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Synthesis of new calix[4]resorcinols with [*N*-diethoxyphosphorylmethyl-*N*-(2,2-dimethoxyethyl)amino]methyl substituents at the upper rim

Liliya I. Vagapova,*[a] Aliya F. Fahertdinova,[b] Alexander R. Burilov[a] and Mikhail A. Pudovik[a]

[a] *A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 8432 275 2253; e-mail: vagapovan@mail.ru*
[b] *Kazan National Research Technological University, 420015 Kazan, Russian Federation*

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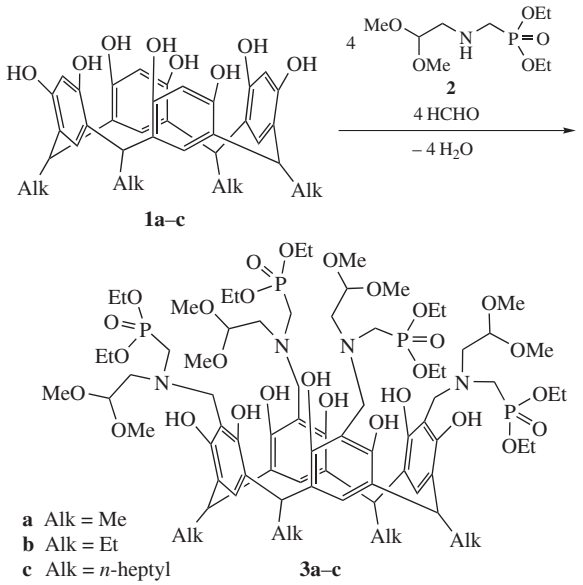
Calix[4]resorcinols containing four [*N*-diethoxyphosphorylmethyl-*N*-(2,2-dimethoxyethyl)amino]methyl substituents at the upper rim of molecule were synthesized by condensation of calix[4]resorcinols with formaldehyde and diethyl *N*-(2,2-dimethoxyethyl)-aminomethylphosphonate.

Calix[4]resorcinols are unique macrocyclic compounds used as building blocks in 'host–guest' chemistry for the design of supramolecular structures.[1–4] The Mannich reaction represents the most convenient method for their functionalization.[5–23] Recently, we synthesized tetrasubstituted calix[4]resorcinols containing aminophosphonate[12] and amino acetal[13,14] groups at the upper rim. These macromolecules can be exposed to chemical modification,[21] as well as the formation of supramolecular aggregates, which possess catalytic activity in hydrolysis of phosphonates,[17,18] complexation with Cu^{II} and La^{III} ions,[19] and extraction of La^{III} and Lu^{III} ions.[20]

In this work, in order to synthesize novel macrocyclic receptors bearing both phosphonate and acetal functions, we studied the reaction of calix[4]resorcinols **1a–c** with phosphorylated amino acetal **2**† and formaldehyde.

It is known from the published data that the Mannich aminoalkylation of calix[4]resorcinols can proceed differently depending on the ratio of reactants, structure of the amines used, length of alkyl substituent at the lower rim of the macrocycle, and type of the solvents used[16,22,23] and can afford products with different number of introduced groups. We showed that variation in the reactant ratio (from 1:1:1 to 1:5:5) in the reaction under study, as well as solvent (ethanol/benzene, methanol), does not affect substantially the synthetic result. New tetrasubstituted derivatives **3a–c**,‡ which have four acetal groups and four phosphonate fragments, were synthesized in high yields.



The structure of the synthesized products was confirmed by ^{1}H NMR and IR spectroscopy, the composition was confirmed by elemental analysis data.

Analysis of ^{1}H NMR spectra of compounds **3a–c** indicates that the position of multiplet of methine protons linking aromatic fragments almost does not change with an increase in the chain length of R substituent in analogy with amino acetal derivatives[13]

† ^{1}H NMR spectra were recorded on a Bruker AVANCE-400 spectrometer (400.13 MHz) relative to residual protons of deuterated solvent ($CDCl_3$). ^{31}P NMR spectra were recorded on a Bruker MSL-400 Fourier NMR spectrometer (162 MHz) relative to external standard 85% H_3PO_4. IR spectra were measured on a Vector-22 (Bruker) spectrometer in the wavenumber range from 4000 to 400 cm^{-1}.

*Diethyl (*N*-2,2-dimethoxyethylamino)methylphosphonate* **2**. Mixture of aminoacetaldehyde dimethylacetal (8.37 g, 79.7 mmol), diethylphosphite (11 g), paraformaldehyde (2.4 g), and *p*-toluenesulfonic acid (120 mg) in benzene (80 ml) was refluxed in the flask equipped with Dean–Stark trap for 3–4 h. The reaction course was monitored by ^{31}P NMR. After the end of reaction, 600 mg of potassium carbonate was added, and the mixture was refluxed for more 10 min. The mixture was filtered, benzene was distilled from the filtrate, and the residue was distilled under oil pump vacuum to afford 16.6 g (82%) of the product **2**, bp 94°(0.04 Torr), n_D^{20} 1.4430. ^{31}P NMR ($CDCl_3$) δ: 26.12. ^{1}H NMR ($CDCl_3$) δ: 1.23 (t, 6H, OCH_2Me, $^3J_{HH}$ 7.11 Hz), 2.57–2.59 (d, 2H, NCH_2, $^3J_{HH}$ 5.40 Hz), 2.91 (d, 2H, PCH_2, $^2J_{PH}$ 12.05 Hz), 3.26 (s, 6H, OMe), 4.00–4.07 (m, 4H, OCH_2), 4.33 (t, 1H, CH, $^3J_{HH}$ 5.40 Hz). IR (ν/cm^{-1}): 1057 (POC), 1129 (COC), 1242 (P=O), 3342 (NH). Found (%): C, 42.35; H, 8.69; N, 5.49; P, 12.13. Calc. for $C_9H_{22}NO_5P$ (%): C, 42.13; H, 8.78; N, 5.39; P, 12.12.

‡ *General procedure for the synthesis of calix[4]resorcinols* **3a–c**. Compound **2** (9.2 mmol) and 37% aqueous formaldehyde (9.2 mmol) were added dropwise to the solution of calix[4]resorcinol **1a–c** (1.84 mmol) in ethanol (7.5 ml) and benzene (7.5 ml). Reaction mixture was kept at room temperature for 3 days, the solvent was distilled off with a water-jet pump, the residue was washed with hexane, and dried *in vacuo*.

*4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetrakis[*N*-diethoxyphosphorylmethyl-*N*-(2,2-dimethoxyethyl)aminomethyl]-2,8,14,20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene* **3a**: yield, 2.86 g (100%), oil. ^{31}P NMR ($CDCl_3$) δ: 24.25. ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, 24H, OCH_2Me, $^3J_{HH}$ 6.98 Hz), 1.75 (d, 12H, $CHMe$, $^3J_{HH}$ 6.98 Hz), 2.80 (d, 8H, NCH_2, $^3J_{HH}$ 6.98 Hz), 2.98 (m, 8H, PCH_2, $^2J_{PH}$ 17.44 Hz), 3.30 (br. s, 24H, OMe), 3.89 (s, 8H, CH_2C_{aryl}), 4.03 (m, 16H, OCH_2, $^3J_{HH}$ 6.98 Hz), 4.47–4.54 (m, 8H, C*H*Me, C*H*OMe), 7.25 (s, 4H, CH_{aryl}). IR (ν/cm^{-1}): 1027, 1054 (POC), 1100, 1127 (COC), 1231 (P=O), 1611 (CH_{ar}), 3301 (OH). Found (%): C, 53.25; H, 7.98; N, 3.29; P, 7.65. Calc. for $C_{72}H_{120}N_4O_{28}P_4$ (%): C, 53.60; H, 7.50; N, 3.47; P, 7.68.

and appears in the range from 4.31 to 4.59 ppm; protons of methine, methoxy, ethoxy groups at phosphorus atom and methylene groups at nitrogen atom manifest themselves in the spectrum as one set of signals; this proves their «cone» conformation.

With an increase in the length of alkyl substituent at the lower rim of calix[4]resorcinols **3a**–**c**, their solubility in water and polar solvents decreases apparently due to increase in their lipophilicity.

The presence of four amino, four phosphoryl groups in the molecules synthesized, which are capable to coordination with metal ions,[24,25] and four reactive acetal groups,[21] as well as hydrophobic cavity with alkyl substituents of various lengths, which enable one to vary the lipophilicity of molecule, makes it possible to consider them promising precursors of spatially arranged polydentate ligands and transmitters upon membrane extraction.[26]

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*4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetrakis[*N*-diethoxyphosphorylmethyl-*N*-(2,2-dimethoxyethyl)aminomethyl]-2,8,14,20-tetraethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene* **3b**: yield, 3 g (99%), oil. ^{31}P NMR ($CDCl_3$) δ: 24.25. ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 12H, Me, $^3J_{HH}$ 7.06 Hz), 1.29 (t, 24H, OCH_2*Me*, $^3J_{HH}$ 7.06 Hz), 2.17 (m, 8H, C*H*$_2$Me), 2.80 (br.s., 8H, NCH_2), 2.99 (m, 8H, PCH_2, $^2J_{PH}$ 11.50 Hz), 3.30 (br.s, 24H, OMe), 3.89 (s, 8H, CH_2C_{aryl}), 4.07 (m, 16H, OCH_2), 4.20 (m, 4H, C*H*Et), 4.48 (t, 4H, C*H*OMe, $^3J_{HH}$ 5.24 Hz), 7.11 (s, 4H, CH_{aryl}). IR (ν/cm^{-1}): 1027, 1055 (POC), 1097, 1134 (COC), 1233 (P=O), 1611 (CH_{arom}), 3307 (OH). Found (%): C, 52.85; H, 8.10; N, 3.48; P, 7.38. Calc. for $C_{76}H_{128}N_4O_{28}P_4$ (%): C, 54.67; H, 7.73; N, 3.36; P, 7.42.

*4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetrakis[*N*-diethoxyphosphorylmethyl-*N*-(2,2-dimethoxyethyl)aminomethyl]-2,8,14,20-tetraheptylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene* **3c**: yield, 3.55 g (99%), oil. ^{31}P NMR ($CDCl_3$) δ: 24.45. ^{1}H NMR ($CDCl_3$) δ: 0.89 (t, 12H, Me, $^3J_{HH}$ 7.06 Hz), 1.34 [m, 64H, (CH_2)$_5$Me, OCH_2*Me*], 2.15 (m, 8H, C*H*$_2$Hex), 2.81 (d, 8H, NCH_2, $^3J_{HH}$ 5.31 Hz), 3.02 (d, 8H, PCH_2, $^2J_{PH}$ 11.42 Hz), 3.30 (s, 24H, OMe), 3.92 (s, 8H, CH_2C_{aryl}), 4.06 (m, 16H, OCH_2), 4.32 (m, 4H, C*H*R), 4.48 (t, 4H, C*H*OMe, $^3J_{HH}$ 5.31 Hz), 7.13 (s, 4H, CH_{aryl}). IR (ν/cm^{-1}): 1027, 1055 (POC), 1097, 1134 (COC), 1233 (P=O), 1611 (CH_{aryl}), 3307 (OH). Found (%): C, 59.15; H, 8.65; N, 2.78; P, 6.38. Calc. for $C_{96}H_{168}N_4O_{28}P_4$ (%): C, 59.12; H, 8.68; N, 2.87; P, 6.35.

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