

SYNTHESIS AND POLYMERIZATION OF γ -NUCLEIC ACID BASE SUBSTITUTED PROPYLMETHYLDIETHOXYASILANES

ZHUO Renxi (卓仁禧), LIU Gaowei (刘高伟) and ZHOU Yuanzhong (周元忠)

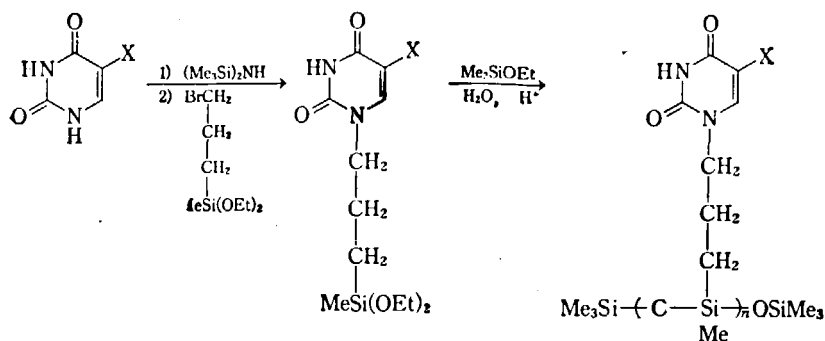
(Department of Chemistry, Wuhan University, Wuhan)

ABSTRACT

Four new organosilicon monomers containing nucleic acid bases or 5-fluorouracil (5-Fu) were synthesized by the alkylation of γ -bromopropylmethyldiethoxysilane with uracil, thymine, adenine and 5-Fu, respectively. Polymerization of the monomers resulted in the formation of six new polysiloxanes with nucleic acid bases as the pendant groups.

The study of nucleic acid analogs has received much attention in recent years. A variety of nucleic acid bases containing polymers with different kinds of main chain structures have been designed and prepared, some of which have been found to possess potential antiviral and antitumor activities as well as other unique biochemical properties^[1,2]. But so far, no reports have appeared in the literature about the nucleic acid analogs with polysiloxane main chain structure. It would be interesting to design and synthesize this type of analogs and to study their properties.

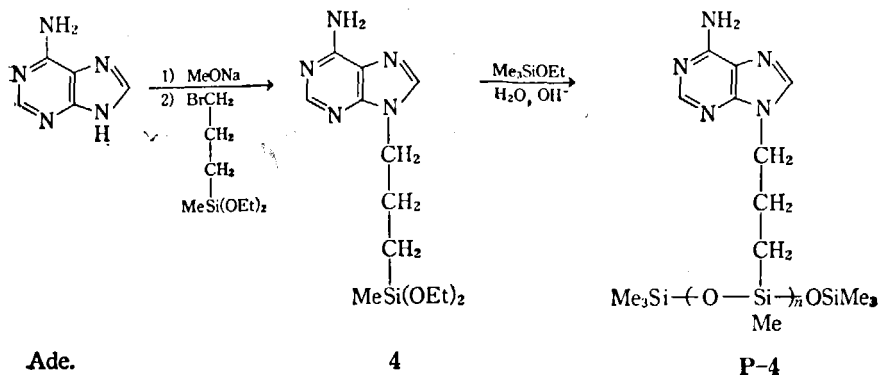
In this paper, we wish to report the synthesis of a new type of polysiloxanes with nucleic acid bases as the pendant groups. Four new organosilicon monomers containing nucleic acid bases or 5-Fu, i.e., γ -(N¹-uracilyl)propylmethyldiethoxysilane (1), γ -(N¹-thyminyll)-propylmethyldiethoxysilane (2), γ -(N⁹-adenyl)propylmethyldiethoxysilane (4) and γ -(N¹-5-fluorouracyl)propylmethyldiethoxysilane (3), were prepared by the alkylation of γ -bromopropylmethyldiethoxysilane with uracil (Ura.), thymine (Thy.), adenine (Ade.) and 5-Fu, respectively^[3]. By hydrolytic polycondensation of the monomers, we obtained four homopolysiloxanes containing uracil (P-1), thymine (P-2), 5-Fu (P-3) or adenine (P-4) as the pendant groups. We have also studied the heteropolycondensation of 1 with dimethyldiacetoxysilane (5) or 1,3-bis(acetoxy)-1,1,3,3-tetramethyldisiloxane (6), which resulted in the formation of two siloxane copolymers (P-1-5 and P-1-6). The reaction scheme is shown as follows:



Ura., X=H
 Thy., X=Me
 5-Fu, X=F

1, X=H
 2, X=Me
 3, X=F

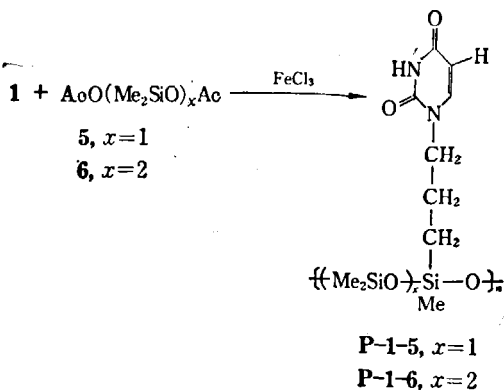
P-1, X=H
 P-2, X=Me
 P-3, X=F



Ade.

4

P-4



EXPERIMENTAL

Uracil was purchased as C.P. grade, thymine as B.R. grade. 5-Fu was recrystallized in water. Adenine was obtained from adenine hydrochloride. All of the reagents were dried before use.

N,N-Dimethylformamide (DMF) of A.R. grade was used in the experiment. To remove any possible content of water in the solvent, it was first dried over potassium hydroxide for twenty-four hours and distilled. The distillate was then azeotropically fractionated with dry benzene through a glass helix packed column under vacuum.

Other reagents used in the experiment were all of C.P. or A.R. grade, dried prior to use when necessary.

Melting points and softening temperatures were measured on a PHMK microscopic apparatus and are uncorrected. Intrinsic viscosities ($[\eta]$) were determined at 30°C using Ubbelohde viscometer with DMF as the solvent except for **P-1**, for which DMSO was used instead. The number average molecular weights ($\bar{M}_n$) were measured by dynamic osmometry in the same solvents as used in the viscosity determination.

$^1\text{H-NMR}$ spectra were recorded on a Varian EM-360L NMR spectrometer at room temperature. UV spectra were run with a Shimadzu UV-240 spectrophotometer at room temperature. And IR spectra were determined (in KBr disc) on a Shimadzu IR-450 spectrophotometer.

γ -Bromopropylmethyldiethoxysilane^[4,5], trimethylethoxysilane^[6], 2,4-bis(trimethylsiloxy)pyrimidines^[7], dimethyldiacetoxysilane (**5**) and 1,3-bis(acetoxy)-1,1,3,3-tetramethyldisiloxane (**6**)^[8] were all prepared according to the literatures cited.

*γ -(N¹-Uracilyl)propylmethyldiethoxysilane (**1**)*

2,4-bis(trimethylsiloxy)pyrimidine (7.6 g, 30 mmol) and γ -bromopropylmethyldiethoxysilane (5.1 g, 20 mmol) were heated together at 180°C for 1.5 hours. The reaction mixture was distilled at the same temperature under reduced pressure (with water suction pump) until no more distillate could be collected. The distillation flask was cooled and chloroform was then added to dissolve the residue. After that, 10 ml of ethanol was added to this solution and the solution was refluxed for 5 hours. The precipitate was filtered off and the filtrate was evaporated under vacuum to dryness. The solid product obtained was purified by recrystallization three times from light petroleum (60–90°C) to give 1.9 g of white plate crystals (**1**).

γ -(N¹-thyminy)propylmethyldiethoxysilane (**2**) and γ -(N¹-5-fluorouracilyl)propylmethyldiethoxysilane (**3**) were prepared by using the similar method.

*γ -(N⁹-Adenyl)propylmethyldiethoxysilane (**4**)*

A suspension of sodium salt of adenine^[9] (7.99 g, 50.9 mmol), γ -bromopropylmethyldiethoxysilane (15.0 g, 58.8 mmol) and DMF (200 ml) was stirred at room temperature for 72

hours and then evaporated to dryness under vacuum to give a solid residue, which was extracted with chloroform. The extracts were evaporated, and the white solid thus obtained was recrystallized three times from carbon tetrachloride to give 12.0 g of **4** as colorless needles.

Poly- γ -(N¹-uracilyl)propylmethylsiloxane (P-1)

To a mixture of **1** (1.00 g, 3.50 mmol), trimethylethoxysilane (82.6 mg, 0.700 mmol), distilled water (3 ml) and ethanol (40 ml), were added 3 drops of concentrated hydrochloric acid to acidify the mixture to approximately pH 3. The mixture was stirred at 80°C for 34 hours and evaporated. The solid residue was soaked with distilled water several times until neutral and then extracted with hot methanol. Evaporating the methanol extracts followed by drying the product under vacuum gave 0.62 g of white solid polymer (P-1).

Similarly prepared were poly- γ -(N¹-thyminy)propylmethylsiloxane (P-2) and poly- γ -(N¹-5-fluorouracilyl)propylmethylsiloxane (P-3).

Poly- γ -(N⁹-adenyl)propylmethylsiloxane (P-4)

To a mixture of **4** (1.00 g, 3.22 mmol), trimethylethoxysilane (76.0 mg, 0.644 mmol), distilled water (3 ml) and ethanol (40 ml), were added 3 drops of 1N aqueous sodium hydroxide solution to adjust the pH value of the mixture to approximately 9. The mixture was stirred at 80°C for 28 hours and evaporated, leaving a white solid product, which was then purified by dissolving it in methanol and precipitating it from water. The precipitates were collected and dried in vacuo to give 0.45 g of white powder polymer (P-4).

Copolymer P-1-5

A mixture of **1** (1.00 g, 3.50 mmol) and dimethyldiacetoxysilane (**5**) (0.678 g, 3.85 mmol) was heated to 120°C, to which about 0.01 g of newly sublimed anhydrous FeCl₃ was added. The heating was maintained for 15 hours before 83 mg (0.70 mmol) of trimethylethoxysilane was introduced, then continued for an additional 7 hours followed by 2.5 hours of vacuumation under 4 mmHg at the heating temperature. The reaction mixture was cooled and dissolved in methanol. Upon treatment of the solution with ether, a precipitate was formed, which was collected, redissolved in methanol and then reprecipitated from 1M aqueous NH₄Cl solution. The precipitate was vacuum dried to yield 0.50 g of glasslike polymer (P-1-5).

Copolymer P-1-6 was similarly obtained by the heteropolycondensation of **1** with 1,3-bis(acetoxy)-1,1,3,3-tetramethyldisiloxane (**6**).

For the monomers and polymers prepared, the yields, physical constants and elemental analysis were listed in Table 1, IR in Table 2, and ¹H-NMR in Table 3. The UV spectra of monomers were also recorded and the data were given in Table 4.

Table 1 Yields, physical constants, $[\eta]$, $\bar{M}_n$ and elemental analysis of monomers and polymers

Compd.	Yield (%)	M.P. or softening temp. (°C)	$[\eta]$ (ml/g)	$\bar{M}_n$ ($\times 10^{-3}$)	Elemental analysis (%)							
					Found				Calcd.*			
					C	H	N	Si	C	H	N	Si
1	33.3	83—5	—	—	49.82	7.60	9.86	9.78	50.32	7.74	9.78	9.81
2	33.3	135—7	—	—	52.01	7.90	9.47	9.56	51.98	8.05	9.33	9.35
3	30.0	107.5—109.5	—	—	47.26	6.91	9.40	—	47.35	6.95	9.20	9.23
4	76.0	135.5—137	—	—	49.85	7.46	22.53	9.28	50.46	7.49	22.63	9.08
P-1	73	87—105	13.3	5.0	44.32	5.96	12.43	13.07	45.20	6.09	12.26	14.75
P-2	84	—	3.8	5.1	—	—	—	13.32	47.97	6.21	12.33	12.36
P-3	~100	—	3.9	2.9	41.82	5.35	12.44	—	41.73	4.81	12.17	12.20
P-4	59	110—125	4.4	4.0	43.05	5.81	27.09	11.67	42.67	5.97	27.65	11.09
P-1-5	50	—	—	—	—	—	—	18.31	41.93	6.33	9.78	19.61
P-1-6	40	—	—	—	40.55	6.94	9.20	—	39.97	6.71	7.77	23.37

* The calculated values for P-4 were based on the repeating unit plus one equivalent of water.

Table 2 IR characteristic absorption bands of monomers and polymers (cm^{-1})

Compd.	Base	Si—Me	Si—O—Et	Si—O—Si
1	1706, 1670 (s)	1262 (m)	1110, 1085, 955 (m)	—
2	1688, 1656 (s)	1256 (m)	1110, 1080, 950 (m)	—
3	1705, 1675 (s)	1258 (m)	1110, 1084 (s); 955 (m)	—
4	1670, 1600 (s)	1259 (m)	1110, 1076 (s); 960 (m)	—
P-1	1680 (br)	1260 (m)	—	1120—960 (br)
P-2	1670 (s)	1259 (m)	—	1130—950 (br)
P-3	1690 (s)	1253 (m)	—	1130—950 (br)
P-4	1650, 1596 (s)	1258 (m)	—	1130—970 (br)
P-1-6	1680 (s)	1260 (m)	—	1140—960 (br, vs)

Table 3 $^1\text{H-NMR}$ chemical shifts (δ ppm) of monomers and polymers*

Compd.	Base ring protons						NCH ₃	CH ₂ CH ₂ CH ₃	CH ₃ Si	SiMe	OCH ₂ CH ₃	OCH ₂ CH ₃
	Purine		Pyrimidine									
	2-H and 8-H	6-NH ₂	3-H	6-H	5-H	5-Me						
1	—	—	10.17	7.21	5.52	—	3.87—3.45	1.97—1.37	0.72—0.32	0.04	3.87—3.45	1.14
2	—	—	9.20	7.05	—	1.93	3.94—3.56	2.0 —1.5	0.8 —0.3	0.13	3.94—3.56	1.22
3	—	—	10.02	7.36	—	—	3.82—3.68	1.87—1.63	0.64—0.56	0.14	3.82—3.68	1.22
4	8.37, 7.82	6.24	—	—	—	—	4.21	2.2 —1.7	0.8 —0.4	0.14	3.75	1.12
P-1	—	—	11.22	7.74	5.66	—	3.75	2.0 —1.4	0.85—0.4	0.18	—	—
P-2	—	—	11.27	7.57	—	1.86	3.9 —3.4	2.0 —1.4	0.8 —0.3	0.16	—	—
P-3	—	—	11.81	8.15	—	—	3.71	2.1 —1.5	1.3 —0.4	0.19	—	—
P-4	8.27, 8.17	7.24	—	—	—	—	4.21	2.2 —1.6	0.7 —0.3	0.05	—	—
P-1-5	—	—	11.50	7.8	5.7	—	4.1 —3.3	2.1 —1.4	0.85—0.35	0.18	—	—
P-1-6	—	—	11.28	7.71	5.64	—	3.73	2.0 —1.3	0.9 —0.3	0.17	—	—

* Solvent (internal reference): 1, $\text{CCl}_4(\text{CHCl}_3)$; other monomers, CDCl_3 (CHCl_3); polymers, d_6 -DMSO (DMSO).

Table 4 UV $\lambda_{\max}$ ($\epsilon \cdot 10^{-3}$) of monomers*

Compd.	pH 1	pH 7	EtOH	pH 13
1	268 (9.75),	267.5 (11.2),	266.5 (10.6),	266.5 (7.28),
2	273 (12.3),	273 (9.57),	271.5 (10.1),	271.5 (7.52)
3	275 (9.16),	275 (9.73),	274 (9.79),	273 (7.14),
4	260 (14.6), $\lambda_{\min}$ 233 (3.35)	261.5 (14.7), $\lambda_{\min}$ 228 (2.56)	261.5 (15.4), $\lambda_{\min}$ 227	262 (14.5), $\lambda_{\min}$ 229 (2.2)

* λ , wavelength in nm; ϵ , molar extinction coefficient.

Solvent systems: pH 1, 0.1N HCl in 60% aq. EtOH;

pH 7, 60% aq. EtOH;

pH 13, 0.1N NaOH in 60% aq. EtOH.

RESULTS AND DISCUSSION

Structural identification of monomers

As can be seen from Table 3, a N—H absorption signal in ^1H -NMR spectrum which appeared in the lower field in the chemical shift range of 9 ppm to 11 ppm, was observed for each of the three organosilicon monomers (1, 2 and 3) containing uracilyl groups. This signal together with its relative intensities to those of all other different protons suggested that the uracil rings were monosubstituted by methyldiethoxysilylpropyl group. This group demonstrated its presence also in the monomers' IR spectra (Table 2) which revealed the characteristic bands not only of the uracil rings but also of the methylsilyl and ethoxysilyl groups. The elemental analysis (Table 1) was in full accordance with this monosubstituted structure. The substitution site on the uracil rings was confirmed by UV spectra (Table 4) which showed a slight decrease in both λ_{max} and ϵ_{max} when the solvent medium changed from alkaline to neutral or acidic. These spectral features were identical with those of N¹-substituted uracil derivatives reported in the literature [10-12].

The monosubstitution on adenine ring of monomer 4 was similarly identified by its ^1H -NMR, IR and elemental analysis. The confirmation of its N⁹-substituted structure was based on the UV spectrum which had the λ_{max} near 260 nm and a positive value of λ_{min} (pH 1)— λ_{min} (pH 7) [13-15].

Structural identification of polymers

In the ^1H -NMR spectra (Table 3) of all polymers prepared, the signals of ethoxysilyl group once existing in their corresponding monomers have disappeared, while other signals still exist. Their IR spectra (Table 2) exhibit the same disappearance, but a new absorption band can be observed which is strong and broad and is characteristic of Si—O—Si structure. These spectral data strongly suggest that the Si—OEt group has been broken down in the polymerization and the siloxane linkage has been formed. The polymer structures were further approved by the elemental analysis, the intrinsic viscosity $[\eta]$ measurement and the number average molecular weight $\bar{M}_n$ determination (Table 1).

REFERENCES

- [1] Takemoto, K. and Inaki, Y., *Adv. Polym. Sci.*, **1981**, *41*, 3.
- [2] Pitha, J., *Polymer*, **1977**, *18*, 425.
- [3] Akashi, M., Kita, Y., Inaki, Y. and Takemoto, K., *Makromol. Chem.*, **1977**, *178*, 1211.
- [4] Миронов, В. Ф., *Изв. АН СССР, Отд. Хим. н.*, **1959**, 1862.
- [5] Померанцева, М. Г., Белякова, З. В., Голубцов, С. А. и Ефремова, Л. А., *Ж. Общ. Хим.*, **1970**, *40*, 1089.
- [6] Крешков, А. П., Мышляева, Л. В. и Хананашвили, Л. М., *Ж. Общ. Хим.*, **1958**, *28*, 2112.
- [7] Robins, M. J. and Hatfield, P. W., *Can. J. Chem.*, **1982**, *60* (5), 547.
- [8] Borisov, S. N. and Sviridova, N. G., *J. Organomet. Chem.*, **1968**, *11* (1), 27.
- [9] 叶大键、刘振华、李贵华、孟令芝、陈欢平, 高分子通讯, **1982**, (3), 161.
- [10] Gacek, M. and Undheim, K., *Acta Chem. Scand.*, **1979**, *B33*, 515.

-
- [11] Baker, B. R. and Jackson, G. D. F., *J. Pharm. Sci.*, **1965**, *54* (12), 1758.
 - [12] Nishitani, T., Iwasaki, T., Mushika, Y. and Miyoshi, M., *J. Org. Chem.*, **1979**, *44* (12), 2019.
 - [13] Ryan, K. J., Acton, E. M. and Goodman, L., *J. Org. Chem.*, **1971**, *36* (18), 2646.
 - [14] Leonard, N. J. and Deyrup, J. A., *J. Am. Chem. Soc.*, **1962**, *84*, 2148.
 - [15] Montgomery, J. A. and Thomas, H. J., *J. Am. Chem. Soc.*, **1965**, *87*, 5442.