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SHORT COMMUNICATIONS

# Preparation of Potentially Antitumor-Active Vinyl Polymers Having 5-Fluorouracil Unit as a Component†

Shoichiro OZAKI,†† Junji OHNISHI, Yasuyuki WATANABE, Tomohiro NOHDA, Toshio NAGASE, Takahiko AKIYAMA, Nobuaki UEHARA,* and Akio HOSHI*

*Department of Resources Chemistry, Faculty of Engineering, Ehime University, Bunkyo-cho, Matsuyama 790, Japan*
** National Cancer Center Research Institute, Tsukiji, Chuo-ku, Tokyo 104, Japan*

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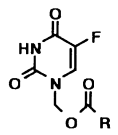
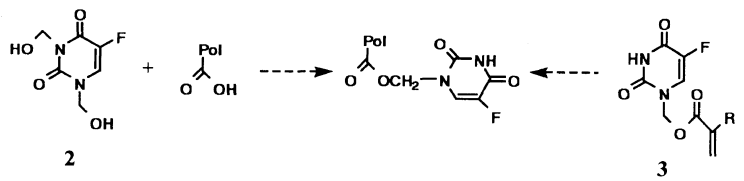
5-Fluorouracil (5-FU) is known to have antitumor activity and is in clinical use. Recently, functional polymers containing 5-FU have been of interest as polymeric drugs for biological and biomedical applications of synthetic polymers.[2,3] As part of a series of synthetic studies on 5-FU derivatives aimed at obtaining improve antitumor agents, it was found that 1-acyloxymethyl-5-fluorouracils **1** have strong antitumor activities.[4,5] This ester function was found to be labile under hydrolytic conditions to generate 5-FU and so it is expected that polymers substituted with 5-FU linked through acyloxymethyl group may have slow release functions, and thus improved pharmacological properties *e.g.*, reduced side effect and higher antitumor activity than the monomer itself. In this communication, we report the preparation of vinyl polymers having 5-FU attached to the main chain through carbonyloxymethyl group by two methods (Scheme 1) and the antitumor activity of them.



**1**



**2** **3**

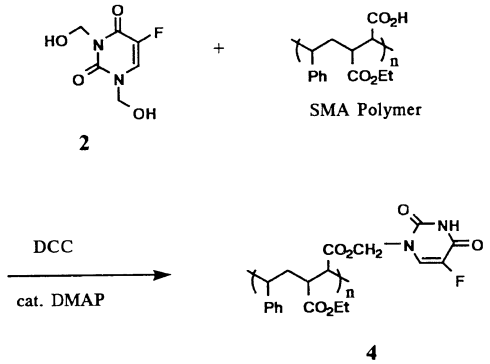
**Scheme 1.**

† 5-Fluorouracil Derivatives Part XVI. For previous paper, see ref 1.
†† To whom correspondence should be addressed.

At first, the desired polymer was prepared by esterification of a carboxylic acid of the polymer chain with 1,3-bis(hydroxylmethyl)5-flurouracil **2**.[3] A copolymer of styrene–maleic acid monoethyl ester (SMA polymer, mean molecular weight 2500) was purified by gel permeation chromatography, dissolved in acetonitrile, and allowed to react with **2** in the presence of dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) at room temperature overnight. After the usual work-up, polymer **4** was obtained as a colorless solid in 62% yield (Scheme 2). The IR spectra of **4** exhibited a characteristic peak at 1660 $cm^{-1}$ (this peak was not detected in SMA polymer itself), which was assigned to the amide linkage of 5-FU. Hydrolysis of **4** under basic conditions (KOH/MeOH, reflux 4 h) gave 5-FU, as determined by HPLC analysis. According to the HPLC data, polymer **4** contained 5.2 molecules of 5-FU per molecule of SMA polymer. This is in good agreement with the value of 5.6 calculated from the elemental analysis data based on nitrogen.

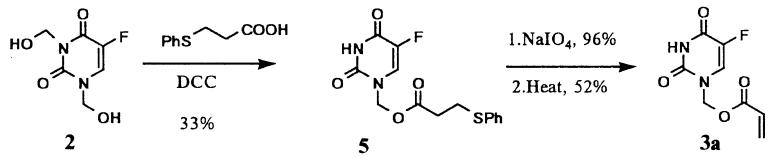
Secondly, vinyl polymers were prepared by radical polymerization of 1-acryloyloxymethyl- and 1-methacryloyloxymethyl-5-fluorouracils (**3a** and **3b**). Compound **3a** was prepared as follows: **2** was treated with 3-(phenylthio)propionic acid under the conditions described above to afford 3-(phenylthio)propionyloxymethyl-5-fluorouracil **5**. After selective oxidation of **5** with sodium periodate at low temperature, the resulting *S*-oxide was thermolized in acetonitrile to give **3a** (Scheme 3). An alternative way to compound **3** was investigated. Compound **2** was directly allowed to react with acryloyl and methacryloyl chlorides to afford **3a** and **3b** in 28 and 53% yields, respectively.

The polymerization and copolymerization of **3** were carried out in degassed refluxing benzene under a nitrogen atmosphere using azobisisobutyronitrile (AIBN) as the radical initiator (Scheme 4). The **3** and vinyl monomer ($M_2$) were allowed to react in the ratio shown in Table I. The results are summarized in Table I. The composition of the polymer thus



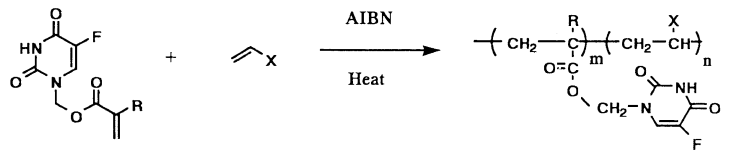

**2** **4**

**Scheme 2.**




**2** **5** **3a**

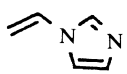
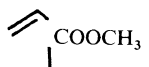
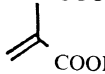
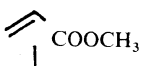
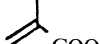
**Scheme 3.**




**3** **6**

**Scheme 4.**

**Table I.** Results of polymerization and copolymerization and copolymerization of **3**

| Run | Monomer | | | Monomer reactivity ratio[a] | | Reaction time/h | Conversion of **3**/% | Polymer | Composition $m:n$ | | Viscosity[c] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $M_1$ | $M_2$ | Ratio | $r_1$ | $r_2$ | | | | | | [$\eta$] Temp/°C | Solvent ratio |
| 1 | **3a** | — | — | — | — | 2 | 70 | **6a** | — | — | 1.08 (22) | 8:2 |
| 2 | **3a** |  | 1:20 | 71[b] | 0.089[b] | 22 | 87 | **6b** | 21 | 79 | 0.265 (23) | 1:1 |
| 3 | **3a** |  | 1:10 | 30[b] | 0.104[b] | 8 | 99 | **6c** | 27 | 73 | 0.57 (19) | 1:0 |
| 4 | **3a** |  | 2:3 | 2.35[b] | 0.63[b] | 10 | 100 | **6d** | 42 | 58 | 0.35 (20) | 1:1 |
| 5 | **3a** |  | 1:7 | 4.35[b] | 0.63[b] | 0.5 | 93 | **6e** | 56 | 44 | 1.52 (22.5) | 7:3 |
| 6 | **3a** |  | 1:2 | 0.35 | 0.20 | 0.6 | 99 | **6f** | 49 | 51 | 0.37 (19) | 7:3 |
| 7 | **3b** | — | — | — | — | 2 | 60 | **6g** | — | — | 0.22 (22) | 7:3 |
| 8 | **3b** |  | 1:5 | 6.87 | 0.12 | 0.7 | 83 | **6h** | 55 | 45 | 0.89 (24) | 7:3 |
| 9 | **3b** |  | 1:3 | 1.07 | 0.02 | 1 | 100 | **6i** | 55 | 45 | 0.20 (24.5) | 7:3 |

[a] Calculated by the Fineman–Ross method.
[b] Calculated by the Mayo–Lewis method.
[c] Intrinsic viscosity was measured in DMSO–morpholine.
[d] Reaction was carried out in the presence of AIBN (0.05 eq.) in refluxing benzene.

**Table II.** Antitumor activity of 5-fluorouracil derivatives against leukemia L-1210 by intraperitoneal injection (*i.p./i.p.*)[a]

| Compd. | Dose[b] | ILS/%[c] | Compd. | Dose[b] | ILS/%[c] |
|---|---|---|---|---|---|
| **1a**[d] | 100 | 106 | **6e** | 30 | 12 |
| **1b**[e] | 100 | 71 | **6f** | 30 | 96 |
| **3a** | 100 | −64 | **6g** | 30 | 2 |
| **3b** | 30 | −6 | **6h** | 30 | −6 |
| **4** | 100 | 11 | FT[f] | 100 | 34 |
| **6a** | 30 | 15 | | 30 | 0 |
| **6b** | 100 | 19 | 5-FU | 100 | 60 |
| **6c** | 100 | 75 | | 30 | 73 |
| **6d** | 100 | 50 | | 30 | 73 |

[a] Six BDF1 mice were used in each group.
[b] mg/kg/day.
[c] Increase span (T/C%-100).
[d] R=$C_{11}H_{23}$.
[e] R=$C_{10}H_{21}$.
[f] 1-(2-Tetrahydrofuryl)5-fluorouracil.

obtained was calculated from their elemental analysis. In the case of copolymerization, the content of 5-FU in the copolymer largely depended on the molecular ratio of the monomers. The ratio was adjusted so that polymer would show the value of the composition ratio ($m:n$) as close to unity as possible. By use of the Fineman–Ross or Mayo–Lewis method,[6] the monomer reactivity ratios ($r_1$ and $r_2$) were calculated. Copolymerization with an acryloyl-type monomer in the polymer chain usually had a higher intrinsic viscosity than those with methacryloyl-type ones. Appropriate choice of monomer may be able to control to a certain extent the viscosity and hydrophilicity of polymers. Copolymer **6c** was the most hydrophilic in all the prepared polymers. This polymerization method is thought to be superior to the esterification method in terms of variability of composition of the polymer and choice of monomer.

The antitumor activity of these polymers against Leukemia L-1210 in mice was also investigated. The results along with those of 1-(2-tetrahydrofuryl)-5-fluorouracil (FT), and 5-FU are summarized in Table II. It is noteworthy that these polymers showed moderate to good antitumor activities in contrast to monomer **3a**, which showed toxicity (negative ILS value). Those having polar functional groups such as imidazole or carboxylic acid showed higher ILS values than those having less polar groups such as nitrile or ester, which can be explained by assuming that more hydrophilic polymers have better activity than less hydrophilic ones. Polymers of **6c**, **6d**, and **6f** showed stronger activities than FT and comparable to 5-FU. These results suggest that polymerizing the monomeric antitumor agent can lead to both increase in antitumor activity and reduction in toxicity. Consequently, the copolymers thus obtained are expected to have promising antitumor activities as polymeric drugs. Screening tests of antitumor activity of these polymers toward other tumors are now in progress at our laboratory. The details of chemical and biological properties of these polymers will be reported later.

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