Composition, structure, and properties of pharmacologically active silicon dimethylglycerolates

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^{1}H and ^{29}Si NMR spectroscopy showed that the product of the reaction of dimethyldiethoxysilane with glycerol in the molar ratio 1 : 2 is an equilibrium mixture of dimethyldiglyceroxysilane and low-molecular-weight condensation products. The change of viscosity of silicon dimethylglycerolates, synthesized using different excesses of glycerol, versus time was studied by viscosimetry. Composition of products of hydrolysis and condensation of silicon dimethylglycerolates is determined by their concentration in the starting aqueous solutions.

Key words: organosilicon compounds, silicon dimethylglycerolates, composition, structure, viscosity, hydrolysis, condensation, ^{1}H and ^{29}Si NMR spectroscopy.

It is known[1—4] that in a number of cases products of the reaction of (alkyl)alkoxysilanes with polyols (silicon polyolates) exhibit high pharmacological activity. They are mainly used as medicines for the local and outward application, which stimulate reparative processes in tissues.

Earlier, we used dimethyldiethoxysilane $Me_2Si(OEt)_2$ for the synthesis of silicon dimethylglycerolates in different excess of glycerol of the composition $Me_2Si[OCH_2CH(OH)CH_2OH]_2 \cdot xHOCH_2CH(OH)CH_2OH$ ($0 \le x \le 1$), which are colorless water-soluble clear liquids of various viscosity, which is controlled by the excess of glycerol. They possess pronounced wound-healing and regenerative activity, easy penetrate living tissues, and thus assist in penetratation of pharmaceutical drugs in them.[5]

The synthesized compounds became a basis for pharmaceutical composition of local application for testing and curing urological diseases.[6] Anesthetic, antiinflammatory, antiseptic, and spasmolytic drugs were used as active medicinal additives in these compositions. Antimicrobal and a number of other medicinal drugs were used for the development of pharmaceutical compositions for curing diseases of reproductive system organs in farm cattle.[7]

Silicon dimethylglycerolates and pharmaceutical compositions derived from them were subjected to pre-clinical studies and showed that their application is safe and efficient and were recommended for deeper studies as potential medicinal and veterinary drugs. However, despite the practical importance of the synthesized products, their structure and composition were studied insufficiently. It is very much due to the fact that silicon glycerolates because of their polyfunctionality have tendency to polycondensation or polymerization transformations, and it is, as a rule, impossible to isolate them in the individual (monomeric) state.[8]

For the practical use of silicon dimethylglycerolates, the important features are the change of their viscosity with time (which is possible in the case of polycondensation or polymerization processes), as well as their hydrolytic characteristics. Hydrolysis occurs during the reaction of silicon dimethylglycerolates with living tissues of an organism (for example, with mucous membrane) and determines their further metabolism. In addition, allowance should be made for hydrolysis when pharmaceutical compositions are developed and used as aqueous solutions.

In the present work, we studied composition, structure, and change viscosity with time of silicon dimethylglycerolates synthesized from dimethyldiethoxysilane and glycerol in various molar ratios, as well as products of their hydrolysis.

Results and Discussion

Synthesis, study of composition and structure of silicon dimethylglycerolates. Synthesis of silicon dimethylglycerolates of the composition $Me_2Si[OCH_2CH(OH)CH_2OH]_2 \cdot xHOCH_2CH(OH)CH_2OH$ ($0 \le x \le 1$) was accomplished by alcoholysis of glycerol dimethyldiethoxysilane in the absence of a catalyst both with equimolar ratio of the starting compounds and in excess of glycerol according to the known procedure.[9] The ethanol formed was removed as an azeotrope containing 19% of dimethyldiethoxysilane until its theoretical amount was gone.

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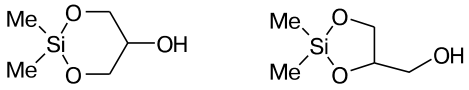
Completion of the reaction was determined by ^{1}H NMR from the absence in the spectrum of residual signals for the protons of ethoxy groups at the silicon atom in the region δ_H 1.08—1.18 (t, 3 H, Me) and 3.69—3.79 (q, 2 H, CH_2).

When the product of the reaction of dimethyldiethoxysilane with glycerol in the molar ratio 1 : 2 (**1**) is distilled *in vacuo*, no dimethyldiglyceroxysilane $Me_2Si[OCH_2CH(OH)CH_2OH]_2$ was isolated: a monomeric cyclic silicon dimethylglycerolate $Me_2Si[OCH_2CH(OH)CH_2O]$ (**2**) is distilled, which slowly polymerizes on standing and depolymerizes on heating.[1,10] Compound **2** is usually considered as a six-membered cycle without giving any evidences of its structure, though compound **2** can theoretically exist as a five-membered heterocycle.

Silicon dimethylglycerolates **1** and **2** were studied by ^{1}H, ^{13}C, and ^{29}Si NMR spectroscopy. When the ^{1}H NMR spectra of compound **2** and glycerol are compared, a downfield shift of the doublet for the secondary OH group in silicon dimethylglycerolate (δ_H 5.03) is observed relatively to that of glycerol (δ_H 4.54), as well as the absence of triplets for the primary OH groups, that indicates formation of six-, rather than five-membered heterocycle. The ^{13}C NMR spectrum demonstrates an equivalency of two OCH_2 groups, that also confirms formation of 5-hydroxy-2,2-dimethyl-1,3-dioxa-2-silacyclohexane and excludes formation of five-membered heterocycle, 4-hydroxymethyl-2,2-dimethyl-1,3-dioxa-2-silacyclopentane.



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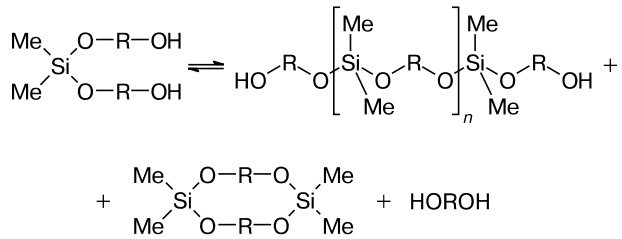
As it is seen from the ^{1}H and ^{29}Si NMR spectra, product **1** is not the individual compound. In this case, the ^{1}H NMR spectrum contains no signals for the protons corresponding to the hydroxy group of compound **2** (δ_H 5.03). Composition of product **1** was suggested based on the analysis of the ratio of integral intensities of the signals for the protons of the Me, CH_2, CH, and OH groups in the corresponding regions of chemical shifts, it includes, together with dimethyldiglyceroxysilane, low-molecular-weight condensation products of linear and cyclic structures (Scheme 1). In this case, the content of glycerol liberated during condensation is 0.69 mol.% (calculated from the ratio of integral intensities of the signals for the protons of primary hydroxy groups of glycerol and the protons of Me groups).

We have found that silicon dimethylglycerolates of the same composition as product **1** can be obtained by the reaction of cyclic silicon dimethylglycerolate **2** and its polymerization[1] product, $[Me_2SiOCH_2CH(OH)CH_2O]_n$, with glycerol (Scheme 2).

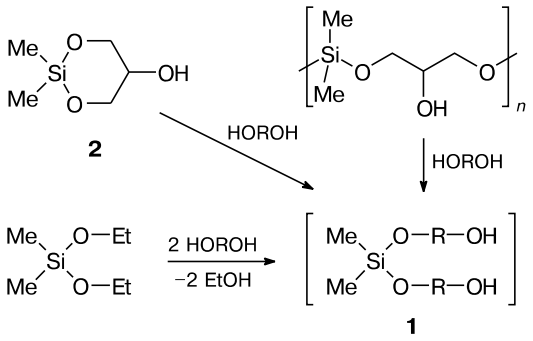
Study of the change of viscosity with time and products of hydrolysis of silicon dimethylglycerolates. The plots of

Scheme 1



R = —$CH_2CH(OH)CH_2$—, —$CH_2CH(CH_2OH)$—; n = 1, 2

Scheme 2



R = —$CH_2CH(OH)CH_2$—

kinematic viscosity (ν) versus time of storage for silicon dimethylglycerolates **1**, **3**—**5**, obtained either without excess of glycerol (**1**; $x = 0$) or in the presence of glycerol in different ratios (**3**—**5**; $x = 0.25$, 0.4, and 1.0, respectively), are given in Fig. 1.

The greatest change in viscosity during first ten days of storage was observed for product **1** obtained without excess of glycerol. In the case of product **5** synthesized with a molar excess of glycerol, no change of viscosity was observed. The constant viscosity was set up when the sys-

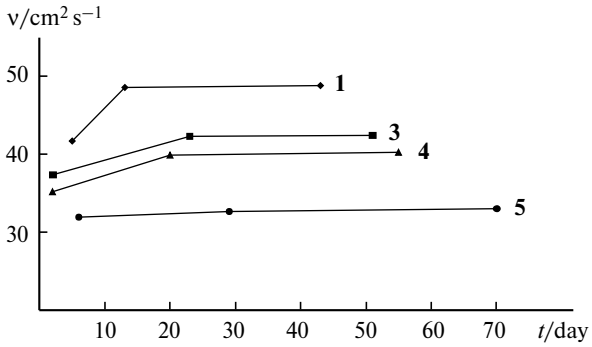


Fig. 1. The kinematic viscosity (ν) versus time for silicon dimethylglycerolates **1** and **3**—**5** of the composition $Me_2Si[OCH_2CH(OH)CH_2OH]_2 \cdot xHOCH_2CH(OH)CH_2$: **1** ($x = 0$), **3** ($x = 0.25$), **4** ($x = 0.4$), and **5** ($x = 1.0$).

tem reaches an equilibrium state with the formation of a mixture of products, with the excess of glycerol interfering the condensation processes, which are accompanied by the growth of viscosity (see Scheme 1).

Study of the products of hydrolysis of silicon dimethylglycerolates were carried out using product **5** as an example. For this purpose, we have prepared 11 series of aqueous solutions in a wide range of concentrations from 0.5 to 99.0 wt.%. Initially all the solutions studied were clear. Formation of layers with time was observed in the solutions containing from 20.0 to 99.0 wt.% of silicon dimethylglycerolates **5** as a result of hydrolysis; in this case, the mass fraction of the upper layer increased from 1.8 to 20.1%, respectively, with the growth of concentration of the starting solutions. The solutions with the starting concentration of silicon dimethylglycerolates **5** from 5.0 to 10.0 wt.% became opaque. The solutions with low concentration of silicon dimethylglycerolates **5** (to 2.5 wt.%) remained clear.

We have also studied the products of hydrolytic transformations for the starting solutions containing ≥50.0 and ≤2.5 wt.% of silicon dimethylglycerolates **5**.

Products **6**—**8** formed when the starting solutions containing 50.0, 97.5, and 99.0 wt.% of silicon dimethylglycerolates **5**, respectively, were divided into layers (the upper layer), were studied by IR spectroscopy.

The IR spectrum of product **6** is identical to the spectrum of polydimethylsiloxane $-[Me_2SiO]_n-$. The spectrum of product **7** exhibits bands characteristic of glyceroxy groups at silicon atom. The spectrum of product **8** contains absorption bands characteristic of the IR spectrum of silicon dimethylglycerolates **5**.

The results obtained by IR spectroscopy were confirmed by elemental analysis, mass spectrometry with electrospray ionization, and ^{1}H NMR spectroscopy.

In the case of 50.0% solution, the products of hydrolysis and subsequent condensation are polydimethylsiloxanes $-[Me_2SiO]_n-$ (**6**) (Scheme 3).

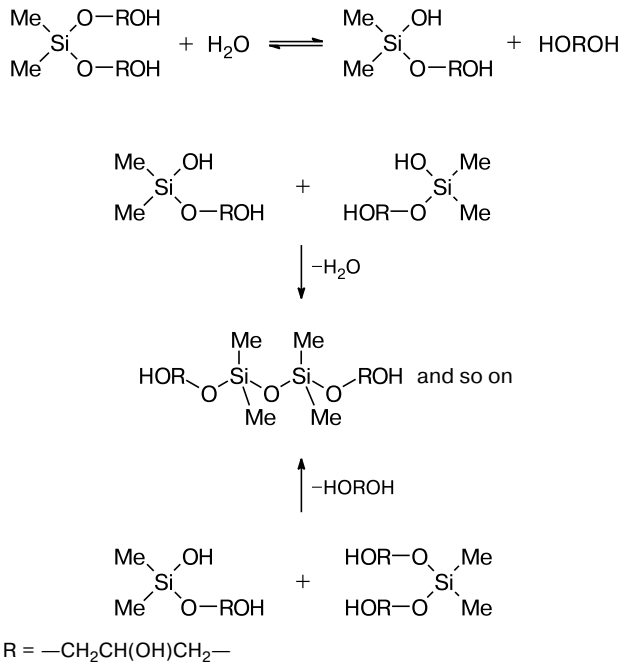
The content of polydimethylsiloxanes in the products of hydrolysis and condensation decreases with the increase in concentration of silicon dimethylglycerolates **5** in the starting solutions. The elemental analysis data indicate that composition of product **7** corresponds to the formula $-[(Me_2SiO)_2CH_2CH(OH)CH_2O]_n-$.

When silicon dimethylglycerolates have been taken in excess (99.0% solution), oligomeric products **8** of the composition $-[Me_2SiOCH_2CH(OH)CH_2O]_n-$ were formed, with water playing the role of a catalyst (Scheme 4).

The mass spectrum of product **8** (Fig. 2) contains four series of peaks in the range of mass numbers m/z from 350 to 1000, which correspond to four series of oligomeric ions with $\Delta m/z = 148$.

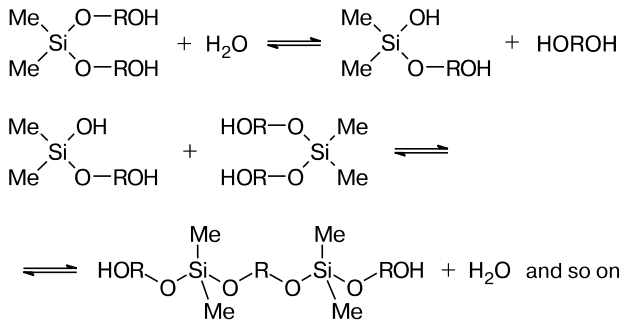
The ions registered can be interpreted as sodium adducts of oligomeric silicon dimethylglycerolates of linear and cyclic structures; the $\Delta m/z$ value corresponds to the

Scheme 3



R = $-CH_2CH(OH)CH_2-$

Scheme 4



R = $-CH_2CH(OH)CH_2-$

molecular weight of the $-Me_2SiOCH_2CH(OH)CH_2O-$ structural unit. The interpretation was performed with allowance for the processes of methanolysis in the solvent (MeOH).

Formation of adducts with cations of alkali metals (Na^+, K^+) is characteristic of conditions for the electrospray ionization, and for the corresponding ions to be registered it is often sufficient to have these cations in trace amounts, which virtually are always present in the mobile phase.[11] The literature data[12] confirm that cationized oligomers of glycerol derivatives are formed readily.

It was found that in the case of the starting aqueous solutions of silicon dimethylglycerolates with the concentration ≥20.0 wt.%, the lower layer formed was a solu-

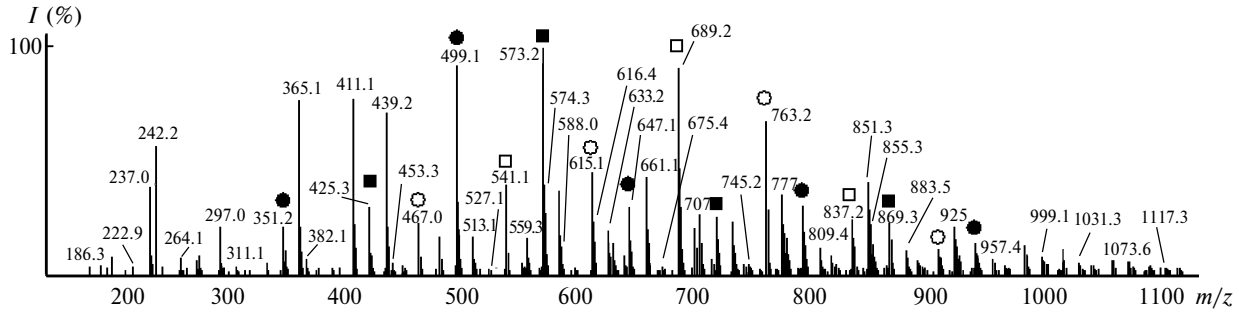
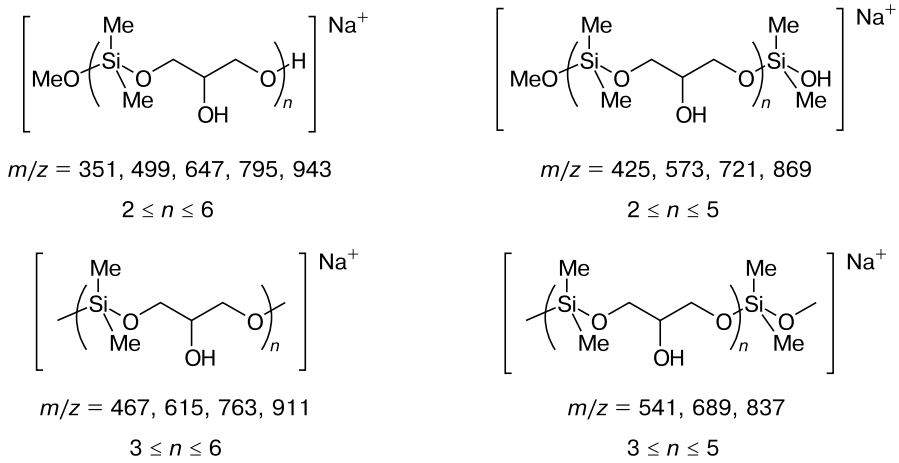


Fig. 2. Mass spectrum of product **8**. Black and white circles and squares show four series of peaks, which correspond to four series of oligomeric ions with $\Delta m/z = 148$.



tion of low-molecular-weight silicon dimethylglycerolates in aqueous glycerol.

The aqueous solutions containing 1.0 and 2.5 wt.% of silicon dimethylglycerolates **5** were studied by mass spectrometry with electrospray ionizaition (Fig. 3). The mass spectra of these solutions are similar: they are characterized by two series of peaks, which corresponds to two series of adducts formed by low-molecular-weight products of hydrolysis and condensation with cations of alkali metals.

It should be noted that the known[2,3] low-molecular-weight products of hydrolysis and/or condensation of a number of organosilicon compound, which contain a large amount of hydroxy groups and whose high pharmacological activity can be explained, in addition to other reasons, by their solubility in water and ability to form dynamic structures with medicinal compounds, which can easy penetrate living tissues.

Thus, the product of the reaction of dimethyldiethoxysilane with glycerol in the molar ratio 1 : 2 was studied

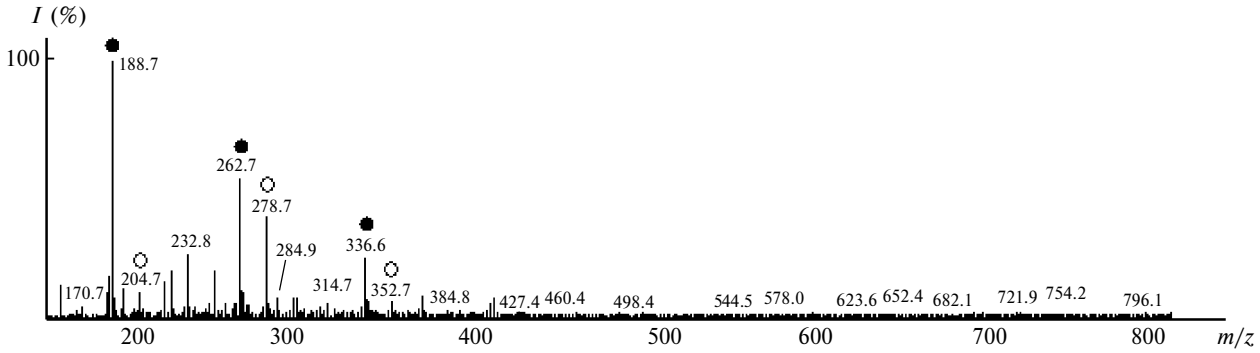
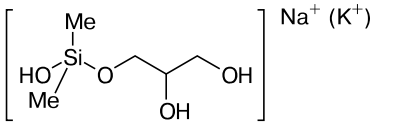
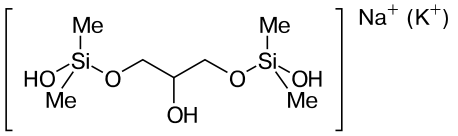


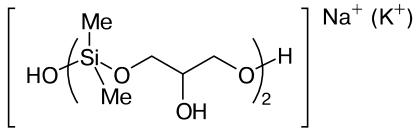
Fig. 3. Mass spectrum of aqueous solution of product **5** (2.5 wt.%). Black and white circles show two series of peaks, which correspond to two series of adducts formed by low-molecular-weight products of hydrolysis and condensation with cations of alkali metals.



m/z = 189 (205)



m/z = 263 (279)



m/z = 337 (353)

by ^{1}H and ^{29}Si NMR spectroscopy. It was shown that the product obtained is not the individual compound; we suggested a structure and composition for it. It was found that product of the same composition can be obtained by the reaction of cyclic or polymeric silicon dimethylglycerolates with glycerol.

Viscosimetry was used for the study of the change of viscosity with time of silicon dimethylglycerolates synthesized in various excesses of glycerol. It was shown that excess of glycerol interferes condensation processes, which is accompanied by growth of viscosity. For silicon dimethylglycerolates in a molar excess of glycerol, no change of viscosity with time was found.

Products of hydrolysis and condensation of silicon dimethylglycerolates were studied by a combination of physico-chemical methods. It was found that their composition is determined by concentration of dimethylglycerolates in the starting aqueous solutions.

Experimental

IR spectra were recorded on a Spectrum One Perkin Elmer IR Fourier-spectrometer in the region 400—4000 cm^{-1} for neat samples. Index of refraction was measured on an IRF-456 refractometer. ^{1}H, ^{13}C, and ^{29}Si NMR spectra were recorded on a Bruker DRX-400 spectrometer (400, 100, and 99 MHz, respectively) in DMSO-d_6, with Me_4Si as a standard. Mass spectra were recorded on a LCMS-2010 Shimadzu GLC-MS spectrometer (MeOH was a solvent; aq. MeOH containing 5% of H_2O was a carrier phase). Kinematic viscosity was measured on an Ubbelode viscosimeter with the capillary internal diameter 2.75 mm, $K = 3.339$ $mm^2 s^{-2}$ at 20.0±0.5 °C (relative error of measurement ±3%).

The starting compounds were purified before use by distillation: glycerol was distilled *in vacuo* over metallic magnesium, dimethyldiethoxysilane was distilled at atmospheric pressure.

Silicon dimethylglycerolate of the composition $Me_2Si[OCH_2CH(OH)CH_2OH]_2 \cdot HOCH_2CH(OH)CH_2OH$ (**5**) was synthesized according to the known procedure,[5] the constants agree with the literature data.

Silicon dimethylglycerolates of the composition $Me_2Si[OCH_2CH(OH)CH_2OH]_2$ (1). ***A.*** Glycerol (76.62 g, 0.832 mol) and dimethyldiethoxysilane (70.67 g, 0.477 mol) were placed into a one-neck round-bottom flask equipped with a three-way adapter, mechanical stirrer, reflux condenser, and a dropping funnel. The reaction mixture was stirred for 15 h at 130 °C, the ethanol formed was evaporated as an azeotrope with dimethyldiethoxysilane first at atmospheric pressure, and then *in vacuo* on a rotary evaporator until the weight of the reaction mixture was constant (that corresponds to the removal of theoretical amount of ethanol) at residual pressure 2—5 Torr and temperature 130 °C. The yield of the product was 100 g (99%).

B. Compound **2** (4.38 g, 0.030 mol) and glycerol (2.72 g, 0.030 mol) were placed in a 10-mL tightly capped vessel. The reaction mixture was thoroughly stirred for 15 min until homogeneous solution was formed. The solution obtained was kept for 6 days at room temperature. The yield of the product was 7.10 g (100%).

C. Poly(4-hydroxy-1,1-dimethyl-1-sila-2,6-dioxahexane) $-[SiMe_2OCH_2CH(OH)CH_2O]_n-$ (a solid resin-like compound obtained upon storage of compound **2** over 1 month) (4.38 g, 0.030 mol of the unit) and glycerol (2.72 g, 0.030 mol) were placed in a 10-mL tightly capped vessel. The reaction mixture was kept over 3 months at room temperature until homogeneous solution was formed. The yield of the product was 7.10 g (100%).

Product **1** is a clear colorless liquid, soluble in water and ethanol and insoluble in chloroform and diethyl ether, kinematic viscosity 48.8 $cm^2 s^{-1}$, n_D^{20} 1.4690. The product composition corresponds to the formula $Me_2Si(C_3H_7O_3)_2$. Found (%): C, 39.91; H, 8.78; Si, 11.48. $C_8H_{20}O_6Si$. Calculated (%): C, 39.98; H, 8.39; Si, 11.69. IR, ν/cm^{-1}: 3367 (OH); 2931, 2879 (C—H); 1258 (Si—C); 1107 (C—O in C—O—H sec.); 1045 (C—O in C—O—H prim.); 1025 (Si—O—C); 863, 802 (Si—Me). ^{1}H NMR, δ: 0.05—0.20 (m, 6 H, Me); 3.20—4.00 (m, 10 H, CH_2, CH); 4.30—5.10 (m, 4 H, OH). ^{29}Si NMR, δ: −13.46; −12.50; −12.27; −6.36—−5.19; −4.47; −4.36—−3.88; −3.25—−2.86.

Products **2**—**5** were obtained by method ***A.***

5-Hydroxy-2,2-dimethyl-1,3-dioxa-2-silacyclohexane (2). The yield of the product was 75%, clear colorless viscous liquid, b.p. 105—107 °C (20 Torr), n_D^{20} 1.4420. Found (%): C, 40.26; H, 8.31; Si, 18.62. $C_5H_{12}O_3Si$. Calculated (%): C, 40.51; H, 8.16; Si, 18.95. IR, ν/cm^{-1}: 3400 (OH); 2936, 2883 (C—H); 1258 (Si—C); 1114 (C—O in C—O—H sec.); 995 (Si—O—C); 862, 805 (Si—Me). ^{1}H NMR, δ: 0.06, 0.12 (both s, 3 H each, Me); 3.63—3.69 (m, 3 H, CH_2, CH); 3.94 (m, 2 H, CH_2); 5.03 (d, 1 H, OH, $J = 4.4$ Hz). ^{13}C NMR, δ: −2.49 (Me); −1.63 (Me); 66.29 (CH); 67.51 (CH_2). ^{29}Si NMR, δ: 0.17 (*cf.* Ref. 10: the yield was 63%, b.p. 147 °C (17 Torr), n_D^{20} 1.4554).

Silicon dimethylglycerolates of the composition $Me_2Si[OCH_2CH(OH)CH_2OH]_2 \cdot 0.25HOCH_2CH(OH)CH_2OH$ (3). The yield of the product was 99%, clear colorless liquid, soluble in water and ethanol and insoluble in chloroform and diethyl ether, kinematic viscosity 42.5 $cm^2 s^{-1}$, n_D^{20} 1.4703. The product composition corresponds to the formula $Me_2Si(C_3H_7O_3)_2 \cdot 0.25C_3H_8O_3$. Found (%): C, 39.88; H, 8.53; Si, 10.59. $C_{8.75}H_{22}O_{6.75}Si$. Calculated (%): C, 39.91; H, 8.42;

Si, 10.67. IR, ν/cm^{-1}: 3368 (OH); 2934, 2880 (C—H); 1264 (Si—C); 1112 (C—O in C—O—H sec.); 1053 (C—O in C—O—H prim.); 1024 (Si—O—C); 862, 801 (Si—Me).

Silicon dimethylglycerolates of the composition $Me_2Si[OCH_2CH(OH)CH_2OH]_2 \cdot 0.4HOCH_2CH(OH)CH_2OH$ (4). The yield of the product was 98%, clear colorless liquid, soluble in water and ethanol and insoluble in chloroform and diethyl ether, kinematic viscosity 40.2 cm^2 s^{-1}, n_D^{20} 1.4709. The product composition corresponds to the formula $Me_2Si(C_3H_7O_3)_2 \cdot 0.4C_3H_8O_3$. Found (%): C, 39.79; H, 8.50; Si, 10.09. $C_{9.2}H_{23.2}O_{7.2}Si$. Calculated (%): C, 39.87; H, 8.44; Si, 10.13. IR, ν/cm^{-1}: 3368 (OH); 2934, 2880 (C—H); 1260 (Si—C); 1112 (C—O in C—O—H sec.); 1053 (C—O in C—O—H prim.); 1024 (Si—O—C); 862, 801 (Si—Me).

Hydrolysis of silicon dimethylglycerolates 5. Hydrolysis was carried out at room temperature. Solutions of silicon dimethylglycerolates **5** of various concentrations (wt.%), which corresponded to various molar ratios **5** : H_2O: 0.5 (1.0 : 66333.0), 1.0 (1.0 : 33000.0), 2.5 (1.0 : 12828.9), 5.0 (1.0 : 351.9), 10.0 (1.0 : 166.7), 20.0 (1.0 : 74.0), 50.0 (1.0 : 18.5), 90.0 (1.0 : 2.1), 95.0 (1.0 : 1.0), 97.5 (1.0 : 0.5), and 99.0 (1.0 : 0.2), were prepared. These solutions were kept over 6 months at room temperature in tightly capped vessels. If the solutions have formed layers, the upper layer was separated using a separatory funnel.

Polydimethylsiloxane (6). The yield of the product was 56%, clear colorless liquid, n_D^{20} 1.4000. Found (%): C, 31.93; H, 8.01; Si, 38.36. C_2H_6OSi. Calculated (%): C, 32.39; H, 8.16; Si, 37.88. IR, ν/cm^{-1}: 2963, 2905, 1412 (C—H in Me); 1261 (Si—C); 1076, 1022 (Si—O—Si); 860, 804 (Si—Me). ^{1}H NMR spectra correspond to those in Ref. 13.

Product of hydrolysis and condensation of the composition $-[(Me_2SiO)_2CH_2CH(OH)CH_2O]_n-$ (7). The yield of the product was 58%, clear colorless viscous liquid, n_D^{20} 1.4290. Found (%): C, 36.83; H, 8.10; Si, 26.37. $C_7H_{18}O_4Si_2$. Calculated (%): C, 37.81; H, 8.16; Si, 25.26. IR, ν/cm^{-1}: 3386 (OH); 2963, 1410 (C—H in Me); 2878 (C—H in CH_2, CH); 1260 (Si—C); 1046 (Si—O—Si); 862, 802 (Si—Me).

Product of condensation of the composition $-[Me_2SiOCH_2CH(OH)CH_2O]_n-$ (8). The yield of the product was 45%, clear colorless viscous liquid, n_D^{20} 1.4435. Found (%): C, 38.89; H, 8.30; Si, 20.00. $C_5H_{12}O_3Si$. Calculated (%): C, 40.51; H, 8.16; Si, 18.95. IR, ν/cm^{-1}: 3384 (OH); 2960 (C—H in Me); 2931, 2878, 1460, 1404, 1335 (C—H in CH_2, CH); 1260 (Si—C); 1053 (Si—O—Si); 862, 802 (Si—Me).

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