0.07 mmol), benzoyl chloride (1 ml) and pyridine (1 ml) was heated at reflux for 5 h under argon atmosphere, and then carefully hydrolysed with water at room temperature. The oily layer was decanted, washed with hot water, triturated in ethanol and filtered. After drying *in vacuo* (40 °C, 0.06 Torr) product **4** was obtained (0.11 g, 65%) as slightly yellow powder. Mp > 400 °C (decomp.). ^{1}H NMR (600.1 MHz, DMSO-d_6, 30 °C) δ: 0.91 (s, 12 H, H-12), 1.25 (s, 12 H, H-12), 4.10 (m, 8 H, H-10^e), 4.43 (m, 8 H, H-10^a), 5.80 (s, 4 H, H-5), 6.88 (d, 8 H, H-7, $^3J_{HH}$ 8.0 Hz), 7.16 (d, 8 H, H-8, $^3J_{HH}$ 8.0 Hz), 7.46 (s, 2 H, H-4^v), 7.50 (t, 16 H, H-16, $^3J_{HH}$ 7.2 Hz), 7.62 (t, 8 H, H-17, $^3J_{HH}$ 7.2 Hz), 7.73 (s, 2 H, H-4^h), 7.95 (d, 16 H, H-15, $^3J_{HH}$ 7.2 Hz). ^{13}C NMR (150.9 MHz, DMSO-d_6, 30 °C) δ: 19.73 (s, C-12), 21.2 (s, C-12), 31.8 (d, C-11, $^3J_{PC}$ 6.3 Hz), 42.5 (s, C-5), 77.7 (d, C-10, $^2J_{PC}$ 8.3 Hz), 121.3 (s, C-8), 128.5 (s, C-16), 128.9 (s, C-4^v), 129.2 (s, C-3), 129.4 (s, C-15), 129.7 (s, C-7), 130.7 (s, C-14), 132.8 (s, C-17), 134.6 (s, C-4^h), 135.4 (s, C-6), 149.3 (d, C-9, $^3J_{PC}$ 6.6 Hz), 163.0 (br. s, C-2), 167.2 (s, C-13). ^{31}P NMR (242.9 MHz, DMSO-d_6, 30 °C) δ: 54.2. IR (KBr, ν/cm^{-1}): 829 (P=S); 971, 1004 (P–O–C); 1751 (C=O). MS (MALDI), *m/z*: 2301 [M + H]$^+$, 2323 [M + Na]$^+$, 2339 [M + K]$^+$ (calc. for [M]$^+$, *m/z*: 2300). Found (%): C, 62.64; H, 4.56; N, 4.45; P, 5.42; S, 5.52. Calc. for $C_{120}H_{104}N_4O_{28}P_4S_4$ (%): C, 62.61; H, 4.52; N, 4.43; P, 5.39; S, 5.57.

‡ The X-ray diffraction data were collected on a Bruker Smart Apex II CCD diffractometer in the ω- and φ-scan modes using graphite monochromated radiation [λ(MoKα) = 0.71073 Å] at 296(2) K. The crystal of **4** is air sensitive and weakly diffracts. The experiment was carried out at room temperature with the crystal in a glass capillary with mother liquor (the crystals would crack on cooling). The structure was solved by the direct method and refined by the full-matrix least-squares using SHELXTL[13] and WinGX[14] programs. The positions of the hydrogen atoms of the OH groups were found in difference Fourier synthesis, whereas the positions of all other H atoms were calculated geometrically. The calixarene molecule consists of a macrocycle platform that is not very mobile and substituents that undergo more active thermal motion. So the functional groups on the *endo*- and *exo*-rims of calixarene, as well as solvent molecules, are disordered and undergo thermal librations, which cannot be modeled accurately. Large number of restraints and constraints were used during the refinements, which may lead to artificially high values of refinement parameters. Mercury program package[15] was used for figures preparation.

Crystal data for **4**: $C_{124}H_{104}N_4O_{28}P_4S_4\cdot 2(CHCl_3)\cdot C_2H_5OH$ (M = 2635.04), colourless prism crystal, monoclinic, space group $P2_1/n$, a = 27.95(1), b = 16.247(8) and c = 29.59(1) Å, β = 104.213(7)°, V = 13029(12) Å^3, Z = 4, d_{calc} = 1.343 g cm^{-3}, μ(MoKα) = 0.319 mm^{-1}. F(000) = 5464, total of 143186 reflections were collected, from which 41174 unique (R_{int} = = 1.3599), 636 parameters and 1044 restraints were used for refinement. Final indices R_1 = 0.1961, wR_2 = 0.2988 for 5928 reflections with [$I > 2\sigma(I)$], GOF = 0.926, largest difference peak/hole 0.739/–1.032 eA^{-3}.

CCDC 1478622 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.

This work was supported by the Russian Foundation for Basic Research (grant no. 16-03-00201-a).

References

1 I. R. Knyazeva, A. R. Burilov, M. A. Pudovik and W. D. Habicher, *Russ. Chem. Rev.*, 2013, **82**, 150.
2 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.
3 I. R. Knyazeva, V. I. Matveeva, V. V. Syakaev, B. M. Gabidullin, A. T. Gubaidullin, M. Gruner, W. D. Habicher, A. R. Burilov and M. A. Pudovik, *Tetrahedron Lett.*, 2014, **55**, 7209.
4 M. K. Kadirov, I. R. Knyazeva, I. R. Nizameev, R. A. Safiullin, V. I. Matveeva, K. V. Kholin, V. V. Khrizanforova, T. I. Ismaev, A. R. Burilov, Yu. H. Budnikova and O. G. Sinyashin, *Dalton Trans.*, 2016, **45**, 16157.
5 V. Král, P. A. Gale, P. Anzenbacher, Jr., K. Jursiková, V. Lynch and J. L. Sessler, *Chem. Commun.*, 1998, 9.
6 T. Gerkensmeier, J. Mattay and C. Näther, *Chem. Eur. J.*, 2001, **7**, 465.
7 T. Gerkensmeier, B. Decker, M. Schwertfeger, W. Buchheim and J. Mattay, *Eur. J. Org. Chem.*, 2002, 2120.
8 M. C. Letzel, B. Decker, A. B. Rozhenko, W. W. Schoeller and J. Mattay, *J. Am. Chem. Soc.*, 2004, **126**, 9669.
9 T. Evan-Salem and Y. Cohen, *Chem. Eur. J.*, 2007, **13**, 7659.
10 B. Kim, R. Balasubramanian, W. Pérez-Segarra, A. Wei, B. Decker and J. Mattay, *Supramol. Chem.*, 2005, **17**, 173.
11 A. R. Burilov, I. R. Knyazeva, M. A. Pudovik, V. V. Syakaev, Sh. K. Latypov, I. Baier, W. D. Habicher and A. I. Konovalov, *Russ. Chem. Bull., Int. Ed.*, 2007, **56**, 364 (*Izv. Akad. Nauk, Ser. Khim.*, 2007, 352).
12 A. I. Kitaigorodsky, *Molecular Crystals and Molecules*, Academic Press, New York, 1973.
13 G. M. Sheldrick, *SHELXTL, v. 6.12, Structure Determination Software Suite*, Bruker AXS, Madison, WI, 2000.
14 L. J. Farrugia, *J. Appl. Crystallogr.*, 1999, **32**, 837.
15 C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Crystallogr.*, 2006, **39**, 453.

Received: 4th October 2016; Com. 16/5064