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The synthesis of phosphorylated silsesquioxanes and the investigation of the ability to aggregation and interaction with aromatic dicarboxylic acids

Rushana R. Khairova [a], Luidmila S. Yakimova [a], Vladimir G. Evtugyn [a, c], Ildar Kh. Rizvanov [b], Ivan I. Stoikov [a, d, *]

[a] A. M. Butlerov Chemical Institute, Kazan Federal University, 420008 Kazan, Kremlevskaya 18, Russian Federation
[b] A.E. Arbuzov Institute of Organic and Physical Chemistry of KSC RAS, 420088 Kazan, Acad. Arbuzov 8, Russian Federation
[c] Institute of Fundamental Medicine and Biology, Kazan Federal University, 420008 Kazan, Kremlevskaya 18, Russian Federation
[d] KIBB KazSC RAS, 420111 Kazan, Lobachevsky 2/31, Russian Federation

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ABSTRACT

For the first time, silsesquioxanes containing aminophosphonate fragments were synthesized by condensation of the aminophosphonate derivatives with trialkoxysilane moieties under acid catalysis conditions. According to 29Si NMR, IR-spectroscopies, the silsesquioxane obtained have ladder-like structure with T_4 and T_6 silicon atoms. Information obtained from the MALDI-TOF mass spectra was used to deduce the structure of both oligomeric derivatives and the silsesquioxane framework. The morphology of the polysilsesquioxanes formed was investigated by transmission electron microscopy. The T_6-silsesquioxanes bearing aminophosphonate moieties contrary to T_4-silsesquioxanes tend to form aggregates of prolate shape. Their aggregation behavior was analyzed by the dynamic light scattering method. T_6-silsesquioxane tends to form submicron-sized aggregates in aqueous solutions. The ability of these silsesquioxanes to recognize aromatic dicarboxylic acids was studied by the UV-spectroscopy.

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Introduction

The synthesis of macromolecules and materials able to molecular recognition of various substrates is one of the main recent research tendencies. For realization of the ability to bind and recognize molecules, polyfunctional moieties containing both acceptor and donor groups are usually introduced in the synthetic receptor structure. Thus, aminophosphonate derivatives provide significant interest due to presence of proton acceptor (phosphoryl and) proton donor (amino groups) [1], from which the acid is an analog of natural compounds used in medicine [2]. It was shown that aminophosphonates exert high antiviral [3], antibacterial [4], antifungal [5], antimicrobial [6], and antitumor activity [7].

Meanwhile the development of low-cost materials becomes relevant. The silicon derivatives are excellent from this point of view. Concerning silsesquioxanes with empirical formulas $SiO_{3/2}$, it

should be noted that even though silsesquioxane chemistry spans over a half of the century, the interest continues to increase [8]. Synthesis of silsesquioxanes with the specified structure has been studied previously [9–13]. Nevertheless the study of the conditions for polycondensation of the organosilicon derivatives and their products calls for more careful investigation. Due to the low toxicity and high thermomechanical stability the appropriate materials based on silsesquioxanes are quite competitive and demanded.

Therefore, we have proposed the hypothesis that the combination of silsesquioxane as a core of hybrid materials containing simultaneously proton donor and acceptor groups can lead to selective receptor function toward biological substrates. Nano-sized building blocks and their capability to effectively recognition of biologically relevant substrates [14,15], combined with low toxicity and availability make it promising to study the condensation products of the organosilicon derivatives.

Thus, the synthesis silsesquioxanes containing aminophosphonate fragments by polycondensation of the aminophosphonate derivatives with trialkoxysilane moieties under acid catalysis conditions and investigating their ability to recognize aromatic dicarboxylic acids is the main goal of this work.

Experimental

The ^{1}H, ^{13}C, ^{29}Si and ^{31}P NMR spectra were recorded on Bruker Avance-400 spectrometer. Chemical shifts were determined relatively to the signals of residual protons of the deuterated solvent (CDCl$_3$). The concentration of the sample solutions was 3–5%. Most of the chemicals were purchased from Aldrich and used as received without additional purification. Organic solvents were purified by standard procedures. IR spectra were recorded with Spectrum 400 IR spectrometer (Perkin Elmer). Elemental analysis was performed with Perkin Elmer 2400 Series II instrument. Mass spectra were recorded with the MALDI-TOF Dynamo Finnigan. The mass spectra were obtained on Bruker Ultraflex III MALDI-TOF instrument. First grade Millipore® water was prepared from distilled water on Simplicity 185.

Synthesis

*General method for synthesis of compounds **1**–**3***

In the presence of 3Å molecular sieves, the mixture of 1.00 g (4.5 mmol) of 3-aminopropyltriethoxysilane in 4.5 mmol dry ketone (acetone, cyclopentanone or cyclohexanone) and catalytic amount of *p*-toluenesulfonic acid was stirred during 30 min. Acetone (in the case of compound **1**) and THF (in the case of compound **2** and **3**) were used as solvents. 0.58 g (4.5 mmol) of diethylphosphite were added to this mixture followed by stirring for 4 h at r.t. The progress of reaction was controlled by ^{31}P NMR spectroscopy. Molecular sieves were filtered off and the acetone was evaporated. The residue was dissolved in diethyl ester.

*(O,O′-Diethyl)-2-(3-(triethoxysilyl)propyl-amino)propane-2-yl-phosphonate (**1**).* Product yield 1.60 g (89%). ^{1}H NMR (CDCl$_3$, δ, ppm, J/Hz): 0.58 (2H, m, CH$_2$Si), 1.23 (6H, t, $^3J_{HH}$ = 7.0, CH$_2$CH$_3$), 1.27 (6H, s, (CH$_3$)$_2$C), 1.33 (9H, t, $^3J_{HH}$ = 7.0, CH$_2$CH$_3$), 1.55 (2H, m, CH$_2$CH$_2$CH$_2$), 2.60 (2H, t, NHCH$_2$CH$_2$), 3.70 (4H, q, $^3J_{HH}$ = 7.0, SiOCH$_2$CH$_3$). ^{31}P NMR (CDCl$_3$, δ, ppm): 31.32. ^{13}C NMR (CDCl$_3$, δ, ppm): 8.00, 16.56, 18.29, 23.02, 24.41, 45.81, 53.41, 58.33, 61.30. ^{29}Si NMR (CDCl$_3$, δ, ppm): −45.79. IR (ν/cm^{-1}): 949 (P=O); 1050, 1076, 1100 (Si–O); 1023 (P–O–C); 3415 (NH). El. Anal. Calcd. (%): C, 48.22; H, 9.36; N, 3.51; P, 7.77; Si, 7.05. Found (%): C, 48.10; H, 9.30; N, 3.50; P, 7.89; Si, 7.15. MALDI-TOF MS: calculated [M$^+$] *m/z* = 398.53, found [M + Na]$^+$ *m/z* = 419.9.

*(O,O′-Diethyl)-1-(3-(triethoxysilyl)propyl-amino) cyclobutane-2-yl-phosphonate (**2**).* Product yield 1.72 g (90%). ^{1}H NMR (CDCl$_3$, δ, ppm, J/Hz): 0.58 (2H, m, CH$_2$Si), 1.23 (6H, t, $^3J_{HH}$ = 7.0, CH$_2$CH$_3$), 1.59–2.08 (8H, m, −(CH$_2$)$_4$−), 1.33 (9H, t, $^3J_{HH}$ = 7.0, CH$_2$CH$_3$), 1.55 (2H, m, CH$_2$CH$_2$CH$_2$), 2.60 (2H, t, NHCH$_2$CH$_2$), 3.70 (9H, q, $^3J_{HH}$ = 7.0, SiOCH$_2$CH$_3$). ^{31}P NMR (CDCl$_3$, δ, ppm): 31.77. ^{13}C NMR (CDCl$_3$, δ, ppm): 7.90, 16.60, 18.28, 24.54, 36.38, 46.78, 58.31, 61.69, 63.62. ^{29}Si NMR (CDCl$_3$, δ, ppm): −47.50. IR (ν/cm^{-1}): 948 (P=O); 1100 (Si–O); 1074 (P–O–C); 2973 (NH). El. Anal. Calcd. (%): C, 45.25; H, 8.66; N, 3.51; P, 7.77; Si, 7.05. Found (%): C, 45.12; H, 8.44; N, 3.39; P, 7.78; Si, 7.11. MALDI-TOF MS: calculated [M$^+$] *m/z* = 424.2, found [M + Na]$^+$ *m/z* = 448.0.

*(O,O′-Diethyl)-2-(3-(triethoxysilyl)propyl-amino)cyclopentane-2-yl-phosphonate (**3**).* Product yield 1.78 g (90%). ^{1}H NMR (CDCl$_3$, δ, ppm, J/Hz): 0.7 (2H, m, CH$_2$Si), 1.22 (6H, t, $^3J_{HH}$ = 7.0, CH$_2$CH$_3$), 1.59–2.08 (10H, m, −(CH$_2$)$_5$−), 1.31 (9H, t, $^3J_{HH}$ = 7.0, CH$_2$CH$_3$), 1.56 (2H, m, CH$_2$CH$_2$CH$_2$), 2.71 (2H, t, NHCH$_2$CH$_2$), 3.70 (9H, q, $^3J_{HH}$ = 7.0, SiOCH$_2$CH$_3$). ^{31}P NMR (CDCl$_3$, δ, ppm): 30.73. ^{13}C NMR (CDCl$_3$, δ, ppm): 7.90, 16.60, 18.28, 24.54, 36.38, 46.78, 58.31, 61.69, 63.62. ^{29}Si NMR (CDCl$_3$, δ, ppm): −44.96. IR (ν/cm^{-1}): 946 (P=O); 1100 (Si–O); 1062 (P–O–C); 2929 (NH). El. Anal. Calcd. (%): C, 47.83; H, 9.15; N,

3.30; P, 6.84; Si, 6.24. Found (%): C, 47.70; H, 9.21; N, 3.41; P, 6.89; Si, 6.15. MALDI-TOF MS: calculated [M$^+$] *m/z* = 438.24, found [M + Na]$^+$ *m/z* = 461.9.

*Polycondensation of the compounds **1**–**3** in hydrochloric acid*

1.00 g (0.25 mmol) of the compounds **1**–**3** were dissolved in 5 ml of methanol and 2.5 mmol (0.76 ml) hydrochloric acid were added dropwise. The mixture was refluxed for 20 days at r.t. or 6 days at 35 °C. The reaction mixture was then passed through the ion exchange resin Amberlit IRA-400.

Dodecaethyl 2,2′,2″,2‴,2⁗,2⁗′-(3,3′,3″,3‴,3⁗,3⁗′-(3,5,9,11-tetrahydroxy-2,4,6,8,10,12,13-heptaoxa-1,3,5,7,9,11-hexasila-bicyclo[5.5.1]tridecane-1,3,5,7,9,11-hexayl)hexakis(propane-3,1-diyl))hexakis(azanediyl)hexakis(propane-2,2-diyl)hexaphosphonate (**4**). Product yield 0.92 g (85%). ^{1}H NMR (CDCl$_3$, δ, ppm): 0.58 (2H, bs, CH$_2$Si), 1.35 (6H, bs, (CH$_3$)$_2$C), 1.68 (6H, bs, CH$_2$CH$_3$), 2.043 (2H, bs, CH$_2$CH$_2$CH$_2$), 2.6 (2H, bs, NHCH$_2$CH$_2$), 4.02 (4H, m, OCH$_2$CH$_3$). ^{31}P NMR (CDCl$_3$, δ, ppm): 31.13. ^{13}C NMR (CDCl$_3$, δ, ppm): 8.00, 16.56, 24.41, 45.81, 53.41, 58.33, 61.30. ^{29}Si NMR (CDCl$_3$, δ, ppm): −69.03. IR (ν/cm^{-1}): 950 (P=O); 1046 (Si–O); 1022 (P–O–C); 3389 (NH). El. Anal. Calcd. (%): C, 40.80; H, 8.10; N, 4.76; P, 10.52; Si, 9.54. Found (%): C, 40.42; H, 8.24; N, 4.79; P, 10.78; Si, 8.31.

Dodecaethyl 1,1′,1″,1‴,1⁗,1⁗′-(3,3′,3″,3‴,3⁗,3⁗′-(3,5,9,11-tetrahydroxy-2,4,6,8,10,12,13-heptaoxa-1,3,5,7,9,11-hexasila-bicyclo[5.5.1]tridecane-1,3,5,7,9,11-hexayl)hexakis(propane-3,1-diyl))hexakis(azanediyl)hexakis(cyclopentane-1,1-diyl)hexaphosphonate (**5**). Product yield 1.15 g (88%). ^{1}H NMR (CDCl$_3$, δ, ppm): 0.58 (2H, bs, CH$_2$Si), 1.23 (6H, bs, $^3J_{HH}$ = 7.0, CH$_2$CH$_3$), 1.59–2.08 (8H, m, −(CH$_2$)$_4$−), 1.55 (2H, bs, CH$_2$CH$_2$CH$_2$), 2.6 (2H, bs, NHCH$_2$CH$_2$), 3.7 (4H, m, OCH$_2$CH$_3$). ^{31}P NMR (CDCl$_3$, δ, ppm): 31.77. ^{13}C NMR (CDCl$_3$, δ, ppm): 7.90, 16.60, 36.38, 46.78, 58.31, 61.69, 63.62. ^{29}Si NMR (CDCl$_3$, δ, ppm): −66.83. IR (ν/cm^{-1}): 950 (P=O); 1046 (Si–O); 1022 (P–O–C); 3306 (NH). El. Anal. Calcd. (%): C, 44.99; H, 8.07; N, 4.37; P, 8.01; Si, 8.77. Found (%): C, 44.69; H, 8.12; N, 4.23; P, 8.13; Si, 8.57.

Dodecaethyl (3,3′,3″,3‴,3⁗,3⁗′-(3,5,9,11-tetrahydroxy-2,4,6,8,10,12,13-heptaoxa-1,3,5,7,9,11-hexasila-bicyclo[5.5.1]tridecane-1,3,5,7,9,11-hexayl)hexakis(propane-3,1-diyl))hexakis(azanediyl)hexakis(-methylene)hexaphosphonate (**6**). Product yield 1.11 g (82%). ^{1}H NMR (CDCl$_3$, δ, ppm): 0.70 (2H, bs, CH$_2$Si), 1.22 (6H, t, $^3J_{HH}$ = 7.0, CH$_2$CH$_3$), 1.59–2.08 (10H, m, −(CH$_2$)$_5$−), 1.56 (2H, bs, CH$_2$CH$_2$CH$_2$), 2.71 (2H, bs, NHCH$_2$CH$_2$), 4.10 (4H, m, OCH$_2$CH$_3$). ^{31}P NMR (CDCl$_3$, δ, ppm): 30.73. ^{13}C NMR (CDCl$_3$, δ, ppm): 7.90, 16.60, 36.38, 46.78, 58.31, 61.69, 63.62. ^{29}Si NMR (CDCl$_3$, δ, ppm): −66.91. IR (ν/cm^{-1}): 951 (P=O); 1045, 1095 (Si–O); 1020 (P–O–C); 3309 (NH). El. Anal. Calcd. (%): C, 46.69; H, 8.34; N, 4.19; P, 9.26; Si, 8.40. Found (%): C, 46.42; H, 8.24; N, 4.39; P, 9.48; Si, 8.31.

*Polycondensation of the compounds **1**–**3** in acetic acid*

A solution of 0.01 mmol of the compounds **1**–**3** was prepared by dropwise addition of 5 ml of acetic acid followed by refluxing for 20 days at r.t. or 6 days at 35 °C. The reaction mixture was dissolved in methanol and passed through the ion exchange resin Amberlit IRA-400.

Octaethyl 2,2′,2″,2‴-(3,3′,3″,3‴-(2,4,6,8-tetrahydroxy-1,3,5,7,2,4,6,8-tetraoxatetrasilocane-2,4,6,8-tetrayl)tetrakis(propane-3,1-diyl))tetrakis(azanediyl)tetrakis(propane-2,2-diyl)tetraphosphonate (**7**). Product yield 1.41 g (79%). ^{1}H NMR (CDCl$_3$, δ, ppm): 0.58 (2H, bs, CH$_2$Si), 1.35 (6H, bs, (CH$_3$)$_2$C), 1.68 (6H, bs, CH$_2$CH$_3$), 2.04 (2H, bs, CH$_2$CH$_2$CH$_2$), 2.60 (2H, bs, NHCH$_2$CH$_2$), 4.02 (4H, m, OCH$_2$CH$_3$). ^{31}P NMR spectrum (CDCl$_3$, δ, ppm): 31.13. ^{13}C NMR (CDCl$_3$, δ, ppm): 8.00, 16.56, 24.41, 45.81, 53.41, 58.33, 61.30. ^{29}Si NMR (CDCl$_3$, δ,

ppm): −59.51, −69.38. IR (ν/cm^{-1}): 950 (P=O); 1046 (Si–O); 1022 (P–O–C); 3389 (NH). El. Anal. Calcd. (%): C, 40.80; H, 8.10; N, 4.76; P, 10.52; Si, 9.54. Found (%): C, 40.42; H, 8.24; N, 4.79; P, 10.78; Si, 8.31.

Octaethyl 1,1′,1″,1‴-(3,3′,3″,3‴-(2,4,6,8-tetrahydroxy-1,3,5,7,2,4,6,8-tetraoxatetrasilocane-2,4,6,8-tetrayl)tetrakis(propane-3,1-diyl))tetrakis(azanediyl)tetrakis(cyclopentane-1,1-diyl)tetraphosphonate (**8**). Product yield 1.63 g (85%). ^{1}H NMR (CDCl$_3$, δ, ppm): 0.58 (2H, bs., CH$_2$Si), 1.23 (6H, t, $^3J_{HH}$ = 7.0, CH$_2$CH$_3$), 1.59–2.08 (8H, m, −(CH$_2$)$_4$−), 1.55 (2H, bs, CH$_2$CH$_2$CH$_2$), 2.60 (2H, bs, NHCH$_2$CH$_2$), 3.70 (4H, m, OCH$_2$CH$_3$). ^{31}P NMR spectrum (CDCl$_3$, δ, ppm): 31.77. ^{13}C NMR (CDCl$_3$, δ, ppm): 7.90, 16.60, 36.38, 46.78, 58.31, 61.69, 63.62. ^{29}Si NMR (CDCl$_3$, δ, ppm): −58.49, −66.62. IR (ν/cm^{-1}): 949 (P=O); 1095, 1045 (Si–O); 1018 (P–O–C); 3306 (NH). El. Anal. Calcd. (%): C, 44.57; H, 8.10; N, 4.33; P, 9.58; Si, 8.68. Found (%): C, 44.42; H, 8.24; N, 4.49; P, 9.78; Si, 8.51.

Octaethyl 1,1′,1″,1‴-(3,3′,3″,3‴-(2,4,6,8-tetrahydroxy-1,3,5,7,2,4,6,8-tetraoxatetrasilocane-2,4,6,8-tetrayl)tetrakis(propane-3,1-diyl))tetrakis(azanediyl)tetrakis(cyclohexane-1,1-diyl)tetraphosphonate (**9**). Product yield 1.62 g (80%). ^{1}H NMR (CDCl$_3$, δ, ppm): 0.70 (2H, bs, CH$_2$Si), 1.22 (6H, t, $^3J_{HH}$ = 7.0, CH$_2$CH$_3$), 1.59–2.08 (10H, m, −(CH$_2$)$_5$−), 1.56 (2H, bs, CH$_2$CH$_2$CH$_2$), 2.71 (2H, bs, NHCH$_2$CH$_2$), 4.10 (4H, m, OCH$_2$CH$_3$). ^{31}P NMR spectrum (CDCl$_3$, δ, ppm): 30.73. ^{13}C NMR (CDCl$_3$, δ, ppm): 7.90, 16.60, 36.38, 46.78, 58.31, 61.69, 63.62. ^{29}Si NMR (CDCl$_3$, δ, ppm): −58.67, −68.39. IR (ν/cm^{-1}): 951 (P=O); 1095, 1045 (Si–O); 1020 (P–O–C); 3309 (NH). El. Anal. Calcd. (%): C, 46.27; H, 8.36; N, 4.15; P, 9.18; Si, 8.32. Found (%): C, 46.42; H, 8.24; N, 4.29; P, 9.32; Si, 8.36.

Probe preparation for MALDI-TOF on various matrixes

To obtain the mass spectra of the studied polycondensed products **4**−**9** of the organosilicon derivatives, their solutions in acetic acid with a concentration of 10^{-2} g/ml were prepared. Matrices containing the 10^{-3} g/ml solutions were prepared by dilution of the reaction mixture. The following matrices were used: the α-cyano-4-hydroxy-cinnamic acid (HCCA) (in methanol), 2,5-dihydroxybenzoic acid (DHB) (in acetonitrile), *p*-nitroaniline (pNA) (in methanol), *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB). In the case of HCCA, DCTB, 0.5 μl of the matrix solution were first poured onto the metal plate, then the solvent was evaporated and 0.5 μl of the analyte colloid solution were distributed on the film formed. In the case of DHB and pNA, 0.5 μl of the analyte colloid solution were first poured on the metal plat and then the solvent was evaporated and 0.5 μl of the matrix solution added on the film formed. The spectra were recorded in positive mode, mass range from 500 Da.

Transmission electron microscopy (TEM)

The TEM imaging was carried out with the JEOL JEM 100CX II microscope on the nickel grid (150 mesh) coated with Formvar®. The colloid suspension obtained by polycondensation was diluted with methanol to the concentrations of 10^{-4} ÷ 10^{-8} g/ml. The optimal concentration was found to be 10^{-7} g/ml. The imaging was performed after evaporation of the solvent for 24 h.

Dynamic light scattering (DLS)

The particle sizes were determined by Zetasizer Nano ZS instrument at 20 °C. The instrument contains 4 mW He–Ne laser operating at a wavelength of 633 nm and incorporates noninvasive backscatter optics (NIBS). The measurements were performed at the detection angle of 173° and the measurement position within
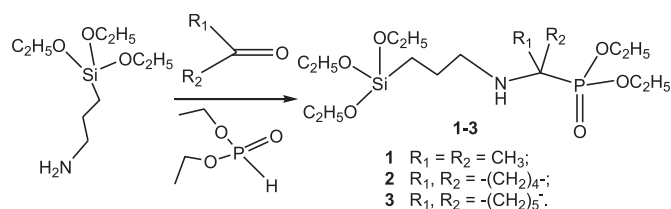
Scheme 1. Conditions: acetone/THF, stirring, mol. sieves 3Å.

the polystyrene cuvette was automatically determined by the software. The 10^{-4} M solutions of the silsesquioxane derivatives **4**−**9** in the first grade Millipore® water were prepared. The experiments were carried out for each solution in triplicate.

UV-spectroscopy

Absorption spectra were recorded on the UV-3600 UV-spectrometer (Shimadzu). Quartz cuvettes with optical path length of 10 mm were used. The 10^{-4} M solutions of the silsesquioxanes **4**−**9** were prepared in the first grade Millipore® water and the spectra recorded after 10 min incubation. Efficiency of the binding of dicarboxylic aromatic acids was estimated by addition of 1.2-fold excess of the acids in water. The experiment was carried out at 25 °C.

Results and discussion

*Synthesis α-aminophosphonate derivatives **1**−**3***

α-Aminophosphonate derivatives of trialkoxysilane were obtained by the Kabachnik–Fields reaction, which is the simplest method for the synthesis of aminophosphonates, in a three-
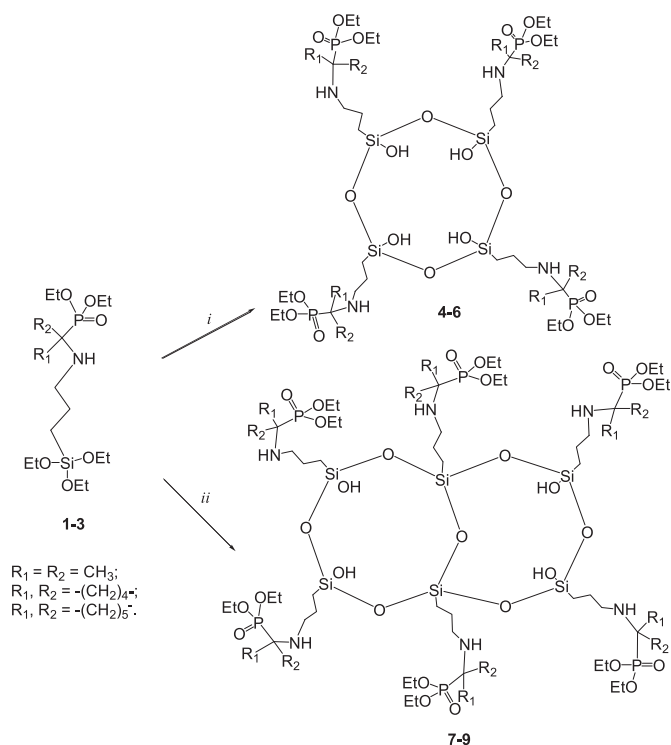
Scheme 2. Conditions: *i*, acetic acid, stirring, 35 °C; *ii*, hydrochloric acid/methanol, stirring, 35 °C.
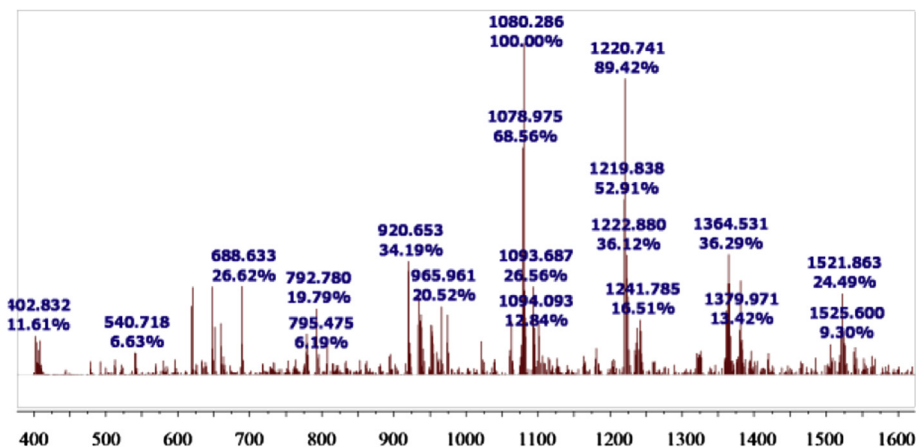
Fig. 1. Mass spectra for the condensed products of compound **4** (DHB are used as matrix).

component system (ketone, dialkyl phosphite and amine). Acetone, cyclopentanone, cyclohexanone were used as ketones in this reaction. The molar ratio of the ketone, dialkyl phosphite and amine was 1:1:1. The optimal amount of p-toluenesulfonic acid was estimated as 0.01 equivalents. The main difficulties are related to removal of water from the reaction mixture because water promotes hydrolytic condensation of the organosilicon derivatives. For this purpose, the Dean–Stark apparatus with freshly dried molecular sieves 3Å was used. It was found the 4 h stirring with successive evaporation in a rotary evaporator led to optimal yields with no further purification. The aminophosphonate derivatives were found to be pure according to ^{1}H, ^{13}C, ^{31}P, ^{29}Si NMR and IR spectroscopy, elemental analysis (Supporting Information). The products **1**–**3** (Scheme 1) were isolated in good yields.

Polycondensation of the compounds *1*–*3*

According to the literature [16,17], acid catalysis of the silsesquioxanes synthesis results in the formation of colloids (Scheme 2). Thus, the colloid solutions of oligosilsesquioxane obtained from α-aminophosphonate derivatives of trialkoxysilane **1**–**3** were investigated. First, acetic acid as active reaction medium was used for the formation of silsesquioxanes with a fixed architecture [17]. Then, the most popular catalyst for the polycondensation, hydrochloric acid, was employed. The optimum temperature of reaction was defined as 35 °C. At room temperature the reaction rate was low. At

higher temperatures the formation of minor products was observed in the ^{31}P NMR spectrum.

MALDI-TOF MS analysis

MALDI-TOF MS analysis was used to achieve the molecular weights and detailed structure of the oligocondensed products **4**–**9**. A series of experiments were conducted with different matrices and analyte-matrix ratio was varied to exclude peaks corresponding to the matrix itself or its complexes with silsesquioxanes. Optimal analyte-to-matrix ratio was found to be 10:1. Based on the literature data on the structure of oligomeric organosilicon products of polycondensation, the following compounds were tested as matrices: DCTB, HCCA, DHB, pNA [18–21].

Polycondensation in acetic acid. Assuming the formation of the silsesquioxane where each silicon atom is bonded to one and a half of oxygen in average and to one alkyl chain, the theoretical molecular weight of repeated group (n), $RSiO_2H$, is 297.35 g/mol, where $R = (-CH)_2NHCH(CH_3)_2P(O)(OC_2H_5)_2$.

Fig. 1 shows mass spectrum in the 400–1650 m/z range for the polycondensed products. Two major peaks are seen at 1080.3 and 1220.7 m/z. Less intensive peaks (about 10–40% of the maximum peak) are observed also and their subdistribution is shifted probably due to the fragmentation of the alkyl substituents and possible cycle opening. The theoretical molecular weight for polycondensed product **4** with $n = 4$ is equal to 1189.4 Da. The formation of such a
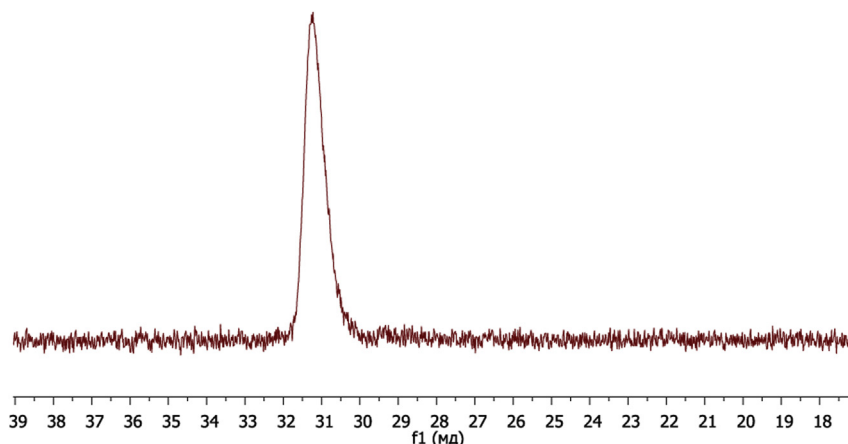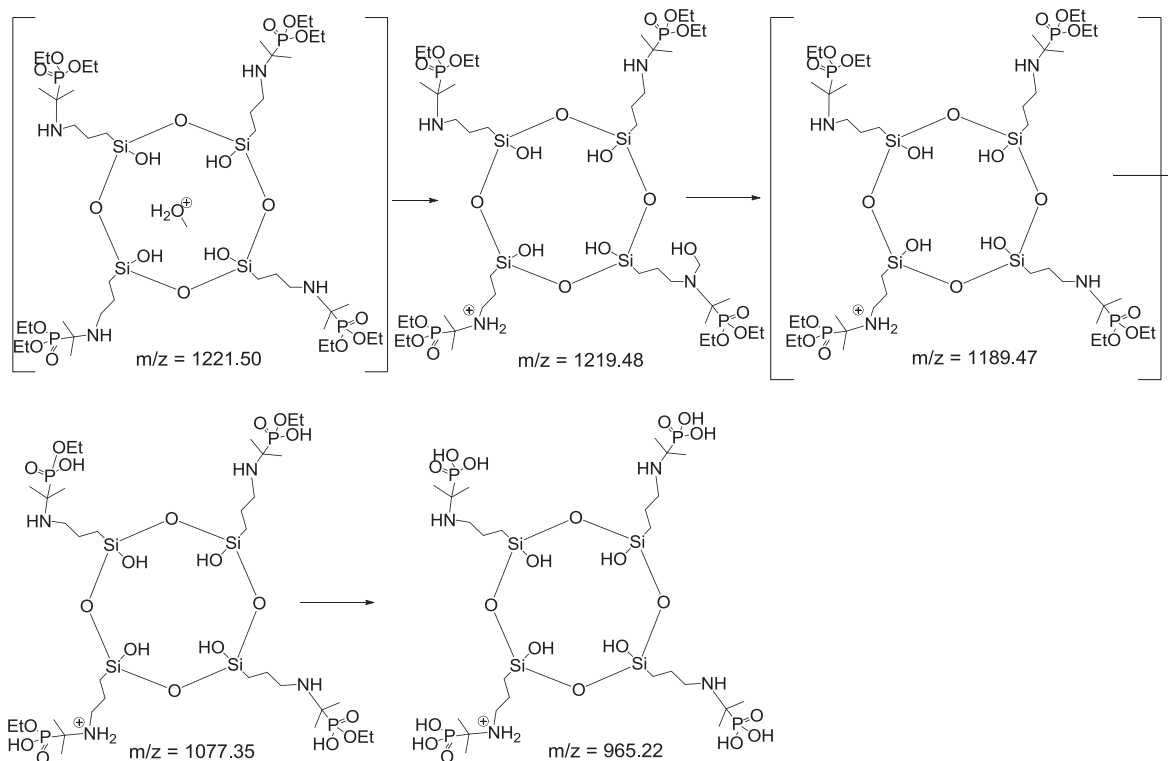

Fig. 2. ^{31}P NMR spectrum of the condensed product **4**.

Scheme 3. Possible structures of the polycondensed product **4** in acetic acid.

structure can occur when two dangling −SiOH groups in close proximity within a given molecule react intramolecularly to form a Si−O−Si bond. When such an intramolecular reaction occurs, closed loop can be formed in the molecule. The intermolecular reaction of this type should result in a shift of a multiple of 297.35 Da leading to the formation of other species having different number of Si atoms.

Based on the mass obtained we can specify the molecular ion peaks corresponded to condensed oligomacrocyclic compounds. According to the MALDI-TOF mass spectra (Fig. 1) incompletely condensed structures containing −SiOH groups of the generic formula $[RSiO_{1.5−x}(OH)_{2x}]_n$ or $T_n(OH)_m$ are formed. The intramolecularly condensed structure $[T_4(OH)_4]$ was deduced for the four-membered ring structure of the product **4**. The

silsesquioxane with four OH groups per molecule has the ladder-type structure [20]. Thus, we can propose synthesized polycondensed product **4** is the silsesquioxane with ladder-type structure. The compounds **5** and **6** polycondensed in acetic acid have the same structure. According to molecular ion masses (Supporting Information) these silsesquioxanes contain four Si−OH groups in the cyclic structure with generic formula $T_4(OH)_4$. The presence many peak of molecular ions in these spectra is due to defragmentation of aminophosphonate fragments and possible cycle opening in particular during the MALDI-TOF ionization because the presence of α-aminophosphonate groups in the polycondensed products was confirmed by ^{31}P NMR spectra. Fig. 2 shows ^{31}P NMR spectrum of the product **4**. The ^{31}P NMR spectrum of the compound **4**
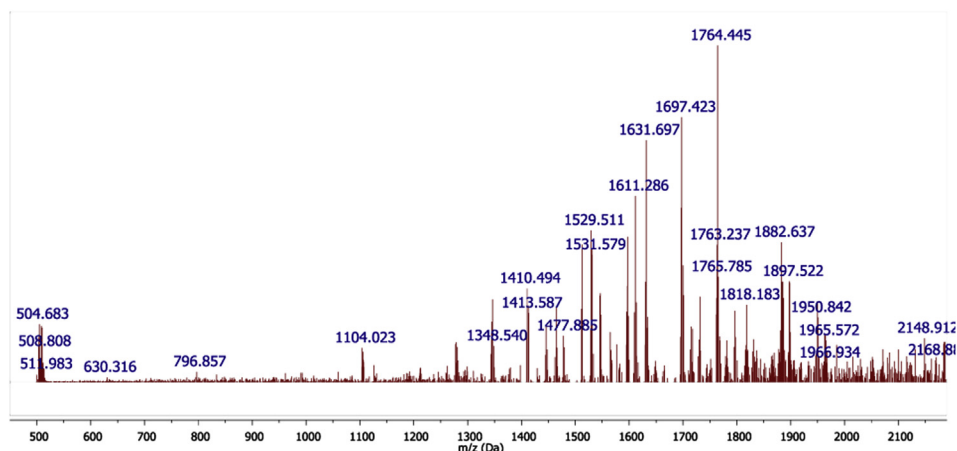
Fig. 3. Mass spectra for the condensed products of compound **8** (HCCA are used as matrix).

m/z = 1921.79

m/z = 1753.6

m/z = 1697.54

m/z = 1613.44
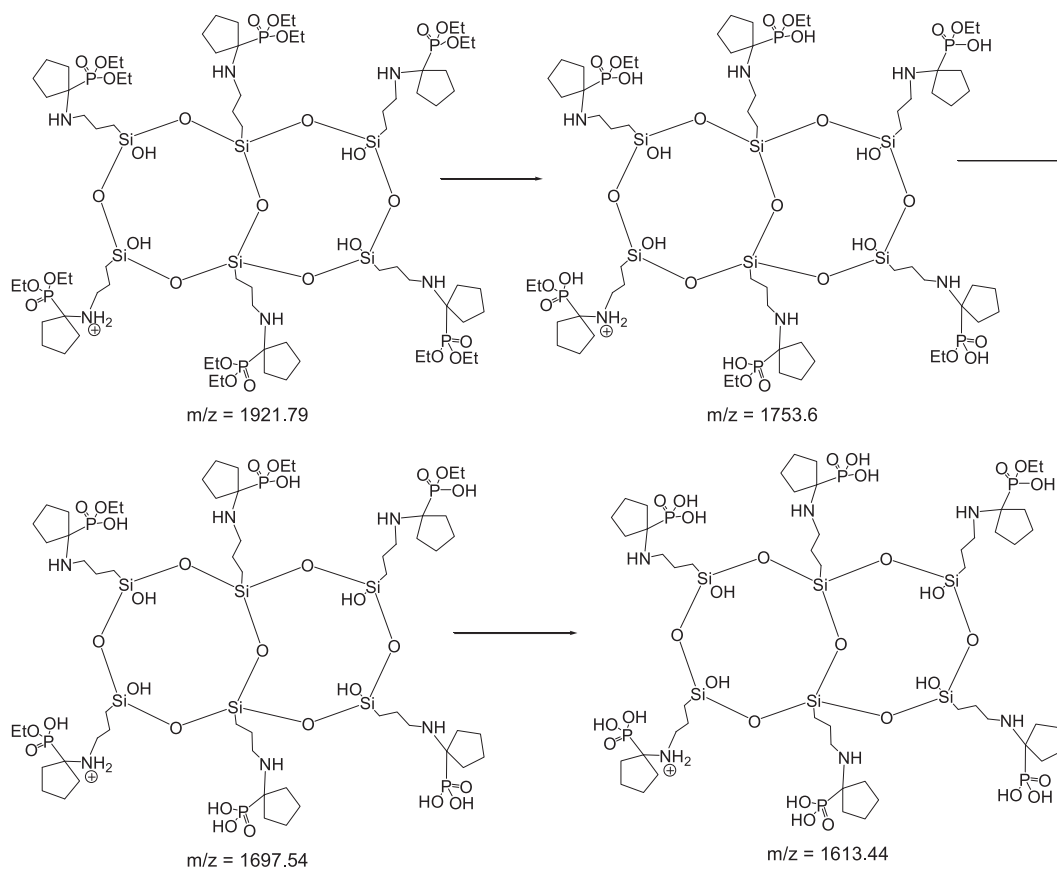
Scheme 4. Possible structures of the polycondensed product **8** in hydrochloric acid.

contains the signals characteristic for α-aminophosphonates with chemical shift near 31 ppm. Possible structures of the polycondensed product **4** in acetic acid are showed on the Scheme 3.

Polycondensation in hydrochloric acid. Polycondensation of the phosphorylated silsesquioxanes **1**–**3** with hydrochloric acid under the same conditions led to the formation of the compounds with other type of structure. In the case of polycondensed products **7**–**9** the cyclic structure with the generic formula $T_6(OH)_4$ is formed according to the MALDI-TOF MS. In the mass spectra (Fig. 3) obtained for the polycondensed products of the compound **2** in acetic acid using HCCA as matrix, most intensive molecular ion peaks with $m/z = 1764.4$, 1697.4, 1631.7 and 1611.3 Da are observed. The mass spectra of the compounds **8** and **9** are presented in Supporting Information. The theoretical molecular weight for polycondensed product **8** with $n = 6$ is equal to 1940.3 Da. Scheme 4 shows the chain corresponding to the defragmentation of the compound **8**, which is well comparable to that obtained by the MALDI-TOF MS on HCCA as a matrix. Maximal molecular ion peak of 1764.4 Da

corresponds to the silsesquioxane structure with Si_6 closed structure where one amino phosphonate moiety was destroyed. The fragmentation of the polycondensed product **8** in hydrochloric acid represents a chain of sequential destruction of the several steps with elimination of the ethoxy group from the aminophosphonate units. The condensed structure $[T_6(OH)_4]$ was deduced for the six-membered ring ladder-type structure of the synthesized product **8**. Nevertheless, the destruction of the aminophosphonate units is happened during the MALDI-TOF MS ionization. As a result, most intensive peaks of the molecular ion are found in the mass spectra.

Table 1 shows the assignment of the main peaks in the mass spectra. General ladder-type structures are confirmed for the three-dimensional silsesquioxanes.

NMR spectroscopy

^{29}Si NMR spectroscopy was also used to characterize the polycondensed products **4**–**9**. As can be seen in Table 2, a series of peaks

Table 1
Assignment of MALDI-TOF MS peaks for the condensed products of the compounds **4**–**9**.

Compound	(m/z) exp	Structure $T_n(OH)_m$	(m/z) cald
4	1220.6	$[T_4(OH)_4]–H_2O$	1221.5
	1080.3	$[T_4(OH)_4]$	1077.3
5	1347.4	$[T_4(OH)_4]$	1349.6
6	1366.2	$[T_4(OH)_4]–H_2O$	1367.7
7	1789.2	$[T_6(OH)_4]$	1784.2
8	1950.8	$[T_6(OH)_3O(C_2H_5)]$	1949.8
9	2043.2	$[T_6(OH)_4]–H_2O$	2042.5

Table 2
The ^{29}Si NMR spectroscopy data of the initial compounds **1**–**3** and the ladder silsesquioxanes synthesized in acetic acid **4**–**6** and in the hydrochloric acid **7**–**9**.

Compounds	Chemical shift, δ, ppm	
1	−45.79	
2	−47.50	
3	−44.96	
4	−69.03	
5	−66.83	
6	−66.91	
7	−59.51	−69.38
8	−58.49	−68.62
9	−58.67	−68.39

is observed in the range from −58 to −70 ppm. The ^{29}Si NMR spectra of the compounds **4**−**6** contain one signal near 69 ppm because silicon atoms have the same environment [9,21–24]. Also, the analysis of the ^{29}Si NMR spectra confirms the formation of one type of the all-*cis* stereoisomers for **4**−**6** [25,26]. Meanwhile the spectra of the compounds **7**−**9** contain two signals at 60 ppm and near 69 ppm. In general, peaks at lower shift are due to Si connected to other Si atoms via oxygen bridges (−69 to −70 ppm), while the peaks of Si atoms linked to an OH group are at a higher shift (around −60 ppm) [22]. For the siloxanes with isopropyl groups at silicon atom the chemical shift of the inner-ring Si atoms (T unit) moves from −71.97 (for bicyclic) to −65.21 and −65.80 ppm (pentacyclic) [9]. According to 29Si NMR spectrum, the formation of the mixture of difficultly separated stereoisomers **7**−**9** (all-cis; all-trans; cis, trans, cis; cis, cis, trans) was observed in the case of polycondensation of **1**−**3** performed in hydrochloric acid [25,26]. Thus, we confirmed that the synthesized siloxane **7**−**9** have bicyclic ladder type structure.

IR spectroscopy

IR spectroscopy method is one of main tools for determining framework of polycondensed products. It allows studying solid samples, what is very important because of their low solubility [27,28]. According to literature data, it was shown, that the position of characteristic asymmetric Si−O−Si absorption bands observed in 1030–1150 cm^{-1} region depends on the structure of the product formed, i.e. the length of repeating Si−O−Si subunits, size of siloxane ring and a molecule symmetry [27]. Transfer from cubic to ladder structure may be observed by IR spectroscopy method. In the case of the cubic structure of the silsesquioxane, one strong absorption band at 1120–1130 cm^{-1} is observed, while two absorption bands at 1150–1135 and 1045 cm^{-1} correspond to the ladder structure [29]. Presence of nonequivalent Si−O bonds in bicyclic and tricyclic ladder siloxanes leads to a number of the absorption bands which form a single wide sorption band due to overlaying. Meanwhile, two peaks are clearly observed in the spectra of ladder siloxanes containing more than five cycles [23].

The absorption band of the P−O−C bond in the aminophosphonate manifested in 1050–970 cm^{-1} caused some difficulty in correlating of vibration signals of Si−O−Si bond in the IR spectrum. However, all the initial compounds **1**−**3** and polycondensed products **4**−**9** have the valence vibrations near 1010–1020 cm^{-1} corresponded to P−O−C bond. The polysilsesquioxanes **4**−**9** spectra demonstrate two nonequivalent bonds Si−O−Si absorption bands. The IR spectrum of polycondensed product **5** and **8** is presented on Fig. 4. In support of formation the Si−O−Si bonds IR

Fig. 4. IR spectra of the compound **2** and polycondensed products **5** and **8**.

Table 3
Values of the valence vibrations of the polycondensed products **4**−**9** in the IR spectra.

Compounds		ν (P−O−C), cm^{-1}	ν (Si−O−Si), cm^{-1}	
			Peak 1	Peak 2
1	Cycle **4**	1008	1041	1092
	Bicycle **7**	1019	1048	1094
2	Cycle **5**	1010	1039	1092
	Bicycle **8**	1019	1045	1109
3	Cycle **6**	1008	1040	1092
	Bicycle **9**	1019	1046	1112

spectrum of initial compound **2** is presented. The polycondensed products **5** and **8** contain two nonequivalent absorption bands at 1092, 1109 and 1039, 1045 cm^{-1}, correspondingly. In accordance to the literature data proves the presence of polycondensed products **5**, **8** of a ladder-like structure. Moreover, it can be concluded that the synthesized siloxane contains more than one and two cycles in the structure because Si−O−Si bands are nonequivalent and broadened [23]. From Table 3, the values of the Si−O−Si valence vibrations of the polycondensed products **4**−**9** are observed in a narrow interval. Based on data obtained, the synthesized oligo-silsesquioxane has a ladder-like structure similar to one presented on Fig. 4.

In summary, we have prepared monocyclic and bicyclic ladder silsesquioxanes and determined their structure.

Self-assembly of the aminophosphonate-containing silsesquioxanes

Molecular self-assembly is a key concept in supramolecular chemistry because assembly of molecules in such systems is directed through noncovalent interactions, for example, hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, π−π interactions, electrostatic interactions [30–33]. The supramolecular assemblies show a variety of different shapes and sizes which can be obtained using molecular self-assembly [29]. Dynamic light scattering (DLS) is one of the methods used for the particle size determination. The ability of the siloxanes **4**−**9** with/without dicarboxylic aromatic acids (phthalic and isophthalic acids) to self-assemble was investigated under the same conditions with the UV-spectroscopy. The systems consisting of the siloxanes **4**−**9** and an aromatic acid did not show self-association abilities. The ability of the systems consisting only siloxane solutions **4**−**9** with no acids to undergo self-association was investigated. It was shown, that the monocyclic siloxanes **4**−**6** as such are not able to form self-associates with the aromatic acids. Contrary to that, bicyclic siloxanes **7**−**9** form nanoscale aggregates with the hydrodynamic diameter of about 220 (**7**), 412 (**8**) and 188 (**9**) nm, respectively (Table 4). The ability of the systems to form nanoscale associates depends on three factors, i.e., the conformation of a macrocycle and nature of the substrates/solvent and of the binding centers. The ability to self-association was experimentally determined by variation of two factors: 1) transition from the monocyclic to bicyclic structure and 2) transition from

Table 4
Size of aggregates (hydrodynamic diameters, d_1, d_2 (nm), and peak area intensity, S_1, S_2 (%), for peaks 1, 2, respectively) obtained for the phosphorylated silsesquioxanes **7**−**9** in water and appropriate polydispersity index (PDI).

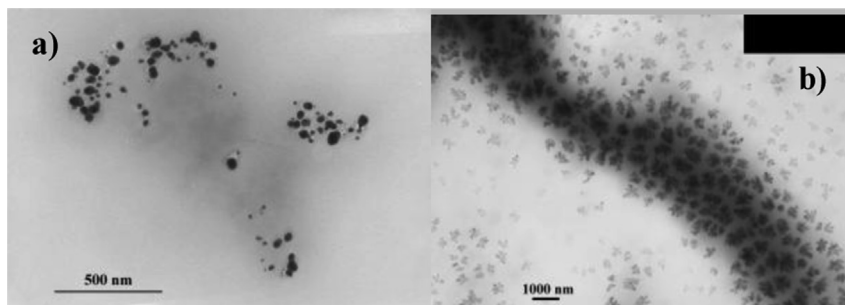| Siloxane	d_1, nm/S_1 %	d_2, nm/S_2 %	PDI
7	219.9 ± 9.8 (94.1 ± 2.1)	4455 ± 222.4 (5.9 ± 2.1)	0.41 ± 0.03
8	411.6 ± 9.6 (97.0 ± 3.0)	63.8 ± 59.90 (3.0 ± 3.0)	0.43 ± 0.03
9	187.8 ± 9.4 (95.2 ± 3.3)	3995 ± 1347 (4.8 ± 3.3)	0.24 ± 0.01
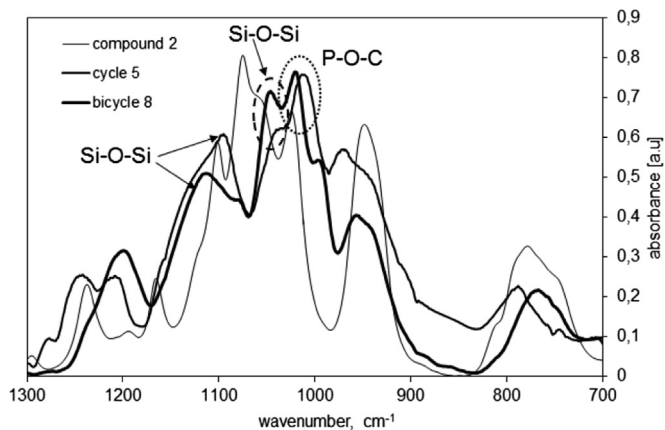
Fig. 5. Image of particles formed during polycondensation of the compound **6** (a) and **9** (b) by transmission electron microscopy. a) 500 nm; b) 1000 nm.

tetraaminophosphonate to hexaaminophosphonate derivatives. The self-association reaches minimum among the systems studied when cyclohexyl is coupled to 1-C atom of aminophosphonate fragment and the polydispersity index testifies approximately unimodal distribution (Table 4).

The surface morphology of the self-assembled aggregates of **9** with hydrodynamic diameter distribution by intensity of about 188 nm in accordance with DLS was investigated by TEM. Fig. 5b shows TEM images of the same surface region of the supramolecular associates consisting of the siloxane **9**. According to the images obtained after the evaporation of the solvent from the particles, column structures were formed due to the aggregation of the particles. Contrary to that, TEM confirmed no aggregation for the monocyclic siloxane **6** (Fig. 5a).

Complexation study

The polycondensed products **4**–**9** are interesting due to existence in their structure of the potential centers of coordination (proton donor NH and two proton acceptors P=O and lone electronic pair of nitrogen). Thus, they are capable to form complexes due to intermolecular coordination bonds between receptor and substrate. The formation of complexes between the synthesized products and acids is possible due to the formation of hydrogen bonds between the proton donor and proton acceptor centers of a host and guest species.

The UV spectroscopy is a universal tool for studying complexation properties of synthetic receptors. Changes in the absorbance spectrum of the polycondensed products **4**–**6** after the addition of the isomeric aromatic dicarboxylic acids (phthalic and isophthalic acids) indicate the formation of their complexes with the substrates. On the contrary, no changes in the absorbance spectrum of the polycondensed products **7**–**9** were found. The terephthalic acid was not used due to its low solubility in the solvent specified. The UV-spectra were recorded for the series of solutions of the mixtures of the polycondensed products **4**–**6** with phthalic/terephthalic acids taken in molar ratio 1:1.2 and those of individual components in the concentration studied. The absorbance changes caused by
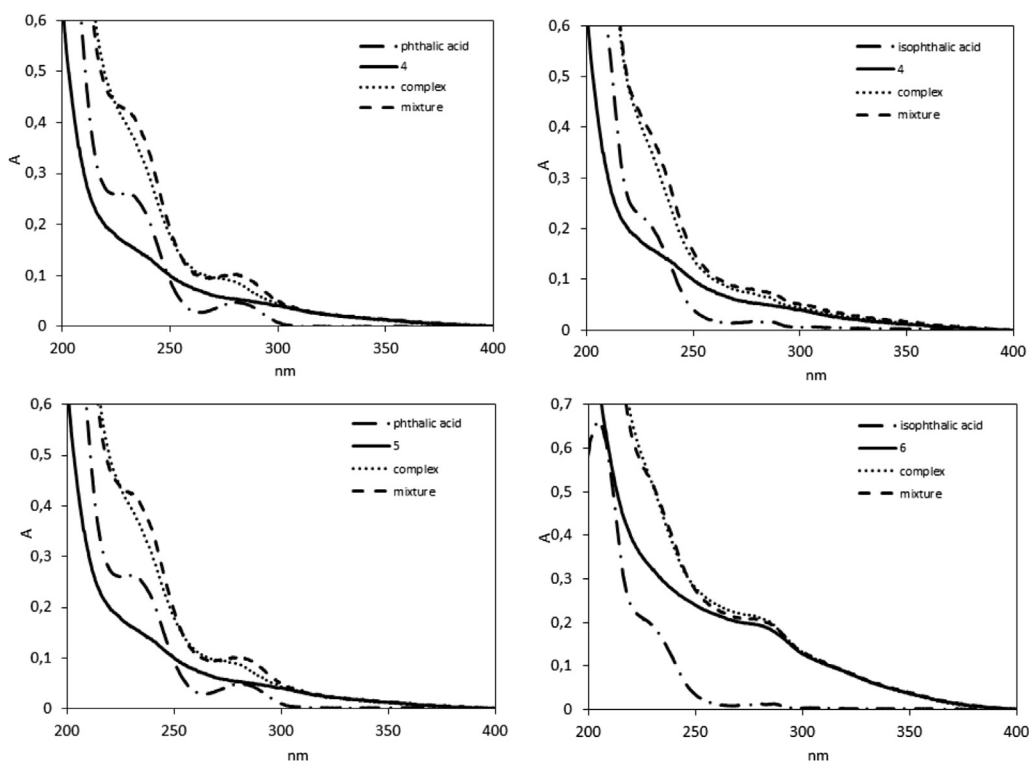

Fig. 6. UV spectra of mixtures of the polycondensed products **4**–**6** with the phthalic/isophthalic acids, taken in molar ratio 1:1.2 and spectra of individual components in the concentration studied.

interaction of the polycondensed products **4**–**6** with aromatic acids in water were found by UV spectroscopy in some cases. If there is no interaction between the components in the mixture, its optical density coincides to the sum of those obtained with individual components in the same concentration. However, for the mixture of polycondensed products **4**–**6** with the phthalic/terephthalic acids showed the deviation of the optical density of mixture ($A_{complex}$) from that of additive spectrum ($\sum A_{mixture}$), $\Delta A = A_{complex} - \sum A_{mixture}$. This deviation testifies to interaction between the polycondensed products and aromatic acid molecules which mostly led hypochromic effect (Fig. 6). The interaction of the polycondensed products with the substrates resulted in decreased absorption intensity at 220–300 nm (Fig. 6). Spectroscopic results showed spectral changes observed due to the interaction between the products **4**–**6** and the substrates. The changes in the spectra of the mistures based on the products **4**–**6** were observed for about all the substrates studied indicating low selectivity of the guest binding. The highest changes were found for the products **4**–**6** in contact with *o*-phthalic acid. It can be explained by optimum orientation and availability of the binding centers of *o*-isomer of aromatic acid to the studied products **4**–**6**.

Conclusion

We have proposed a strategy for the synthesis of a number of phosphorylated silsesquioxanes and established their poly-condensation conditions. The monocyclic T_4 and bicyclic T_6 ladder silsesquioxanes were synthesized. Their ability to recognize the aromatic dicarboxylic acids (phthalic and isophthalic acids) was investigated by UV-spectroscopy. Self-association of the synthesized siloxanes was studied by DLS and TEM. As was found, the compounds with a type T_4 structure did not associate in solution, but bind phthalic and isophthalic acids. Compounds of the T_6 type do not bind phthalic and isophthalic acids, but tend to form nanoscale particles. It was shown, that the monocyclic siloxanes **4**–**6** do not form self-associates in the presence of aromatic acids. The opposite tendency was observed for bicyclic siloxanes **7**–**9**. Thus, nanoscale aggregates with the hydrodynamic diameter of about 220 (**7**), 412 (**8**) and 188 (**9**) nm, respectively, were major particles in these systems. Further study of phosphorylated silses-quioxanes seems to be important and interesting because they are promising receptors for binding important biologically active acids.

Acknowledgments

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2014.09.002.

References

[1] O.A. Mostovaya, M.N. Agafonova, A.V. Galukhin, B.I. Khayrutdinov, D. Islamov, O.N. Kataeva, I.S. Antipin, A.I. Konovalov, I.I. Stoikov, J. Phys. Org. Chem. (2014) 2757–2765.
[2] A. Mucha, P. Kafarski, Y. Berlicki, J. Med. Chem. 54 (2011) 5955–5980.
[3] D.-Y. Hu, Q.-Q. Wan, S. Yang, B. Song, P.S. Bhadury, L.-H. Jin, F. Liu, Z. Chen, W. Xue, J. Agric. Food Chem. 56 (2008) 998–1001.
[4] Y. Xu, K. Yan, B. Song, G. Xu, S. Yang, W. Xue, D. Hu, P. Lu, G. Ouyang, L. Jin, Z. Chen, Molecules 11 (2006) 666–676.
[5] S. Yang, X.-W. Gao, C.-L. Diao, B.-A. Song, L.-H. Jin, G.-F. Xu, G.-P. Zhang, W. Wang, D.-Y. Hu, W. Xue, X. Zhou, P. Lu, Chin. J. Chem. 24 (2006) 1581–1588.
[6] S.A. Dake, D.S. Raut, K.R. Kharat, R.S. Mhaske, S.U. Deshmukh, R.P. Pawar, Bioorganic Med. Chem. Lett. 21 (2011) 2527–2532.
[7] R.R. Chinthaparthi, I. Bhatnagar, C. Sekhar, R. Gangireddy, S.C. Syama, S.R. Cirandur, Arch. Pharm. Chem. Life Sci. 346 (2013) 667–676.
[8] R.H. Baney, M. Itoh, A. Sakakibara, T. Suzukit, Chem. Rev. 95 (1995) 1409–1430.
[9] M. Unno, T. Matsumoto, H. Matsumoto, J. Organomet. Chem. 692 (2007) 307–312.
[10] N.A. Tebeneva, E.A. Rebrov, A.M. Muzafarov, ACS Symp. Ser. 729 (1999) 21–25.
[11] Y.A. Pozdnyakova, A.A. Korlyukov, E.G. Kononova, K.A. Lyssenko, A.S. Peregudov, O.I. Shchegolikhina, Inorg. Chem. 49 (2010) 572–577.
[12] O.I. Shchegolikhina, Y.A. Pozdnyakova, Y.A. Molodtsova, S.D. Korkin, S.S. Bukalov, L.A. Leites, K.A. Lyssenko, A.S. Peregudov, N. Auner, D.E. Katsoulis, Inorg. Chem. 41 (2002) 6892–6904.
[13] O.I. Shchegolikhina, Y.A. Pozdnyakova, A.A. Chetverikov, A.S. Peregudov, M.I. Buzin, E.V. Matukhina, Rus. Chem. Bull. Int. Ed. 56 (2007) 83–90.
[14] B. Song, S. Yang, Y. Hong, G. Zhang, L. Jin, D. Hu, J. Fluor. Chem. 126 (2005) 1419–1424.
[15] I.S. Antipin, I.I. Stoikov, E.M. Pinkhassik, N.A. Fitseva, I. Stibor, A.I. Konovalov, Tetrahedron Lett. 38 (33) (1997) 5865–5868.
[16] V.V. Gorbachuk, L.S. Yakimova, A.A. Vavilova, R.V. Ziatdinova, I.K. Rizvanov, A.A. Trifonov, A.I. Samohina, V.G. Evtugyn, I.I. Stoikov, Silicon (2014), http://dx.doi.org/10.1007/s12633-014-9179-1.
[17] E.V. Egorova, N.G. Vasilenko, N.V. Demchenko, E.A. Tatarinova, M. Muzafarov, Dokl. Akad. Nauk. 424 (2009) 200–204.
[18] D.P. Fasce, R.J.J. Williams, R. Erra-Balseiis, Y. Ishikawa, H. Nonami, Macro-molecules 34 (2001) 3534–3539.
[19] S.V. Asmussen, S.L. Giudicessi, R. Erra-Balsells, C.I. Vallo, Eur. Polym. J. 46 (2010) 1815–1823.
[20] P. Eisenberg, R. Erra-Balsells, Y. Ishikawa, J.C. Lucas, A.N. Mauri, H. Nonami, C.C. Riccardi, R.J.J. Williams, Macromolecules 33 (2000) 1940–1947.
[21] M. Unno, R. Tanaka, S. Tanaka, T. Takeuchi, S. Kyushin, H. Matsumoto, Or-ganometallics 24 (2005) 765–768.
[22] H. Mori, M.G. Lanzendorfer, A.H.E. Muller, J.E. Klee, Macromolecules 37 (2004) 5228–5238.
[23] M. Unno, A. Suto, T. Matsumoto, Russ. Chem. Rev. 82 (4) (2013) 289–302.
[24] F.J. Feher, T.A. Budzichowski, R.L. Blanski, K.J. Weller, J.W. Ziller, Organome-tallics 10 (1991) 2526–2528.
[25] M. Unno, K. Takada, H. Matsumoto, Chem. Lett. 6 (1998) 489–490.
[26] F.J. Feher, J.J. Schwab, D. Soulivong, J.W. Ziller, Main. Group Chem. 2 (1997) 123–132.
[27] H. Seki, T. Kajiwara, Y. Abe, T. Gunji, J. Organomet. Chem. 695 (2010) 1363–1369.
[28] E.S. Park, H.W. Ro, C.V. Nguyen, R.L. Jaffe, D.Y. Yoon, Chem. Mater. 20 (2008) 1548–1554.
[29] J.F. Brown Jr., L.H. Vogt Jr., P.I. Prescott, J. Am. Chem. Soc. 86 (1964) 1120–1125.
[30] V.V. Gorbachuk, L.S. Yakimova, O.A. Mostovaya, D.A. Bizyaev, A.A. Bukharaev, I.S. Antipin, A.I. Konovalov, I. Zharov, I.I. Stoikov, Silicon 3 (1) (2011) 5–12.
[31] I.I. Stoikov, E.A. Yushkova, A.A. Bukharaev, D.A. Biziaev, S.Y. Selivanovskaya, M.A. Chursina, I.S. Antipin, A.I. Konovalov, I. Zharov, J. Phys. Org. Chem. 25 (2012) 1177–1185.
[32] I.I. Stoikov, E.A. Yushkova, A.Y. Zhukov, I. Zharov, I.S. Antipin, A.I. Konovalov, Tetrahedron 64 (2008) 7489–7497.
[33] E.A. Yushkova, I.I. Stoikov, Langmuir 25 (2009) 4919–4928.