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A Synthesis of Novel Polyamine Macrocycles with Organosilyl Groups

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Polyamine macrocycles having organosilicon moieties were synthesized through new addition reaction of lithium alkylamide toward vinylsilane derivatives. 6-Ethyl-3,3-dimethyl-3-sila-6,9-diazaundecane in the presence of lithium alkylamide took place polyaddition reactions, consisting of diamine and organosilicon units alternatively. By increasing possibilities of intramolecular nucleophilic attack, the 9- and 18-membered polyamine macrocycles with organosilicon moieties were obtained in good yield.

Since Pedersen had discovered unique characteristics of macrocyclic ethers against cationic compounds,[1] numerous types of macrocyclic compounds have been synthesized and investigated in terms of their characteristics such as ion separation, solubilization, anion activation, and physiological activity.[2] Among macrocyclic compounds, macrocycles comprising hetero atom(s) (other than oxygen) such as nitrogen and sulfur are anticipated as promising compounds for several kinds of physiological activities owing to their strong interaction toward transition metal cations.[3] For example, several kinds of polyamine macrocycles are being investigated as drugs for anti-human immunodeficiency virus (especially complexed with certain kind of transition metals)[4] and as radiometal carriers[5] for radioimmunotherapy and radioimmunoimaging.[6] If organosilicon groups can be incorporated into the polyamine macrocycles, scope for opportunities of the macrocyclic compounds will be expanded. Namely, introduction of organosilicon moiety can be anticipated to control physicochemical properties such as hydrophobicity, pH dependency, which in turn determine the physiological characteristics of the polyamine macrocycles. There are only few reports, however, available about multiheteromacrocycles consisting of nitrogen and organosilicon moieties so far.[7] This paper communicates a novel reaction route for polyamine macrocycles with organosilicon moiety through lithium alkylamide catalyzed addition reaction between divinylsilanes and ethylenediamine derivatives.

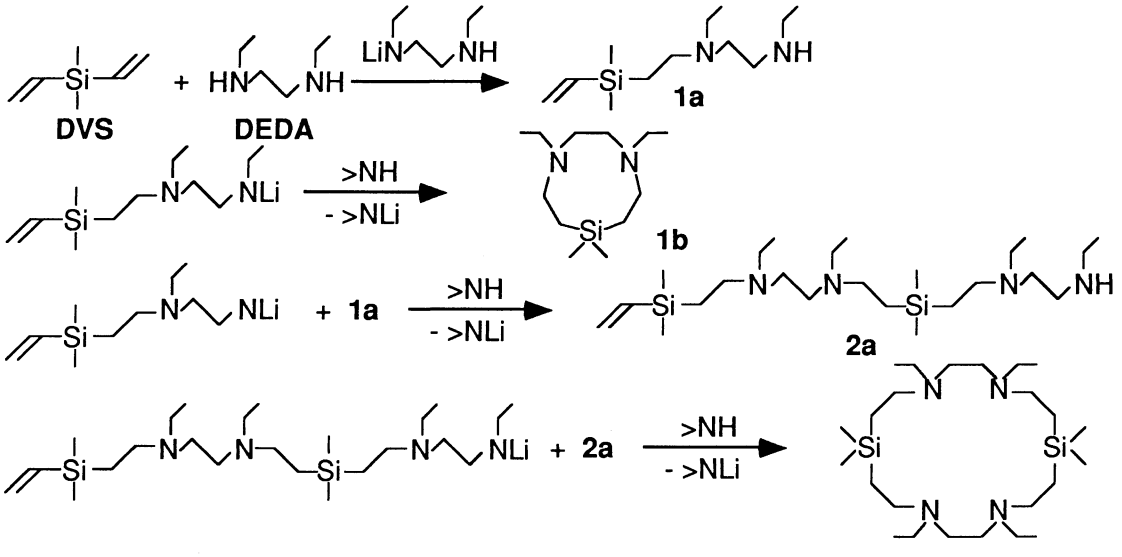
We have been studying on reactivities of lithium alkylamide toward conjugated olefins.[8] Recently, we have found vinylsilane derivatives to have almost the same reactivity toward lithium alkylamide as para-alkyl substituted styrene derivatives in the vinyl addition reactions.[9] When dimethyldivinylsilane (DVS) and N,N'-diethylethylenediamine (DEDA) were used as reactants, lithium alkylamide induced anionic polyaddition reactions to form new end-reactive oligomers consisting of organosilyl and amino groups alternatively, which possess unique characteristics such as pH sensitivity, anion affinity and temperature dependency (LCST).[10] In the self-

polyaddition reactions of DVS with DEDA,[11] dimer fraction[12] was 9.9% out of total oligomer yield, which was higher than that anticipated from oligomer distribution in usual reactions implying that some unexpected reaction might have taken place. Actually, ^{1}H NMR of the DMF soluble oligomers (MW = few hundreds) did not show clearly the presence of vinyl end group, suggesting a possible occurrence of cyclization of oligomers in the reaction system.

To increase possibilities of intramolecular attack in terms of nucleophilic additions of amide anion (N^-), the reactions were carried out under several reaction conditions. With decreasing concentration of reactant (**1a**), dimer fraction increased significantly. Actually, the **1a**-dimers was formed in 38.9% yield under the condition of $[\mathbf{1a}]_0$ / $[LDA]_0$ = 0.1 / 0.01 (mol/l / mol/l) in hexane at 20 ℃, along with compounds (11.5%) found in molecular weight region of the starting material.

Fractionation of the dimeric fraction, **2**, from the monomeric fraction, **1**, can easily be carried out by distillations in vacuo (**2**: 135 ℃ / 0.3 mmHg; **1**: 68 ℃ / 0.3 mmHg). ^{1}H NMR spectrum[13] of the fractionated **2** showed small vinyl proton signals as compared with other proton signals in the main chain such as $C\underline{H}_2N$ and $C\underline{H}_2Si$, indicating the **1a**-dimers thus formed to be mostly a cyclic compound (**2b**[14]) with a small amount of a linear dimer (**2a**). This was also confirmed using gas chromatography.[15] Namely, **2a** was separated from cyclic dimer, **2b**, by treating with acetic anhydride which reacted with sec-amino end group of **2a**. From these analyses, it was concluded that 91.8% of the **1a**-dimers was a cyclic compound under the above reaction conditions. It was also confirmed using NMR and GC analyses[16] that 96.4% of the monomeric fraction, **1**, is a 9-membered cyclic compound (**1b**[14]) though 9-membered ring is known to have considerable ring strain. As conclusion, new 9- and 18-membered polyamine macrocycles with organosilicon group(s) were synthesized in 11.1% and 35.7% yields, respectively (Scheme 1).

In the presence of potassium cation, yield of **2b** increased up to 50% owing to a cage effect. The reac-tion, however, did not proceed in the presence of copper ion. The results ob-tained are summarized in Table 1.



Scheme 1.

In our recent preliminary investigations these macrocycles have unique properties such as complexation with transition metals and cytotoxicity. Detailed studies on properties of the present multiheteromacrocycles will be published elsewhere.

Table 1. Synthesis of Cyclic Polyamines with Organosilyl Groups Through Addition Reaction of Lithiated 6-Ethyl-3,3-dimethyl-3-sila-6,9-diazaundecane (**1a**-Li)[a]

Run	Additive	$[\mathbf{1a}]_o$ mol/l	$[LDA]_o$ mol/l	Solv.	Temp ℃	Time d	**1a**[b] %	Yield[c] % **1b**	**2a**	**2b**	>Dimers
1	–	1.0	0.10	THF	50	3	4.7[d]	–	9.9[d]	–	85.4
2	–	0.5	0.05	Hexane	20	6	0.2	5.4	1.9	13.0	79.5
3	–	0.1	0.01	Hexane	50	4	1.1	10.3	4.3	25.3	59.0
4	–	0.1	0.01	Hexane	20	8	0.4	11.1	3.2	35.7	49.6
5	t-BuOK	0.1	0.01	Hexane	20	4	0.1	8.8	0	50.0	41.1
6	t-BuOK	0.1	0.01	THF	20	4	0.3	14.4	0.9	40.6	43.8
7	$CuCl_2$	0.1	0.01	Hexane	20	4	100.0	0	0	0	0
8	$CuCl_2$	0.1	0.01	THF	20	4	100.0	0	0	0	0

a) Lithium diisopropylamide (LDA) was used for metalation of **1a**. Concentration of additive: 0.05 mol/l. b) Unreacted **1a** was determined by GC. c) Ratios of cyclic and linear compounds in **1** and **2** were determined both from ^1H NMR directly and GC after acetylation of the linear compounds by acetic anhydride. d) Degree of cyclization was not determined. Data of the mixture of linear and cyclic compounds are listed.

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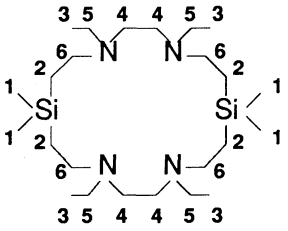
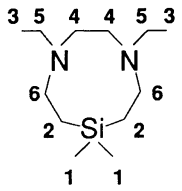
11) The polyaddition reaction between DVS and DEDA was carried out as 2-step method as follows: 6-Ethyl-3,3-dimethyl-3-sila-6,9-diazaundecane (1:1 adduct of DVS and DEDA; **1a**) was synthesized according to our previous paper[9] using lithium diisopropylamide (LDA) as lithiating agent of DEDA. Self polyaddition reaction of **1a** was carried out under the conditions of $[\mathbf{1a}]_0 / [\mathrm{LDA}]_0$ = 1.0 / 0.10 (mol/l /mol/l) in THF at 50 ℃ to form new oligomers, the molecular weight of which attained up to 2000.[9]

12) Elution times of **1** and **2** fractions were determined using gel permeation chromatography calibrated by polystyrene standard samples and they were identified by GC/MS spectroscopy [M^+(2:2) = 456; M^+(1:1) = 228]. For GPC measurements, Shimadzu LC 6A liquid chromatograph was used with equipment of RI detector [RID 6A ; column: TSK-Gel G4000H8+G3000H8+G2500H8; Eluent: THF(98%) + triethylamine (2%) (1 ml/min)]. GC/MS spectra were obtained using a Hewlett Packard 5890 Series II equipped with 5971A mass selective detector (column: DB1, 30 m • 0.25 mm *i.d.*• 0.25 μm).

13) ^{1}H, ^{13}C, and ^{29}Si NMR spectra were recorded on JEOL EX-400 spectrometer at 399.65 MHz, 100.40 MHz, and 79.30 MHz, respectively. Spectra were recorded in $CDCl_3$ (0.2 wt% for ^{1}H NMR and 20.0 wt% for ^{13}C, and ^{29}Si NMR measurements). Signals were assigned according to our previous papers,[9] ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, ^{1}H-^{13}C long range COSY and ^{29}Si NMR spectra. **2b**: ^{1}H NMR($CDCl_3$) :δ = 0.00 (12H, s, H-1), 0.73 (8H, m, H-2), 1.02 (12H, t, J=7.3, H-3), 2.48 - 2.57 (24H, m, H-4,5,6); ^{13}C NMR($CDCl_3$): δ = -3.67 (C-1), 11.07 (C-2), 11.48 (C-3), 46.79 (C-5), 48.13 (C-6), 49.90 (C-4), (broad band proton decoupling, δ from TMS); ^{29}Si NMR($CDCl_3$) δ = 1.52, (broad band proton decoupling, δ from TMS).



Macrocycle **2b**



Macrocycle **1b**

14) Nomenclature of cyclic compounds: **1b**: 4,7-diethyl-1,1-dimethyl-4,7-diaza-1-silacyclononane; **2b**: 4,7,13,16-tetraethyl-1,1,10,10-tetramethyl-4,7,13,16-tetraaza-1,10-disilacyclooctadecane.

15) GC was recorded using a Hewlett Packard 5890 Series II equipped with FID detector (column: DB1, 30 m • 0.25 mm *i.d.*• 0.25 μm).

16) **1b**: ^{1}H NMR($CDCl_3$) : δ = -0.07 (6H, s, H-1), 0.86 (4H, t, J=6.3 Hz, H-2), 1.02 (6H, t, J=7.3 Hz, H-3), 2.44 (4H, s, H-4); 2.51 (4H, q, J=7.3 Hz, H-5), 2.66 (4H, t, J=6.3 Hz, H-6); ^{13}C NMR($CDCl_3$): δ = -32.41 (C-1), 12.86 (C-3), 16.81 (C-2), 50.76 (C-6), 51.80 (C-5), 54.74 (C-4)(broad band proton decoupling, δ from TMS); ^{29}Si NMR($CDCl_3$) δ = 2.00 (broad band proton decoupling, δ from TMS).

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