Synthesis of new α-aminophosphonates containing sterically hindered phenol fragments based on the reaction of 3,5-di(*tert*-butyl)-4-oxo-2,5-cyclohexadienylidenemethylphosphonates with aliphatic amines*

E. M. Gibadullina,[a] T. R. Shaekhov,[a] A. K. Badrtdinov,[b] Yu. K. Voronina,[a] and A. R. Burilov[a]*

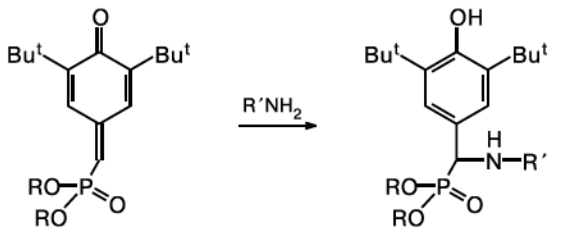
[a]A. E. Arbuzov Institute of Organic and Physical Chemistry Kazan Scientific Center of the Russian Academy of Sciences, 8 ul. Akad. Arbuzova, 420088 Kazan, Russian Federation. Fax: +7 (843 2) 75 2253. E-mail: elmirak@iopc.ru
[b]Kazan National Research Technological University, 68 ul. K. Marksa, 420015 Kazan, Russian Federation

A reaction of aliphatic amines (*n*-butylamine, *sec*-butylamine, *tert*-butylamine, dodecylamine, 1,12-diaminododecane) with α-phosphorylated methylenequinones (dimethyl {[3,5-di(*tert*-butyl)-4-oxo-2,5-cyclohexadienylidene]methyl}phosphonate and diphenyl {[3,5-di(*tert*-butyl)-4-oxo-2,5-cyclohexadienylidene]methyl}phosphonate)) to form 1,6-nucleophilic addition products was studied. This approach was used to obtain α-aminophosphonates containing sterically hindered phenol fragments in high yields.

Key words: α-aminophosphonate, antioxidant, sterically hindered phenol, aliphatic amines, [3,5-di(*tert*-butyl)-4-oxo-2,5-cyclohexadienylidenemethyl]phosphonate, 1,6-addition.

Sterically hindered 2,6-dialkylphenols, being biomimetics of natural antioxidant α-tocopherol (vitamin E), belong to the know class of widely used phenolic antioxidants.[1] These compounds possess high biological activity; among them are found highly efficient antioxidants, low toxic antiinflammatory non-steroid agents, antihypertensive, cardiac, and antibacterial drugs.[2—7] The authors of inventions[8—10] suggested to use α-aminophosphonic acid derivatives containing sterically hindered phenols as compounds for treatment and prevention of atherosclerosis, as well as degenerative joint disease. Aminophosphonates containing sterically hindered phenols were obtained either in the three-component system aldehyde—amine—hydrogen phosphite (the Kabachnik—Fields reaction),[10] or in the two-component system azomethine—hydrogen phosphite (the Pudovik reaction).[8,9] It should be noted that these reactions were carried out in the presence of catalysts, many of which are expensive and used in stoichiometric amounts. By now, there is known just a limited number of catalyst-free syntheses of α-aminophosphonate derivatives. Such structures can bee synthesized with the use of phosphorus-containing 2,6-di(*tert*-butyl)-4-methylene-2,5-cyclohexadienone, which due to the high reactivity is considered as a convenient agent for the synthesis of sterically hindered phenols of complicated structures.[11—14] It was shown[15,16] that phosphorylated methylenequinones reacted with nitrogen-containing compounds (aniline, piperidine, and hydrazine) with the formation of the 1,6-addition products. In this work, an approach was suggested to the synthesis of new α-alkylaminophosphonates containing sterically hindered phenols, which used phosphorus-containing 2,6-di(*tert*-butyl)-4-methylene-2,5-cyclohexadienones, *viz.*, dimethyl {[3,5-di(*tert*-butyl)-4-oxo-2,5-cyclohexadienylidene]methyl}phosphonate and diphenyl {[3,5-di(*tert*-butyl)-4-oxo-2,5-cyclohexadienylidene]methyl}phosphonate, and primary aliphatic amines (Scheme 1). The aliphatic amines, *viz.*, *n*-butylamine, *sec*-butylamine, *tert*-butylamine, dodecylamine, reacted

Scheme 1



1a,b **2a,b; 3a,b; 4a; 5a,b**

R = Me (**a**), Ph (**b**)
R′ = C_4H_9 (**2**), $CH(CH_3)C_2H_5$ (**3**), $C(CH_3)_3$ (**4**), $C_{12}H_{25}$ (**5**)

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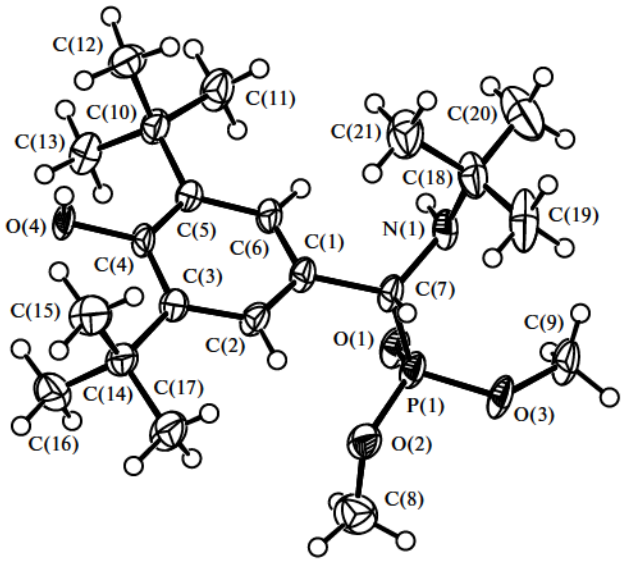


Fig. 1. Structure of molecules **2a**, **3b**, and **4a** according to the X-ray diffraction data shown for compound **4a**. Ellipsoids are given with 50% probability.

with methylenequinones **1a**,**b** in the ratio 1 : 1 at room temperature in dioxane with the formation of 1,6-addition products **2a**,**b**—**5a**,**b** in high yields. The compounds obtained are white powdered compounds.

The structure and composition of these compounds were established by ^{1}H and ^{31}P NMR and IR spectroscopy, mass spectrometry (MALDI-TOF), and elementhal analysis. Molecular and crystal structure of compounds **2a**, **3b**, and **4a** was determined by X-ray diffraction analysis (Fig. 1, Table 1).

According to the X-ray diffraction data, the geometric parameters of the molecules lie within the standard ranges

Table 1. Principal bond distances in structures **2a**, **3b**, and **4a**

Bond	2a	3b	4a
P(1)—O(1)	1.468(3)	1.4664(16)	1.465(2)
P(1)—O(2)	1.557(3)	1.5820(16)	1.571(2)
P(1)—O(3)	1.562(3)	1.5763(16)	1.580(2)
P(1)—C(7)	1.804(4)	1.811(2)	1.811(3)

for this class of compounds. The crystal packing of the compounds under study is determined by the hydrogen bonds between the hydrogen atoms of the hydroxy groups and the oxygen at the phosphorus atom. It should be noted that, despite the fact that the hydroxy group is flanked by two *tert*-butyl groups usually interfering with the formation of hydrogen bonds, the geometry of the phosphonate fragment structure is arranged in such a way that this interaction is possible and defines the structure of compounds under study (Fig. 2).

The reaction of methylenequinones with long-chain aliphatic diamine will allow one to obtain compounds possessing complexation properties. To accomplish this synthetic objective, we reacted methylenequinones **1a**,**b** with 1,12-diaminododecane in dioxane (Scheme 2). It was found that, irrespective of the ratio of the starting reagents, the reaction of methylenequinones with diamine led to the 1 : 2 nucleophilic addition products in high yields. The structure and composition of compounds **6a**,**b** was determined by ^{1}H and ^{31}P NMR and IR spectroscopy, mass spectrometry (MALDI-TOF), and elemental analysis.

In conclusion, we have shown that the reaction of 3,5-di(*tert*-butyl)-4-oxo-2,5-cyclohexadienylidenemethylphosphonates with aliphatic amines is a convenient

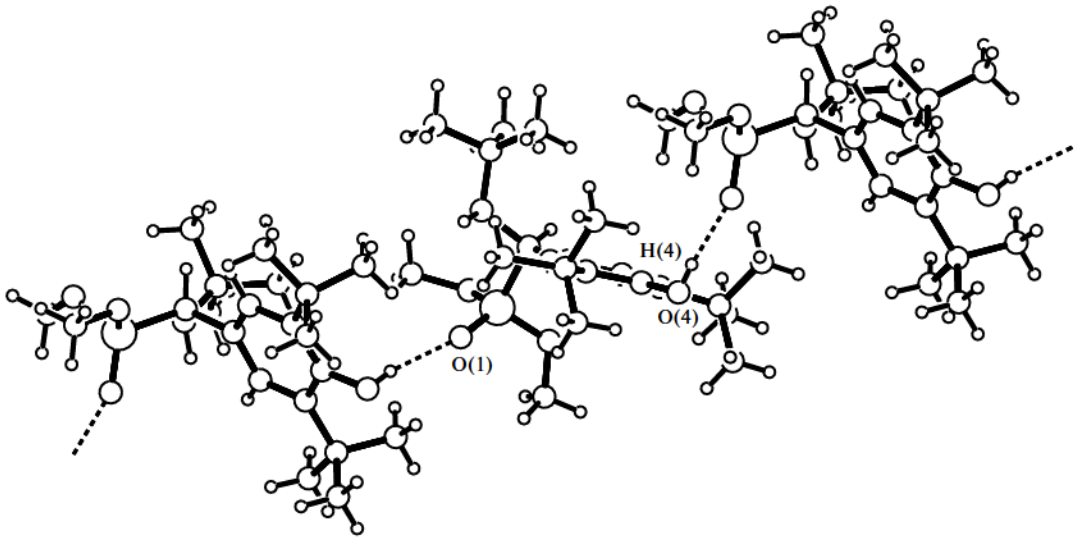
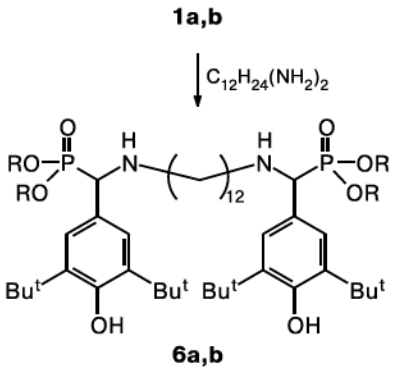


Fig. 2. The system of hydrogen bonds in crystals of compounds **2a**, **3b**, and **4a** shown for compound **4a**.

Scheme 2



method for the synthesis of α-aminophosphonates containing sterically hindered phenol fragments.

Experimental

^{1}H and ^{31}P NMR spectra were recorded on a Bruker MSL-400 spectrometer (^{1}H, 400.13 MHz; ^{31}P, 161.94 MHz) at 300 K equipped with a gradient block generating pulse gradient fields to 50 G cm^{-1}. A 5-mm inverse sensor with a gradient coil along the *z*-axis was used. Chemical shifts in δ scale are given relative to the residual signals of solvents ($CDCl_3$, $\delta(^1H) = 7.26$, DMSO-d_6, $\delta(^1H) = 2.5$). IR spectra were recorded on a Bruker Vector 22 IR Fourier-spectrometer within the frequency range of 400—4000 cm^{-1}. The samples were studied as emulsions in Nujol. Mass spectra MALDI-TOF were obtained on a Bruker ULTRAFLEX III TOF/TOF instrument (marix *p*-nitroaniline). Elemental analysis was performed on a Carlo-Erba EA 1108 analyzer. Crystals of compounds **2a**, **3b**, and **4a** were grown from $CHCl_3$. The unit cell parameters and intensities of reflections for the compounds were measured on a Smart Apex II CCD diffractometer (T = 100 K, λ(Mo-Kα) irradiation, graphite monochromator, φ- and ω-scan mode, $\theta_{max} = 28.80°$). The structures were solved by direct method using the SIR program[17] and refined first in isotropic and then in anisotropic approximation using the SHELXL-97 program.[18] Positions of hydrogen atoms were calculated geometrically and refined in isotropic approximation. All the calculations were carried out using the WinGX (see Ref. 19) and APEX2 programs.[20] Molecular images and analysis of intermolecular interactions were performed using the ORTEP3 and PLATON programs.[21,22] Crystallographic parameters and refinement details of structures of compounds **2a**, **3b**, and **4a** are given in Table 2. The atomic coordinates and geometric parameters of the structures were deposited with the Cambridge Structural Database 933597, 933596, and 933595 compounds **2a**, **3b**, and **4a** respectively).

Solvents were purified and dehydrated according to the known procedures.[23] Dimethyl [3,5-di(*tert*-butyl)-4-oxocyclohexa-2,5-dienylidenemethyl]phosphonate (**1a**) and diphenyl [3,5-di(*tert*-butyl)-4-oxocyclohexa-2,5-dienylidenemethyl]-phosphonate (**1b**) were synthesized as described earlier.[14,24]

Synthesis of compounds 2—6 (general procedure). A corresponding aliphatic amine was added to a solution of methylenequinone **1a** or **1b** in dioxane (1 ml). The reaction mixture was kept at ~20 °C for 1 h, the solvent was evaporated *in vacuo*, the residue was treated with pentane. A product formed was dried *in vacuo* until the weight stopped changing.

Table 2. Crystal parameters of compounds **2a**, **3a**, and **4a**

Parameter	2a	3b	4a
Color, habit	Prismatic colorless	Prismatic colorless	Prismatic colorless
Molecular formula	$C_{21}H_{38}NO_4P$	$C_{31}H_{42}NO_4P$	$C_{21}H_{38}NO_4P$
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	*P*21/*n*	*P*21/*n*	*P*21/*n*
Unit cell parameters[18]			
a/Å	9.299(10)	9.556(1)	11.092(4)
b/Å	18.25(2)	30.088(4)	17.785(6)
c/Å	13.67(1)	10.082(2)	12.127(4)
β/deg	100.34(2)	97.874(2)	94.526(4)
V/Å[19]	2281(4)	2871.4(7)	2385.0(13)
Z	4	4	4
Molecular weight	399.49	523.63	399.49
d_{calc}/g cm^{-3}	1.163	1.211	1.113
Absorption coefficient, μ/cm^{-1}	0.142	0.131	0.138
F(000)	872	1128	872
Number of reflections collected (R_{int})	7419 (0.0704)	22334 (0.0442)	18301(0.0809)
Number of observed reflections with $I > 2\sigma(I)$	2159	4516	3294
Number of refined parameters	263	350	263
R_1 ($I \geq 2\sigma(I)$)	0.0711	0.0551	0.0724
wR_2 (on all the reflections)	0.1958	0.1470	0.2090
Residual electron density/e Å^{-3}, ρ_{max}/ρ_{min}	0.419/ −0.643	1.173/ −0.345	0.906/ −0.618
GOOF	0.938	1.027	1.038

Dimethyl {[3,5-di(*tert*-butyl)-4-hydroxyphenyl](*n*-butylamino)-methyl}phosphonate (2a). The yield was 0.31 g (98%), m.p. 93—94 °C (from pentane). Found (%): C, 62.19; H, 9.58; N, 3.44; P, 7.86. $C_{21}H_{38}NO_4P$. Calculated (%): C, 63.13; H, 9.59; N, 3.51; P, 7.75. ^{1}H NMR ($CDCl_3$), δ: 0.88 (t, 3 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.2 Hz); 1.34 (m, 4 H, $C\underline{H}_2C\underline{H}_2CH_3$)); 1.45 (s, 18 H, Bu^t); 2.55 (m, 2 H, $C\underline{H}_2NH$)); 3.50, 3.69 (both d, 3 H each, OMe, $^3J_{P,H}$ = 10.3 Hz); 3.93 (d, 1 H, PCH, $^2J_{P,H}$ = 18.8 Hz); 5.18 (s, 1 H, OH); 7.18 (s, 2 H, H arom.). ^{31}P NMR ($CDCl_3$), δ: 26.6. IR, ν/cm^{-1}: 3623 (OH); 3350 (NH); 1622 (arom.); 1258 (P=O); 1038, 1059 (POC). MS (MALDI-TOF): *m/z*: 399.6 $[M]^+$.

Diphenyl {[3,5-di(*tert*-butyl)-4-hydroxyphenyl](*n*-butylamino)-methyl}phosphonate (2b). The yield was 0.50 g (96%), m.p. 110—112 °C (from pentane). Found (%): C, 70.91; H, 8.34; N, 2.64; P, 5.86. $C_{31}H_{42}NO_4P$. Calculated (%): C, 71.10; H, 8.08; N, 2.67; P, 5.92. ^{1}H NMR ($CDCl_3$), δ: 0.89 (t, 3 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.2 Hz); 1.36 (m, 4 H, $C\underline{H}_2C\underline{H}_2CH_3$)); 1.44 (s, 18 H, Bu^t); 2.56 (m, 2 H, $C\underline{H}_2NH$); 4.01 (d, 1 H, PCH, $^2J_{P,H}$ = 18.9 Hz); 5.18 (s, 1 H, OH); 6.81 (d, 2 H, H arom., $^3J_{H,H}$ = 8.4 Hz); 7.04, 7.13, 7.30 (all m, 10 H, H arom.). ^{31}P NMR ($CDCl_3$), δ: 18.5. IR, ν/cm^{-1}: 3627 (OH); 3346 (NH); 1594, 1619 (arom.); 1261 (P=O); 1181 (POC).

Dimethyl {[3,5-di(*tert*-butyl)-4-hydroxyphenyl](*sec*-butylamino)methyl}phosphonate (3a). The yield was 0.30 g (94%), m.p. 125—126 °C (from pentane). Found (%): C, 62.13; H, 9.53; N, 3.43; P, 7.85. $C_{21}H_{38}NO_4P$. Calculated (%): C, 63.13; H, 9.59; N, 3.51; P, 7.75. ^{1}H NMR ($CDCl_3$), δ: 0.85 (m, 3 H, $CH_2C\underline{H}_3$); 0.98 (m, 3 H, $CHC\underline{H}_3$); 1.37 (m, 2 H, $C\underline{H}_2CH_3$); 1.41 (s, 18 H, Bu^t); 2.45 (m, 1 H, NHC$\underline{H}$); 3.33, 3.47 (both d, 3 H, OMe, $^3J_{P,H}$ = 10.3 Hz); 3.72, 3.74 (both d, 3 H, OMe, $^3J_{P,H}$ = 10.3 Hz); 4.04, 4.09 (both d, 1 H, PCH, $^2J_{P,H}$ = 21.0 Hz); 5.18 (s, 1 H, OH); 7.17 (m, 2 H, H arom.). ^{31}P NMR ($CDCl_3$), δ: 27.79. IR, ν/cm^{-1}: 3457 (NH); 1590, 1635 (arom.); 1230 (P=O); 1040, 1061 (POC). MS (MALDI-TOF): *m/z*: 399.5 $[M]^+$.

Diphenyl {[3,5-di(*tert*-butyl)-4-hydroxyphenyl](*sec*-butylamino)methyl}phosphonate (3b). The yield was 0.51 g (98%), m.p. 141—143 °C (from pentane). Found (%): C, 71.02; H, 8.42; N, 2.70; P, 5.96. $C_{31}H_{42}NO_4P$. Calculated (%): C, 71.10; H, 8.08; N, 2.67; P, 5.92. ^{1}H NMR ($CDCl_3$), δ: 0.90 (t, 3 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.2 Hz); 1.04 (m, 3 H, $CHC\underline{H}_3$); 1.41 (s, 18 H, Bu^t); 1.56 (m, 2 H, $C\underline{H}_2CH_3$); 2.75 (m, 1 H, C$\underline{H}$NH); 4.39, 4.43 (both d, 1 H, PCH, $^2J_{P,H}$ = 18.9 Hz); 5.18 (s, 1 H, OH); 6.78, 6.83 (both d, 2 H, H arom., $^3J_{H,H}$ = 8.4 Hz); 7.04, 7.13, 7.30 (all m, 10 H, H arom.). ^{31}P NMR ($CDCl_3$), δ: 17.6; 17.7; 17.8. IR, ν/cm^{-1}: 3627 (OH); 3346 (NH); 1594, 1619 (arom.); 1261 (P=O); 1181 (POC). MS (MALDI-TOF): *m/z*: 522.9 $[M]^+$.

Dimethyl {[3,5-di(*tert*-butyl)-4-hydroxyphenyl](*tert*-butylamino)methyl}phosphonate (4a). The yield was 0.31 g (99%), m.p. 140—142 °C. Found (%): C, 62.13; H, 9.58; N, 3.47; P, 7.89. $C_{21}H_{38}NO_4P$. Calculated (%): C, 63.13; H, 9.59; N, 3.51; P, 7.75. ^{1}H NMR ($CDCl_3$), δ: 0.99 (s, 9 H, Bu^t); 1.43 (s, 18 H, Bu^t); 3.41, 3.75 (both d, 3 H each, OMe, $^3J_{P,H}$ = 10.3 Hz); 4.06 (d, 1 H, PCH, $^2J_{P,H}$ = 24.0 Hz); 5.13 (s, 1 H, OH); 7.20 (s, 2 H, H arom.). ^{31}P NMR ($CDCl_3$), δ: 27.1. IR, ν/cm^{-1}: 3631 (OH); 3471 (NH); 1590, 1634 (arom.); 1227 (P=O); 1038, 1061 (POC). MS (MALDI-TOF): *m/z*: 399.4 $[M]^+$.

Dimethyl {[3,5-di(*tert*-butyl)-4-hydroxyphenyl](dodecylamino)-methyl}phosphonate (5a). The yield was 0.28 g (98%), m.p. 38—40 °C (from pentane). Found (%): C, 67.71; H, 10.58; N, 2.25; P, 5.56. $C_{29}H_{54}NO_4P$. Calculated (%): C, 68.07; H, 10.64; N, 2.74; P, 6.05. ^{1}H NMR (DMSO-d_6), δ: 0.83 (t, 3 H, Me, $^3J_{H,H}$ = 6.8 Hz); 1.21 (br.s, 20 H, $(C\underline{H}_2)_{10}$Me)); 1.37 (s, 18 H, Bu^t); 2.37 (m, 2 H, NHC$\underline{H}_2$);. 3.41, 3.61 (both d, 3 H each, OMe, $^3J_{P,H}$ = 10.3 Hz); 3.93 (d, 1 H, PCH, $^2J_{P,H}$ = 19.1 Hz); 7.12 (s, 2 H, H arom.). ^{31}P NMR (DMSO-d_6), δ: 27.5. IR, ν/cm^{-1}: 3640 (OH); 3329 (NH); 1590, 1635 (arom.); 1245 (P=O); 1030, 1060 (POC). MS (MALDI-TOF): *m/z*: 511.3 $[M]^+$.

Diphenyl {[3,5-di(*tert*-butyl)-4-hydroxyphenyl](dodecylamino)-methyl}phosphonate (5b). The yield was 0.14 g (98%), m.p. 82—84 °C (from pentane). Found (%): C, 73.43; H, 9.08; N, 1.95; P, 4.56. $C_{39}H_{58}NO_4P$. Calculated (%): C, 73.67; H, 9.19; N, 2.20; P, 4.87. ^{1}H NMR ($CDCl_3$), δ: 0.90 (t, 3 H, Me, $^3J_{H,H}$ = = 6.5 Hz); 1.26 (br.s, 20 H, $(C\underline{H}_2)_{10}$Me)); 1.41 (s, 18 H, Bu^t); 2.66 (m, 2 H, NHC$\underline{H}_2$); 4.29 (d, 1 H, PCH, $^2J_{P,H}$ = 17.6 Hz); 5.21 (s, 1 H, OH); 6.81 (d, 2 H, H arom., $^3J_{H,H}$ = 8.4 Hz); 7.03—7.06, 7.11—7.18, 7.26—7.30 (all m, 10 H, H arom.). ^{31}P NMR ($CDCl_3$), δ: 17.3. IR, ν/cm^{-1}: 3625 (OH); 3321 (NH); 1592, 1615 (arom.); 1263 (P=O); 1184 (POC). MS (MALDI-TOF): *m/z*: 658.4 $[M + Na]^+$.

Tetramethyl {[dodecan-1,12-diylbis(azandiyl)]bis{[3,5-di-(*tert*-butyl)-4-hydroxyphenyl]methylene}}bis(phosphonate) (6a). The yield was 0.62 g (95%), m.p. 82—84 °C (from pentane). Found (%): C, 64.53; H, 9.58; N, 3.05; P, 7.16. $C_{46}H_{82}N_2O_8P_2$. Calculated (%): C, 64.76; H, 9.69; N, 3.28; P, 7.26. ^{1}H NMR ($CDCl_3$), δ: 1.22 (br.s, 20 H, $(C\underline{H}_2)_{10}CH_2$)); 1.44 (s, 36 H, Bu^t); 2.48—2.56 (m, 4 H, NHC$\underline{H}_2$); 3.50, 3.71 (both d, 6 H each, OMe, $^3J_{P,H}$ = 10.1 Hz); 3.96 (d, 2 H, PCH, $^2J_{P,H}$ = 18.6 Hz); 5.19 (br.s, 2 H, OH); 7.18, 7.19 (both s, 4 H, H arom.). ^{31}P NMR ($CDCl_3$), δ: 27.9. IR, ν/cm^{-1}: 3638 (OH); 3328 (NH); 1591, 1648 (arom.); 1242 (P=O); 1035, 1061 (POC). MS (MALDI-TOF): *m/z*: 854.5 $[M]^+$, 877.5 $[M + Na]^+$.

Tetraphenyl {[dodecan-1,12-diylbis(azandiyl)]bis{[3,5-di-(*tert*-butyl)-4-hydroxyphenyl]methylene}}bis(phosphonate) (6b). The yield was 0.23 g (95%), m.p. 120—122 °C (from pentane). Found (%): C, 71.52; H, 8.18; N, 2.32; P, 5.26. $C_{66}H_{90}N_2O_8P_2$. Calculated (%): C, 71.97; H, 8.24; N, 2.54; P, 5.62. ^{1}H NMR ($CDCl_3$), δ: 1.24 (br.s, 20 H, $(C\underline{H}_2)_{10}CH_2$)); 1.40 (s, 36 H, Bu^t); 2.61—2.70 (m, 4 H, NHC$\underline{H}_2$); 4.28 (d, 2 H, PCH, $^2J_{P,H}$ = 18.2 Hz); 5.20 (br.s, 2 H, OH); 6.80 (d, 4 H, H arom., $^3J_{H,H}$ = 8.2 Hz); 7.01—7.29 (m, 20 H, H arom.). ^{31}P NMR ($CDCl_3$), δ: 17.3. IR, ν/cm^{-1}: 3633 (OH); 3328, 3290 (NH); 1592, 1648 (arom.); 1208 (P=O); 1118 (POC). MS (MALDI-TOF): *m/z*: 1101.6 $[M]^+$.

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