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Functional Monomers and Polymers Containing Nucleic Acid Bases: Experiments on Template Polymerization

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Functional Monomers and Polymers Containing Nucleic Acid Bases: Experiments on Template Polymerization

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ABSTRACT

In order to see how the specific base-base interactions observed between complementary nucleic acid bases can be realized for free-radical polymerization systems, the template polymerization of methacrylate type monomers containing nucleic acid bases in the presence of template polymers containing complementary bases was studied. Stereoregular polymers were chosen as the template polymers. The radical copolymerization of the monomers containing complementary nucleic acid bases was also studied in different solvents.

The nucleic acids, DNA and RNA, contain two types of purine bases, adenine and guanine, and also the pyrimidine bases, thymine (in the case of RNA, uracil) and cytosine. The most essential function of the nucleic acid bases is considered to be the formation of base-base pairs through hydrogen bonding between purines and pyrimidines, such as thymine (or uracil) with adenine, and cytosine with guanine, which plays an important role in realizing the replication and transcription of genetic codes for the protein synthesis. The

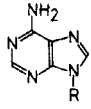
interaction among such purine and pyrimidine bases is a common subject of interest among scientists in the fields of organic, physical, and macromolecular chemistry and biochemistry. Since 1968, numerous studies have been devoted to the preparation and polymerization of a series of new monomeric species having nucleic acid bases, and their application in pharmaceutical fields [1-4].

On the other hand, template polymerization as seen in the replicative biopolymer synthesis has recently received much attention. From such a point of view, vinyl polymerization has been studied in the presence of some polymers which were expected to serve as the templates [5-19]. The so-called template or matrix polymerization, however, seems to be strictly selective, because interaction between the monomeric or polymeric species and the template polymers might be realized not so specifically. It appears, however, substantially to be one of the most attractive problems, if the template polymerization among suitable monomer-polymer pairs having complementary nucleic acid bases could succeed.

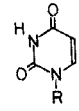
In the present paper, emphasis is focused on our systematic work on the functional monomers and polymers containing nucleic acid bases, particularly on experiments with template polymerization of the compounds, as well as preliminary work about copolymerization and polymer-polymer interaction studies. Investigations by other groups are also referred to briefly.

COPOLYMERIZATION STUDIES

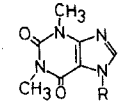
In order to see first how the specific base-base interactions observed between complementary nucleic acid bases can be realized for free-radical polymerization systems, the radical copolymerization of vinyl-type monomers containing complementary nucleic acid bases was studied in different solvents, using AIBN as an initiator



Adenine
(MAOA)



Uracil
(MAOU)



Theophylline
(MAOThe)

R : $CH_2=C(CH_3)-CO-OCH_2CH_2-$

TABLE 1. Copolymerization of MAOU with MAOA

Comonomers					
M_1	M_2	Solvent	r_1	r_2	r_1r_2
MAOU	MAOA	DMSO	1.1	0.99	1.1
		DMF	0.53	0.58	0.30
		Pyridine	0.8	0.8	0.6
		Ethanol	0.80	0.40	0.32
		Dioxane	0.55	0.55	0.30
MAOThe	MAOU	Ethanol	1.0	1.0	1.0
		Dioxane	0.85	1.0	0.85
MAOThe	MAOA	Ethanol	1.9	0.8	1.5
		Dioxane	0.7	1.0	0.7
MAOThe	MMA	DMSO	1.4	1.2	1.7
		Ethanol	3.7	0.80	3.0
		Dioxane	0.90	0.45	0.41

[16]. Some of the results obtained from the copolymerization of N-β-methacryloyloxyethyluracil (MAOU) with N-β-methacryloyloxyethyl adenine (MAOA) are shown in Table 1. In contrast to usual free-radical copolymerizations, it was found that the copolymerization behavior depends upon the solvents used, and the copolymerization tends to become alternative when either dioxane or ethanol is used as the solvent. From the fact that the rate of copolymerization reaches the maximum value when the monomer feed ratio is kept at 1:1, and that the tendency is much larger than in the case of $\phi = 1$, it was suggested that some base-base pair interaction between complementary vinyl monomers plays a role during the copolymerization.

Detailed spectroscopic and NMR studies on the behavior of the monomers in various solvents, as well as the tacticity of the polymers, were recently made [18]. MAO type monomers having adenine, thymine (MAOT), uracil, and theophylline were polymerized at 60°C by use of AIBN as the initiator, and the polymers obtained were further converted to poly(methyl methacrylate). From the high resolution NMR spectra of poly(methyl methacrylate) thus derived, the stereoregularity of the polymers originally prepared was determined. The NMR spectra measured at 150°C in dimethyl sulfoxide-d_6 showed

TABLE 2. Activation Parameters

Monomer	Solvent	$\Delta\Delta H^{\ddagger}$ (cal/mole)	$\Delta\Delta S^{\ddagger}$ (e. u.)
MAOA	DMSO	2100	4.4
	DMF	790	0.57
MAOU	DMF	490	-0.26
	Dioxane	360	-0.46
	Ethanol	300	-1.5
MAOT	DMSO	1100	0.51
	DMF	870	0.28
MAOThe	DMSO	620	0.06
MMA	DMSO	900	0.12

three peaks based on α-methyl protons, which were assigned to the components on the syndiotactic, heterotactic and isotactic triads. The rate of polymerization was found to be influenced by the type of bases and solvents used, while the stereoregularity of the polymers seems not to be affected by them. Activation parameters, $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values for the polymerization of different MAO-type monomers in various solvents were estimated as shown in Table 2, and from the results, it was found that for the polymerization of the monomer having adenine as the side group in dimethyl sulfoxide solution, syndiotactic placement appears to be favored by the additional enthalpy of activation required for isotactic placement [20].

Further copolymerization studies were made in chloroform solution, taking account of the specific base-base interaction between complementary MAO-type monomers [19]. The copolymerization was found to be accelerated more either at lower monomer concentration or at lower polymerization temperature. When N-β-methacryloyloxyethylcarbazole was used as a comonomer, the rate of copolymerization showed a similar trend as the case of usual free-radical copolymerizations. The r_1 and r_2 values obtained indicate that the copolymerization proceeds by an alternating reaction, particularly in the case of copolymerization between monomers having complementary nucleic acid bases. The results suggest that the hydrogen-bonding interaction between adenine and thymine plays a role in the propagation step.

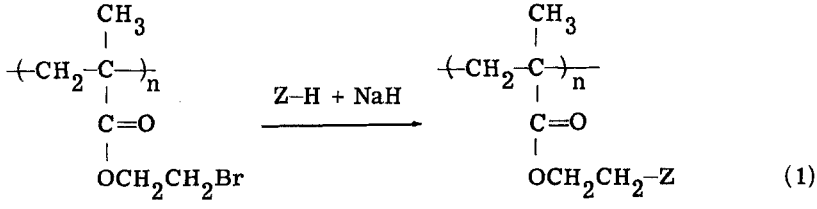
TABLE 3. Anionic Polymerization of β-Bromoethyl Methacrylate (-78°C)

Initiator	Solvent	Time (hr)	Conversion (%)	Tacticity (%)[a] I	H	S	$M_n \times 10^{-4}$[b]
n-BuLi	Toluene	3	80	75	15	10	2.9
PhMgBr	Toluene	48	70	81	11	8	3.1
$LiAlH_4$	Ether	0.25	60	88	7	5	1.6[c]
Et_2AlNPh_2	Toluene	72	90	4	12	84	1.9

[a]Measured by NMR (100 MHz, at 60°C in $CDCl_3$).
[b]Measured by membrane osmometer (at 37°C in toluene).
[c]Measured by vapor pressure osmometer (at 57°C in DMF).

STEREOREGULAR POLYMERS CONTAINING NUCLEIC ACID BASES

For the synthesis of the template polymers, we first prepared β-bromoethyl methacrylate, and by polymerizing the monomer with anionic initiators at -78°C, poly(bromoethyl methacrylate) of high isotacticity and syndiotacticity was obtained (Table 3). The reaction of these stereoregular polymers with nucleic acid bases was then carried out, and thus the stereoregular methacrylate polymers containing nucleic acid bases were successfully prepared in high conversions [21]]Eq. (1)]. NMR and UV spectroscopic studies of the polymers were also made.



(1)

Z = adenine, uracil, and theophylline units

Complex formation between poly-MAOA and poly-MAOT or poly-MAOU was further studied in a dimethyl sulfoxide-ethylene glycol

mixture by UV spectroscopy [22]. For the polymer pairs containing complementary nucleic acid bases, both hypochromicity and hyperchromicity were found. The stereoregularity of the polymers is also important for the complex formation. For the Job plots of atactic poly-MAOU and three types of stereoregular poly-MAOA, for example, the following order of interaction was obtained: atactic poly-MAOU-atactic poly-MAOA > atactic poly-MAOU-isotactic poly-MAOA > atactic poly-MAOU-syndiotactic poly-MAOA. In general, the ability to form complexes of atactic polymers is higher than those of the stereoregular polymers, and it is noteworthy that the ability depends selectively on the stereoregularity of poly-MAOU rather than that of poly-MAOA.

STUDIES ON TEMPLATE POLYMERIZATION

The polymerization of MAOA in the presence of atactic poly-MAOT was first carried out at 60°C in pyridine solution [17, 23]. The time-conversion curves obtained indicate that the polymerization proceeds much faster in the presence of atactic poly-MAOT than in its absence, the initial rate of polymerization being about four times that in the absence of atactic poly-MAOT. During the course of the template polymerization gel was formed, because poly-MAOA was insoluble in pyridine while atactic poly-MAOT was soluble in it. Such enhancement of the rate was not seen for the polymerization of MAOT in the presence of poly-MAOT. The results suggest that a specific base-base pairing between adenine and thymine plays a role in accelerating the polymerization. The molecular weight of the atactic poly-MAOT used as the template, however, appeared not to influence on the conversion (Table 4).

The polymerization of MAOA was next performed in the presence of atactic poly-MAOT in the temperature range between 20 and 70°C in pyridine solution. The result shows that the relative conversion after 3 hr tended to increase with increasing temperature.

In order to see how the stereoregularity of the template polymers can affect the polymerization behavior, the polymerization was next studied in the presence of isotactic, syndiotactic, or atactic poly-MAOU. The polymerization of MAOA was performed at 20°C in three types of solvents, that is, dimethyl sulfoxide, dimethylformamide, and pyridine. It is to be noted that both poly-MAOU and the MAOA monomer are soluble in these solvents, while the poly-MAOA formed is only soluble in dimethyl sulfoxide.

In the completely homogeneous (dimethyl sulfoxide) solution, the presence of isotactic or syndiotactic poly-MAOU had little or no influence on the rate of polymerization of MAOA, while atactic poly-MAOU retarded slightly the polymerization of MAOA, while syndiotactic

TABLE 4. Polymerization of MAOA in the Presence of Poly-MAOT in Pyridine Solution[a]

Molecular weight of poly-MAOT $\bar{M}_n \times 10^4$	Conversion (%)	Relative conversion
—[b]	18.5	1.0
15.4	54.1	2.9
12.6	45.0	2.4
6.9	59.2	3.2
3.7	45.0	2.4
3.6	54.2	2.9
1.9	53.5	2.9

[a] [MAOA] = [poly-MAOT] = 2.0×10^{-2} mole/liter; [AIBN] = 1.0×10^{-3} mole/liter; 60°C; 3 hr.

[b] Blank.

and atactic poly-MAOU accelerated the polymerization only slightly. Finally in pyridine solution, acceleration of the polymerization of MAOA was found to be substantial in the presence of isotactic poly-MAOU, and a fairly large acceleration was seen also in the presence of syndiotactic and atactic poly-MAOU. The order of the acceleration in different solvents, pyridine > dimethylformamide > dimethyl sulfoxide, may be comparable with that of the stability of adenine-uracil interaction in these solvents. The effect of stereoregularity of the template polymers was also observed for the polymerization of MAOThe.

The polymerization of MAOA in the presence of isotactic poly-MAOU appeared not to be accelerated in pyridine solution at 40°C, unlike the case of polymerization at 20°C. In pyridine solution, the rate of polymerization was enhanced at 60°C, and the order of the acceleration was: atactic poly-MAOU > isotactic poly-MAOU > syndiotactic poly-MAOU. A similar tendency of temperature dependence was obtained for atactic poly-MAOT.

It is known that the free-radical polymerization of methyl methacrylate proceeds by a stereospecific template-type mechanism to give stereoregular poly(methyl methacrylate) if the stereoregular polymethyl methacrylate is present in the reaction system [10, 12, 13]. In our results, however, such a replication of stereoregularity onto the polymers formed seems not to be shown: the tacticity of

TABLE 5. Polymerization of MAOA and MAOT in the Presence of Poly-MAOA in Chloroform Solution[a]

Monomer	Template polymer	Conversion (%)	Relative conversion
MAOA	None	35	1
	i-Poly-MAOA	33	0.94
	s-Poly-MAOA	30	0.84
MAOT	None	43	1
	i-Poly-MAOA	30	0.70
	s-Poly-MAOA	31	0.72

[a][Monomer] = [poly-MAOA] = 4.0×10^{-2} mole/liter; [AIBN] = 2.0×10^{-3} mole/liter; 60°C; 3 hr.

TABLE 6. Polymerization of MAOA and MAOT in the Presence of Poly-MAOA in Dimethyl Sulfoxide Solution[a]

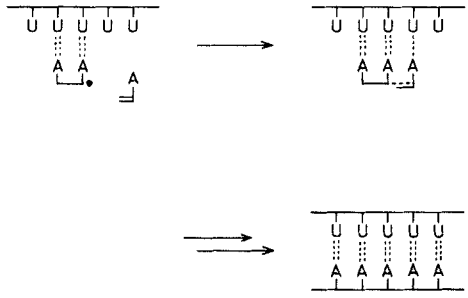
Monomer	Template polymer	Conversion (%)	Relative conversion
MAOA	None	33	1
	i-Poly-MAOA	34	1.03
	s-Poly-MAOA	31	0.98
MAOT	None	42	1
	i-Poly-MAOA	33	0.78
	s-Poly-MAOA	39	0.82

[a][Monomer] = [polymer] = 4.0×10^{-2} mole/liter; [AIBN] = 2.0×10^{-3} mole/liter; 60°C; 3 hr.

poly-MAOA obtained by the polymerization of its monomer in the presence of stereoregular poly-MAOA was similar to that obtained by usual free-radical polymerization in the absence of the template polymers.

Template polymerization of both MAOT and MAOA was also studied in the presence of stereoregular poly-MAOA (Tables 5 and 6). In these

cases, however, acceleration of the polymerization was observed neither in homogeneous dimethyl sulfoxide solution nor in heterogeneous chloroform solution. In the polymerization of MAOT, even slight deceleration was observed, which suggests the absorption of the monomer onto the template polymers.



(2)

From the results of trials of the template polymerization, polymerization mechanism was proposed: Eq. (2) shows how the monomer affords a growing molecular chain which immediately forms a complex with the template polymer; the propagation step appears to consist of a reaction between the growing complexed radical and the monomer.

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