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Phosphorylated Aminoacetal in the Synthesis of New Acyclic, Cyclic, and Heterocyclic Polyphenol Structures

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ABSTRACT: *New phosphorylated aminoacetal has been synthesized by the Kabachnik–Fields reaction; its reactivity has been studied in acid-catalyzed condensation with linear polyphenols (2-methylresorcinol, resorcinol, pyrogallol) and the Mannich reaction with macrocyclic polyphenol (calix[4]resorcinol). It has been determined for the first time that acid-catalyzed reaction of phosphorus-containing acetal with resorcinol and its derivatives in ethanol in the presence of hydrochloric acid gives new phosphorylated piperazines in addition to the compounds of diarylmethane series. Condensation of macrocyclic polyphenol (calix[4]resorcinol) with formaldehyde and N-((dihexylphosphoryl)methyl)-2, 2-dimethoxyethylamine (the Mannich reaction) has resulted in novel tetrasubstituted calixarene containing aminophosphine oxide and acetal groups on the "upper rim" of molecule.* © 2014 Wiley Periodicals, Inc. Heteroatom Chem. 25:178–185, 2014; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21153

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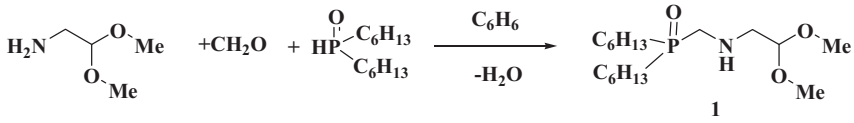
INTRODUCTION

It has been known that acetals are promising compounds for the synthesis of both macro- and heterocyclic structures. In particular, *N*-benzyl(hetaryl) aminoacetals represent attractive precursors for the synthesis of many five- to seven-membered heterocycles and alkaloids [1–4], as well as diarylmethane derivatives [5, 6] with a broad range of pharmacological activity.

We have shown earlier that condensation of functionally substituted acetals with resorcinol and its derivatives in acidic media is a convenient method to prepare unique linear and cyclic polyphenols, namely, P,N-containing calix[4]resorcinols [7, 8], derivatives of diarylmethane series [9–11] including those on macrocyclic framework [12], and imidazolidine-2-ones containing polyphenol fragments [13]. It was determined that synthesized calix[4]resorcinols can be utilized in micellar



SCHEME 1 Synthesis of N-((dihexylphosphoryl)methyl)-2,2-dimethoxyethylamine 1.

catalysis [14, 15] and are able to complexation with rare earth metal ions [16, 17] and extraction of carbon nanotubes [18]. Derivatives of diarylmethane series are of interest as polydentate ligands [19].

It should be noted that the type of the products, which are formed during acid-catalyzed reaction of resorcinol and its derivatives with functionally substituted acetals, depends substantially on the structure of the latter, as well as experimental conditions.

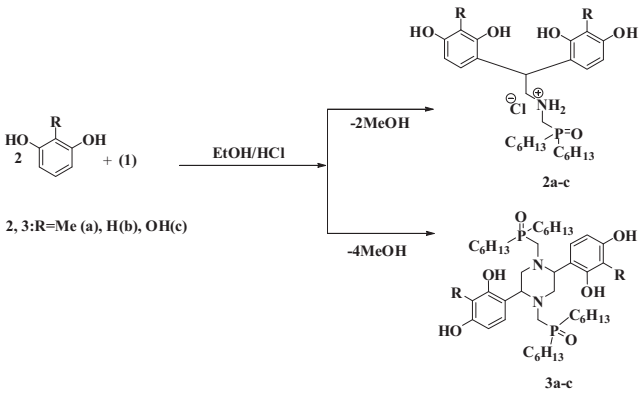
We followed research in this direction studying the properties of previously unknown acetal containing the aminophosphine oxide fragment. Aminophosphine oxide derivatives are used as alkali and rare metal extractants due to their ability to complexation [20, 21]. A combination of several functional groups in one molecule (acetal and secondary amino group) would allow the use of the compounds of this type as a universal synthetic block for the design of macrocyclic and linear polyphenols, promising polydentate ligands containing the phosphine oxide fragment.

RESULTS AND DISCUSSION

Phosphorylated acetal **1** was synthesized according to the Kabachnik–Fields reaction of aminoacetaldehyde dimethylacetal with paraform and dihexylphosphinous acid in benzene catalyzed by *p*-toluenesulfonic acid with the yield of 91% (Scheme 1).

The reaction of 2-methylresorcinol with *N*-((dihexylphosphoryl)methyl)-2,2-dimethoxy-ethylamine **1** in ethanol in the presence of concentrated hydrochloric acid yields two types of products. In MALDI mass spectra of reaction mixture, there were signals of *N*-[2,2-bis(2,4-dihydroxy-3-methylphenyl) ethyl]-*N*-((dihexylphosphoryl)-methyl)amine hydrochloride **2a**, *m/e* = 520 ([M – HCl + H]$^+$), and also product of cyclization, 2,5-bis(2,4-dihydroxy-3-methylphenyl)-1, 4-(bis(dihexylphosphorylmethyl)) piperazine **3a**, *m/e* = 791 [M + H]$^+$ (Scheme 2). Treatment of reaction mass by acetone enables one to isolate compounds **2a** and **3a**.

The formation of compound **3a** was unexpected, but it is an interesting fact. Piperazine derivatives attract the attention of researchers in organic synthesis due to its pronounced biological activities [22, 23].



SCHEME 2 Interaction of resorcinol and its derivatives with N-((dihexylphosphoryl)methyl)-2,2-dimethoxyethylamine 1 in acidic media.

However, there were no published data on the synthesis of piperazine derivatives containing aryl substituents in addition to phosphine oxide fragments.

2,5-Bis(2, 4-dihydroxy-3-methylphenyl)-1, 4-(bis (dihexylphosphorylmethyl))piperazine **3a** was isolated with the yield of 15% in the case of 2-methyl resorcinol and the yield of *N*-[2,2-bis(2,4-dihydroxy-3-methylphenyl)ethyl]-*N*-((dihexylphosphoryl)methyl)amine hydrochloride **2a** was 60%.

A subsequent study of the reaction showed that condensation of acetal **1** with resorcinol and pyrogallol in ethanol in the presence of concentrated hydrochloric acid at the (acetal-to-polyphenol = 1:2) reagent ratio proceeds in analogy with that described above for the formation of the derivatives of diarylmethane series **2b,c** with the yields of 20% and 35%, respectively, and tetrasubstituted piperazines **3b,c**. It should be noted that the latter are formed in trace amounts and were detected only in the reaction mixture by means of MALDI mass spectrometry.

With an aim to study the effect of reaction conditions on the type, yield, and ratio of formed products, we varied temperature (20–80°C), time of experiment, as well as reagent ratio and types of solvents and acids.

It was determined that temperature of the reaction and an increase in time of experiment do not influence substantially the ratio and yield of products **2a–c** and **3a–c**. On the other hand, the reagent ratio was found to have a significant effect only on the yield of compounds **2b** and **2c**.

Condensation of polyphenols with acetal **1** at a 5:1 reagent ratio is followed by an increase in the yields of compounds **2b** and **2c** up to 57% and 52%, respectively.

The effect of solvents and catalysts on this reaction is worth noting. For example, substitution of Lewis acid ($BF_3.(OEt_2)$) for Brønsted acid (HCl) in the reactions of resorcinol and 2-methylresorcinol with aminoacetal **1** leads to uncontrolled formation of oligomers in ethanol; and conduction of this reaction in a nonpolar solvent (chloroform) with trifluoroacetic acid does not give the products of condensation. There are unreacted polyphenol and ammonium salt of compound **1** in the reaction mixture.

Thus, optimal conditions for the synthesis of derivatives of diarylmethane series **2a–c** are as follows: conduction of the reaction in ethanol and hydrochloric acid at 5:1 reagent (polyphenol:acetal) ratio and heating the reaction mixture for 1 h at 55–60°C. It should be noted that dropwise addition of hydrochloric acid to the solution of aminophosphine oxide **1** and polyphenol in ethanol at 10°C is desirable to avoid oligomerization.

The structure and composition of products **2a–c** and **3a** were confirmed by ^1H, ^{31}P, and ^{13}C NMR spectroscopy; IR spectroscopy; mass spectrometry; elemental analysis; and X-ray diffraction analysis (**3a**).

In ^{31}P NMR spectrum of compounds **2a–c**, there is one signal at 43–44 ppm. In ^1H NMR spectra of compounds **2a–c**, signals of methyl groups of hexyl substituent at the phosphorus atom appear as a triplet (0.85–0.87 ppm); methylene groups of hexyl substituent as multiplets (1.26–1.42 ppm); methylene groups of hexyl substituent at the phosphorus atom as a multiplet (1.77 ppm); signals of methyl groups as a singlet (for compound **2a**, 1.99 ppm); methylene groups bonded to phosphorus and nitrogen atoms as doublets (2.80 (CD_3OD) and 3.28–3.29 ppm (d_6-DMSO)); methylene groups between the nitrogen atom and the methine group as a doublet (3.57–3.58 (d_6-DMSO), 3.01 (CD_3OD)); protons of methine groups as a triplet (4.48, 4.82–4.99 ppm); protons at ortho- (6.08–6.33 ppm) and meta- (6.39–6.74 ppm) positions of aromatic nuclei as singlets; protons of hydroxyl groups (8.45–8.94 ppm) and protons of amino group (9.41 ppm) as broad singlets. In IR spectra, absorption bands of P=O (1205–1207 cm^{-1}), $C{=}C_{ar}$ (1606–1625 cm^{-1}), and OH (3242–3249 cm^{-1}) groups are detected.

In IR spectrum of **3a**, absorption bands of P=O (1210 cm^1), $C{=}C_{ar}$ (1604 cm^{-1}), and OH (3184, 3500 cm^{-1}) groups are detected.

According to X-ray analysis, a molecule of compound **3a** in a crystal is in special position at the center of inversion. Bond lengths, valence, and torsion angles have the values, which are in the ranges intrinsic for each type of bond. Configuration of the phosphorus atom is tetrahedral, and $O^1P^1C^2$, $O^1P^1C^{12}$, $O^1P^1C^{18}$ angles are 114.77(2)°, 112.67(1)°, and 110.95(1)°, respectively (Fig. 1).

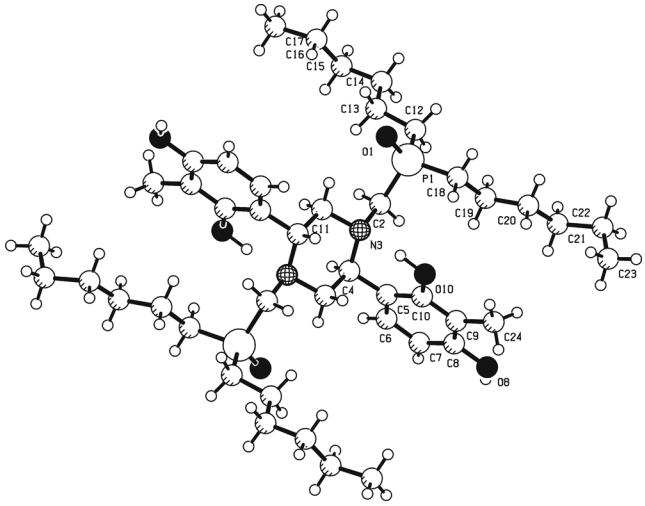


FIGURE 1 Molecular structure of compound **3a**.

The presence of phosphoryl and hydroxyl groups results in the formation of classical hydrogen bond between neighboring molecules in crystal; the distance from the hydrogen atom of the hydroxyl group of one molecule to the oxygen atom of the phosphoryl group of another one corresponds to 2.73 Å; and angle $O^8H^8\cdots O^1$ is 172.3°. Two-dimensional layers directed along the main diagonal of the parallelogram of the unit cell are formed by these interactions (Fig. 2).

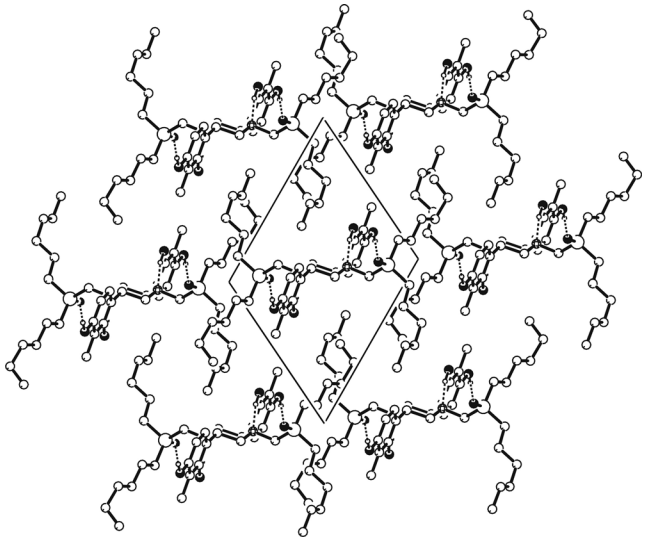


FIGURE 2 Crystal packing of compound **3a**.

It should be noted that tetrasubstituted piperazine **3a** was isolated by us as free amine. This was achieved by drying compound **3a** under vacuum of oil pump at 6×10^{-2} mmHg (0.06 Torr) for 3 h at t = 40°C. Preparation of diarylmethane derivatives **2a–c** with free amino group for subsequent participation in complexation was of certain interest. Long drying of these compounds under vacuum (0.06 Torr) also results in the destruction of salt structure and formation of free bases, which, however, have extremely poor solubility in organic solvents, thus complicating their subsequent application. Therefore, with an aim to retain salt form, solvent removal from products **2a–c** was realized under mild conditions (15 Torr, 30°C).

Following our studies, we chose calix[4] resorcinol **4** as polyphenol to synthesize a macrocyclic polydentate ligand containing aminophosphine oxide fragments. It should be noted that these macromolecules are obtained at acid-catalyzed condensation of aldehydes (acetals) with resorcinols; therein orthopositions between hydroxyl groups of resorcinol rings remain free for subsequent functionalization [24].

We have shown earlier that these positions are active in electrophilic substitution reactions with methylene carbocations (the Mannich reaction, benzylation, and so on) [25, 26].

The presence of secondary amino group in the phosphine oxide molecule **1** allows its use for modification of "upper rim" of calix[4] resorcinol by the Mannich reaction. Condensation of calix[4]resorcinol **4** with formaldehyde and aminophosphine oxide **1** at a 1:5:5 reagent ratio in an ethanol/benzene mixture at room temperature yielded new tetrasubstituted macrocycle **5** (Scheme 3).

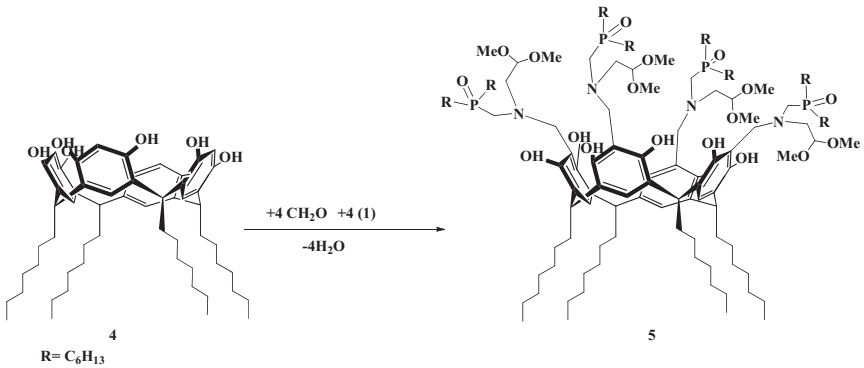
It is known from published data that, depending on the reagent ratio, structure of amines, length of alkyl substituent on the "lower rim" of macrocycle, as well as type of used solvents, various numbers of aminoalkyl groups can be introduced in the calix[4]resorcinol molecule according to the Mannich reaction [27–29]. We demonstrated that variation of stoichiometric reagent ratios (from 1:1:1 to 1:5:5) in the reaction under study as well as a solvent (ethanol/benzene, methanol) does not affect remarkably the synthetic result; compound **5** is exclusively formed in all experiments; only its yield changed.

The most optimal experimental conditions, which enable one to prepare macrocycle **5** with the maximum yield, are ethanol/benzene medium, calix [4]resorcinol-to-formaldehyde-to-aminophosphine oxide **1** reagent ratio of 1:5:5, and room temperature.

The product **5** represents an oily substance; the presence of aminophosphine oxide substituents in macrocycle **5** considerably improves its solubility both in polar (alcohols, DMSO, acetone) and nonpolar (benzene, chloroform, diethyl ether) solvents compared to its precursor **4**. Unfortunately, the attempts to grow the crystal, which is suitable for X-ray diffractometry and is required for the determination of the cavity size and geometry of functional groups of macrocycle **5**, were ineffective.

The structure of compound **5** was assigned by NMR (^{1}H, ^{31}P, ^{13}C) and IR spectroscopy; composition was proved according to elemental analysis data. In ^{31}P NMR spectrum of compound **5**, there is one signal at 46 ppm. In ^{1}H NMR spectrum of compound **5**, there is no signal at 6.2 ppm corresponding to orthoproton of resorcinol rings in the calix[4]resorcinol matrix; this indicates the formation of a product of tetrasubstitution of macrocycle.

Compound **5** was synthesized from the *rccc*-isomer of calix[4]resorcinol **4**, which, according to the literature data, does not transform into another isomer even at high temperature [30–32]. In our case, the reaction proceeds at room temperature and this transformation is even less possible. It may be concluded that at ambient temperature, compound



SCHEME 3 Synthesis of calix[4]resorcinol **5**, containing aminophosphine oxide and acetal groups.

5 adopts an *rccc*-configuration. The analysis of ^{1}H NMR spectra of compounds **4** and **5** shows that four methine protons that link aromatic fragments and four protons at four position of resorcinol rings are equivalent and the position of these signals in spectra almost does not change after chemical functionalization of macrocycle **4** and corresponds to (4.28 ppm (**4, 5**)) the protons of methine groups and (7.20 (**4**) and 7.09 ppm (**5**)) the protons of aromatic rings. In ^{1}H NMR spectrum of compound **5**, the protons of methine groups linking methoxy groups (4.31 ppm); methoxy groups (3.19 ppm); protons of methylene groups bonded to the nitrogen atom and methine group (2.86 ppm), phosphorus atom (3.38 ppm), or resorcinol ring (3.82 ppm) also appear as one set of signals; this indicates on the high symmetry of obtained macrocycle. The character of absorption bands of hydroxyl groups in IR spectra of compounds **4** (2256 cm^{-1}) and **5** (3300 cm^{-1}) almost does not differ and is recorded in the range, which is intrinsic for hydrogen-bonded hydroxyl groups. The combination of the mentioned data confirms that, despite relatively bulky substituents in orthoposition of aromatic rings of calix[4]resorcinol **5**, in $CDCl_3$ solution, the spectrum corresponding to averaged "cone" conformation is observed.

It is known from the published data that the formation of zwitterionic structures in aminomethylated calix[4]resorcinols is possible due to intramolecular hydrogen bonds between hydroxy groups and nitrogen atoms [33–35]. The analysis of spectral data for compound **5** showed that ^{13}C NMR signals of aromatic carbon atoms that are linked to hydroxyl groups are equivalent and appear in spectrum as singlet (151.1 ppm); in addition, there are no absorption bands in the range of 2500–2600 cm^{-1} in IR spectrum of macrocycle **5**; these facts indicate the absence of an zwitterionic structures in our case [35].

It was shown earlier that calix[4]arenes containing aminophosphonate fragments on the upper rim of molecule are effective and selective amino acid transfer agents compared with their linear counterparts [36] and lipophilic derivatives of aminophosphine oxides participate both in membrane transport of amino acids and as metal ion extractants from acidic media [20, 21, 37]. It is anticipated that the presence of lipophilic cavity with a long alkyl chain and four thermally and hydrolytically stable aminophosphine oxide fragments in synthesized calix[4]resorcinol would increase the binding efficiency and selectivity with organic and inorganic substrates compared with their linear counterparts and unsubstituted calix[4]resorcinol. We are currently exploring the extraction ability of the synthesized compounds toward soft metals ions.

EXPERIMENTAL

Spectroscopic Measurements

NMR experiments were performed on a Bruker AVANCE-600 spectrometer (Karlsruhe, Germany) at 303 K equipped by 5 mm broadband probehead working at 600.1 MHz in ^{1}H and 150.9 MHz in ^{13}C experiments. Chemical shifts in ^{1}H and ^{13}C spectra were reported relative to the solvent as internal standard ($CDCl_3$, CD_3OD, d_6-DMSO). ^{31}P NMR spectra were recorded on a Bruker AVANCE II-400 (Karlsruhe, Germany, 161.9 MHz for ^{31}P), and chemical shifts were reported relative 85% H_3PO_4 as external standard. Assignment was accomplished by means of COSY, 2D ^{1}H-^{13}C HSQC, and 2D ^{1}H-^{13}C HMBC experiments. IR spectra were recorded on a Bruker Vector-22 fourier spectrometer (Karlsruhe, Germany) in the wave number range from 4000 to 400 cm^{-1}. MALDI mass spectra were obtained on an ULTRAFLEX III mass spectrometer (Bruker Daltonic GmbH, Bremen, Germany). Measurements were conducted with the use of plastic and metal plates. 2,5-Dihydroxybenzoic acid (2,5-DHB) was used as matrix.

X-Ray Measurements

Crystal data for **3a**: $C_{22}H_{38}NO_3P$, M = 395.42; molecule in crystal is in special position at the centre of inversion. colorless crystal 0.1 × 0.1 × 0.2 mm, triclinic, space group *P*-1, $Z = 2$, $a = 11.035(2)$, $a = 10.427(6)$ $b = 10.692(6)$, $c = 12.020(7)$ Å, $\alpha = 111.858(7)$, $\beta = 104.361(7)$, $\gamma = 101.083(8)$, $V = 1142.9(11)$ Å^3, $\rho_{calc} = 1.134$ g cm^{-3}, $\mu = 0.138$ mm–1, $\lambda = 0.71073$ Å, $T = 150$ K, Bruker Smart Apex II CCD diffractometer, 7043 reflections collected ($\pm h$, $\pm k$, $\pm l$), 4165 independent and 1828 observed reflections [$I \geq 2\ \sigma(I)$], 234 refined parameters, $R = 0.0996$, $wR^2 = 0.1753$, max. Residual electron density 0.590(–0.400) eÅ^{-3}. CCDC 973062.

Synthesis

The starting calix[4]resorcinol **4** was prepared as described in [30].

N-((Dihexylphosphoryl)methyl)-2,2-dimethoxyethylamine, **1**. Mixture of dihexylphosphinous acid (1 g, 4.58 mmol), aminoacetaldehyde dimethylacetal (0.48 g, 4.58 mmol), and paraformaldehyde (0.137 g, 4.58 mmol) was heated under reflux

in the flask equipped with Dean–Stark adapter and reflux condenser for 3 h in the presence of *p*-toluenesulfonic acid (0.01 g). After completion of the reaction, potassium carbonate (0.12 g) was added to the reaction mixture and heated under reflux for additional 10 min; mixture was cooled and washed three times with water. Organic layer was separated and solvent was removed.

There is an oily product in residue. Yield: 1.4 g (91%) compound **1**, n_D^{20} 1.47. Anal. calcd for $C_{17}H_{38}NO_3P$: C, 60.87; H, 11.42; N, 4.18; P, 9.23. Found: C, 60.35; H, 11.56; N, 4.27; P, 9.13. IR (ν, cm^{-1}): 1127 (COC), 1242 (P=O), 3338 (NH). ^{31}P NMR ($CDCl_3$), δ = 47.33 (s). ^1H NMR ($CDCl_3$): δ = 0.79 (t, $^3J_{HH}$ = 7.10 Hz, 6H, CH_2CH_3), 1.21 (br. s., 8H, CH_2), 1.29 (m, 4H, CH_2), 1.48 (m, 4H, CH_2), 1.62 (m, 4H, CH_2P), 2.69 (br. s., 2H, NCH_2), 2.83 (m, $^2J_{PH}$ = 12.10 Hz, 2H, PCH_2), 3.26 (s, 6H, OCH_3), 4.32 (t, $^3J_{HH}$ = 5.40 Hz, 1H, CH). MS (MALDI): m/z = 374 $[M + K]^+$.

Reaction of 2-Methylresorcinol, Resorcinol, and Pyrogallol with Aminophosphine Oxide, **1**

To the solution of 2-methylresorcinol (1.64 g, 13.24 mmol) and aminophosphine oxide **1** (1.21 g, 3.61 mmol) in EtOH (6 mL) in a three-necked flask equipped with a condenser, magnetic stirrer, thermometer, and dropping funnel, hydrochloric acid (3 mL) was added dropwise at 10°C. The reaction mixture was stirred at room temperature for 2 h and further heated from 55 to 60°C. After 1 h of heating, solvent was removed under the vacuum of water pump, residue was washed with dry acetone, dried under the vacuum of oil pump (0.06 Torr, 3 h, 40°C), and 0.22 g (15.4%) compound **3a** was obtained.

Solvent was removed from acetone filtrate under the vacuum of water pump; residue was precipitated from ethanol to diethyl ether and dried under the vacuum of water pump (15 Torr, 30°C) to a constant weight. 1.2 g (60%) of compound **2a** was obtained.

N-[2,2-Bis(2,4-dihydroxy-3-methylphenyl)ethyl]-N-((dihexylphosphoryl)methyl)amine Hydrochloride, **2a**. Yield 1.2 g (60%); mp 124–125°C. Anal. calcd for $C_{29}H_{47}NO_5ClP$: C, 62.63; H, 8.52; P, 5.57; N, 2.52; Cl, 6.38. Found: C, 62.58; H, 8.46; P, 5.58; N, 2.54; Cl, 6.36. IR (ν, cm^{-1}): 1205 (P=O), 1606 (C=C), 2620 (NH^+), 3249(OH). ^1H NMR (d_6-DMSO), δ 0.87 (t, $^3J_{HH}$ = 6.7 Hz, 6H, CH_3), 1.26–1.34 (br. s., 12H, CH_2), 1.42 (m, 4H, CH_2), 1.77 (m, 4H, CH_2P), 1.99 (s, 6H, CH_3), 3.28 (d, $^2J_{PH}$ = 5.7 Hz, 2H, PCH_2N), 3.57 (d, $^3J_{HH}$ = 6.9 Hz, 2H, CH_2N), 4.99 (t, $^3J_{HH}$ = 7.7 Hz, 1H, CH), 6.33 (d, $^3J_{HH}$ = 8.4 Hz, 2H, CH_{ar}), 6.74 (d, $^3J_{HH}$ = 8.4 Hz, 2H, CH_{ar}), 8.4, 8.9, 9.1 (br. s., 5H, OH, NH). ^{13}C NMR (d_6-DMSO), δ = 9.2 (CH_3C_{ar}), 13.8 (CH_3CH_2), 20.5, 21.8, 29.9, 30.6 ($CH_3(CH_2)_4$), 27.4 (CH_2P, $^1J_{PC}$ = 66 Hz), 34.2 ($CHCH_2$), 45.4 (PCH_2NH, $^1J_{PC}$ = 59 Hz), 51.6 (CH_2CH), 106.6 (C_{ar}), 111.4 ($C_{ar}CH_3$), 118.5 ($C_{ar}CH$), 124.8 (C_{ar}), 153.1 ($C_{ar}OH$), 154.8 ($C_{ar}OH$). ^{31}P NMR (d_6-DMSO), δ = 43.98 (s). MS (MALDI), m/z: = 520 $[M - HCl + H]^+$, 542 $[M - HCl + Na]^+$, 558 $[M - HCl + K]^+$.

N-[2,2-Bis(2,4-dihydroxyphenyl)ethyl]-N-((dihexylphosphoryl)methyl)amine Hydrochloride, **2b**. We synthesized **2b** in analogy with previous study from 0.82 g (7.5 mmol) of resorcinol, 0.5 g (1.5 mmol) of aminophosphine oxide in ethanol (6 mL) and hydrochloric acid (1.5 mL). Residue was precipitated from methanol to diethyl ether.

Yield: 0.45 g (57%); mp 85–86°C. Anal. calcd for $C_{27}H_{43}NO_5ClP$: C, 61.41; H, 8.21; P, 5.87; N, 2.65; Cl, 6.71. Found: C, 61.38; H, 8.36; P, 5.68; N, 2.64; Cl, 6.76. IR (ν, cm^{-1}): 1208 (P=O), 1606 (C=C), 2626 (NH^+), 3260 (OH). ^{31}P NMR (d_3-CD_3OD): δ = 43.37(s). ^1H NMR (d_3-CD_3OD), δ = 0.85 (t, $^3J_{HH}$ = 6.70 Hz, 6H, CH_2CH_3), 1.29 (br. s., 12H, CH_2), 1.38 (m, 4H, CH_2), 1.57 (m, 4H, CH_2), 2.80 (d, $^2J_{PH}$ = 8.1 Hz, 2H, PCH_2N), 3.01 (d, $^3J_{HH}$ = 6.6 Hz, 2H, $NHCH_2$), 4.48 (t, $^3J_{HH}$ = 6.60 Hz, 1H, CH), 6.08 (d, $^3J_{HH}$ = 8.37 Hz, 2H, CH_{ar}), 6.23 (s, 2H, CH_{ar}), 6.70 (d, $^3J_{HH}$ = 8.37 Hz, 2H, CH_{ar}), 8.88, 8.94 (br. s., 4H, OH), 9.19 (br. s., 1H, NH). ^{13}C NMR (d_6-DMSO), δ = 14.8 (CH_3CH_2), 21.5, 22.8, 30.7, 31.9 ($CH_3(CH_2)_4$), 27.9 (CH_2P, $^1J_{PC}$ = 66.0 Hz), 35.4 ($CHCH_2$), 43.1 (PCH_2NH, $^1J_{PC}$ = 59.0 Hz), 51.6 (CH_2CH), 103.6 (CH_{ar}), 107.1 ($C_{ar}H$), 118.1 ($C_{ar}CH$), 130.2 (CH_{ar}), 156.6 ($C_{ar}OH$), 157.9 ($C_{ar}OH$). MS (MALDI), m/z = 491 $[M - HCl + K]^+$.

N-[2,2-Bis(2,3,4-trihydroxyphenyl)ethyl]-N-((dihexylphosphoryl)methyl)amine Hydrochloride, **2c**. We synthesized **2c** from 0.5 g (1.5 mmol) aminophosphine oxide **1** and 0.95 g (7.5 mmol) of pyrogallol in 6 mL ethanol and 2 mL hydrochloric acid in analogy with previous study, residue was reprecipitated from acetone to diethyl ether. Yield 0.43 g (52%); mp 128–130°C. Anal. calcd for $C_{27}H_{43}NO_7ClP$: C, 57.90; H, 7.74; P, 5.53; N, 2.50; Cl, 6.33. Found: C, 57.81; H, 7.82; P, 5.53; N, 2.51; Cl, 6.37. IR (ν, cm^{-1}): 1207 (P=O), 1608 (C=C), 2624 (NH^+), 3265 (OH). ^{31}P NMR (d_6-DMSO): δ = 43.71(s). ^1H NMR (d_6-DMSO): δ = 0.86 (t, $^3J_{HH}$ = 6.7 Hz, 6H, CH_2CH_3), 1.27 (br. s., 8H, CH_2), 1.33 (m, 4H CH_2), 1.42 (m, 4H, CH_2), 1.80 (m, 4H, PCH_2CH_2), 3.29 (br. s., 2H, PCH_2), 3.56 (d, $^3J_{HH}$ = 7.70 Hz, 2H, $NHCH_2$), 4.82 (t, $^3J_{HH}$ = 7.70 Hz, 1H, CH), 6.23 (d, $^3J_{HH}$ = 8.41 Hz, 2H, CH_{ar}), 6.39 (d, $^3J_{HH}$ = 8.41 Hz,

2H, CH_{ar}), 8.45, 8.62 (br. s., 4H, OH). MS (MALDI), m/z = 524 [M – HCl + H]$^+$, 546 [M – HCl + K]$^+$.

2,5-Bis(2,4-dihydroxy-3-methylphenyl)-1,4-(bis (dihexylphosphorylmethyl))-piperazine, **3a**. Yield 0.22 g (15%); mp 225–226°C. Anal. calcd for $C_{44}H_{76}N_2O_6P_2$: C, 66.81; H, 9.68; P, 7.83; N, 3.54. Found: C, 66.58; H, 9.88; P, 7.59; N, 3.56. IR (ν, cm^{-1}): 1210 (P=O), 1604 (C=C), 3184, 3150 (OH). ^{31}P NMR (d_6-DMSO), δ = 45.55(s). ^{1}H NMR (d_6-DMSO), δ = 0.84 (t, $^3J_{HH}$ = 6.80 Hz, 6H), 0.86 (t, $^3J_{HH}$ = 6.80 Hz, 6H, CH_3), 1.17–1.22 (br. s., 24H, CH_2), 1.55 (br. s., 8H, CH_2), 1.74 (m, 8H, CH_2), 2.02 (s, 6H, $C_{ar}CH_3$), 2.80–2.92 (br. s., 4H, NCH_2P), 3.67–3.70 (br. s., 4H, CH_2CH), 4.44 (br. s., 2H, CH), 6.44 (d, $^3J_{HH}$ = 8.40 Hz, 2H, CH_{ar}), 7.02 (br. s., 2H, CH_{ar}). ^{13}C NMR (d_6-DMSO), δ = 8.3 (CH_3), 13.8 (CH_3CH_2), 20.3, 21.1, 21.7, 30.6 ($CH_3(CH_2)_4$), 27.0 (CH_2P, $^1J_{PC}$ = 66.0 Hz), 35.4 ($CHCH_2$), 50.1 (PCH_2NH, $^1J_{PC}$ = 59.0 Hz), 57.5 (CH_2CH), 107.6 (MeCH_{ar}), 111.8 (C_{ar}Me), 118.5 (C_{ar}CH), 124.6 ($CH_{ar}C_{ar}$-OH), 154.5 (C_{ar}OH), 156.9 (C_{ar}OH). MS (MALDI), m/z = 791 [M + H]$^+$, 813 [M + Na]$^+$, 829 [M + K]$^+$.

4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetrakis[N-dihexylphosphoryl-methyl(2,2-di-methoxyethyl)amino)methyl]-2,8,14,20-tetra-hexylpentacyclo[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, **5**. To the solution of calix[4]resorcinol **4** (0.74 g, 0.84 mmol) in the mixture of benzene (5 mL) and ethanol (5 mL), aminophosphine oxide **1** (1.39 g, 4.15 mmol) and formaldehyde (0.38 g, 33% aqueous solution) were added dropwise. The reaction mixture was stirred at room temperature for 1 day; solvent was further removed under the vacuum of water pump. Residue was washed three times with hexane. There was an oily product in residue. Yield: 1.90 g (98%). Anal. calcd for $C_{128}H_{232}N_4O_{20}P$: C, 67.69; H, 10.30; N, 2.47; P, 5.46. Found C, 67.35; H, 10.56; N, 2.37; P, 5.31. IR (ν, cm^{-1}): 1127 (COC), 1238 (P=O), 1610 (C=C), 3300 (OH). ^{31}P NMR ($CDCl_3$), δ = 46.83 (s). ^{1}H NMR ($CDCl_3$): δ = 0.88–0.90 (m, 36H, CH_2CH_3), 1.30 (br. s., 96H, CH_2); 1.48–1.72 (m, 32H, CH_2P, CH_2CH_2P), 2.14 (m, 8H, CH_2), 2.86 (br. s., 8H, NCH_2), 3.19 (s, 24H, OCH_3), 3.38 (d, $^2J_{PH}$ = 12.1 Hz, 8H, PCH_2), 3.82 (s, 8H, CH_2C_{ar}), 4.28 (t, $^3J_{HH}$ = 7.6 Hz, 4H, $C_{ar}CH$,), 4.31 (t, $^3J_{HH}$ = 5.4 Hz, 4H, CH(OMe)$_2$), 7.09 (s, 4H, $C_{ar}H$), 9.4 (br. s., 8H, OH). ^{13}C NMR ($CDCl_3$), δ = 14.2 (($CH_2)_5CH_3$), 14.3 (($CH_2)_6CH_3$), 21.6–32.2 [($CH_2)_5$P, ($CH_3(CH_2)_4CH_2$], 31.0 (CH_2P, $^1J_{PC}$ = 56.0 Hz), 33.9 (CHC_{ar}), 34.2 ($CHCH_2$N), 52.8 (NCH_2P, $^1J_{PC}$ = 78.0 Hz), 52.9 (CH_2C_{ar}, $^3J_{PC}$ = 5.6 Hz), 54.3 (CH(OC$H_3)_2$), 54.6 (NCH_2CH), 103.8 (CH(OC$H_3)_2$), 110.1 ($C_{ar}CH_2$), 122.6 (C_{ar}CH), 124.1 (CH_{ar}), 151.1 (C_{ar}OH).

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