THE SYNTHESIS AND POLYMERIZATION OF 5-HYDROXYMETHYLURACIL ACRYLATE AND METHACRYLATE

by

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ABSTRACT

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Polymerizable derivatives of 5-hydroxymethyluracil were prepared using acrylic acid and methacrylic acid, and polymerizations were carried out. These derivatives may at some future time find applications as anticancer drugs and antiviral drugs with reduced side effects or as selective chromatographic plastics used in chromatography. The products prepared in the reactions were: 1) 5-hydroxymethyluracil acrylate and 2) 5-hydroxymethyluracil methacrylate. These products were slightly soluble in ethyl acetate. The assigned structures for the products are supported by infrared spectroscopy, nuclear magnetic resonance spectroscopy and elemental analysis.

The esterification of 5-hydroxymethyluracil with the two acids proceeded quite readily with excellent yields. The purification of the monomer was accomplished by selective adsorption of impurities on silica gel in ethyl acetate solvent.

Polymerization of the acrylate and methacrylate monomers was

achieved by the free radical polymerization initiator α,α'-azobisisobutyronitrile (AIBN). The degree of polymerization seemed to be related to the time of polymerization. Viscosity studies were performed on the polymers using a Cannon-Fenske viscometer.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS AND SYMBOLS

ABBREVIATION OR SYMBOL	DEFINITION
AIBN	α,α'-Azobisisobutyronitrile
c	Concentration in g/ml
^{o}C	Degrees centigrade
cm^{-1}	Reciprocal centimeters
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
g	Grams
5-HMU	5-Hydroxymethyluracil
5-HMUA	5-Hydroxymethyluracil acrylate
5-HMUMA	5-Hydroxymethyluracil methacrylate
Ig	Immunoglobulin
IR	Infrared
J value	Coupling constants cycles per second
K, a	K and a are the slope and intercept respectively, of a plot of log $[\eta]$ versus log of molecular weight of a series of fractionated polymer samples whose molecular weights have been determined by absolute methods.
ml	Milliliter
$\overline{M}$	Average molecular weight
NMR	Nuclear magnetic resonance
PDM	p-phenylenediamine mustard
PDM-PGA	The drug carrier complex p-phenylenediamine mustard bound to polyglutamic acid

ABBREVIATION OR SYMBOL	DEFINITION
PDM-PGA-Ig	The drug carrier complex linked to the immunoglobulin
PGA	Polyglutamic acid
Poly-5-HMUA	Poly-5-hydroxmethyluracil acrylate
Poly-5-HMUMA	Poly-5-hydroxymethyluracil methacrylate
RNA	Ribonucleic acid
t	Efflux time of solution in seconds
t_o	Efflux time of pure solvent in seconds
TLC	Thin layer chromatography
TMS	Tetramethylsilane
UV	Ultraviolet
α	Alpha
β	Beta
δ	Delta, chemical shift in ppm
$[\eta]$	Intrinsic viscosity
η_{red}	Reduced viscosity

CHAPTER I

GENERAL INTRODUCTION AND HISTORICAL

Chemotherapeutic polymer research has increased greatly during the last decade bringing forth new advances in cancer treatment.[1-4] Polymeric drug research has three approaches: 1) insoluble chemotherapeutic polymers (used for surgical implantation); 2) soluble chemotherapeutic polymers; and 3) chemotherapeutic polymers which are soluble and have a directing group to zero in on the cancer.[1, 3] Drugs which are soluble and have a directing group may prove to be the most valuable of all the chemotherapeutic polymers because they would not poison the entire body of the experimental animals.[1] Cancer is attacked by selective cytotoxic drugs which may not be as selective as one might want them to be and which may also bring on toxic side effects if not controlled.[5] Medicine needs better methods for the detection of chemotherapeutic drugs not only in the blood stream but also in the tissues.[5] Recently, drugs have been developed and administered to experimental animals demonstrating the phenomena and success of directing groups.[1-4] A cancer drug must meet three kinetic criteria for favorable therapeutic action: 1) adequate drug concentration; 2) effective drug penetration; and 3) sufficient duration of drug exposure.[5] All three of these criteria could be met by a soluble

polymeric drug that could be transported by the blood to the cancer cell causing death of the cell. Effective exposure of the cell to the drug could be accomplished by binding the drug to a tumor or cancer specific immunoglobulin.[1, 2] Since the binding of an anticancer immunoglobulin to a cancer cell is almost irreversible, the drug would have ample time to be ingested by or incorporated into the cell causing it to die. The idea of carrying drugs or hormones has been demonstrated, promising a brighter future in cancer research.[1, 2, 6, 7]

V. Chytry', et al., have synthesized a new insulin bound polymeric drug which may find great use in the treatment of diabetics.[6] The insulin was bound to the polymer carrier by reacting the insulin with the nitro group of p-nitrophenyl ester in a copolymer of N-(2-hydroxypropyl)methacrylamide and N-methacryloyldiglycyl p-nitrophenyl ester. The polymeric insulin was assayed at 60 wt% insulin and retained a calculated 10% of the radioimmunoreactivity of the original insulin.[6] The polymeric insulin decreased the blood glucose levels in rats slower than crystalline insulin but showed a slower and slightly longer period of onset hypoglycemia.[6]

Independent researchers have attacked diabetes from an isolated artificial organ approach, using polymers in the membrane of an artificial pancreas.[8] The membrane which isolates the beta-islet cells of the artificial pancreas allows molecular weights up to 50,000 to pass through. The membrane stopped larger protein molecules such as the immunoglobulins (the main component of the body's defense system).

In this way the researchers felt they have discovered a means to stop tissue rejection of an implanted artificial organ.[8]

Searle Research Laboratories have developed an immunoglobulin directed chemotherapeutic drug which was proven to have had an increased effectiveness against lymphoma in mice.[2] Often in building polymeric drugs, the researcher finds that the drug becomes insoluble in plasma and therefore mobility and versatility of the drug is greatly reduced. The preferred method would be to build the polymeric drug using soluble blocks to make the final polymeric drug product also soluble.[3]

First work on binding the chemotherapeutic drugs which exhibited tumor suppression used alkylating agents which yield a substituted rabbit antitumor immunoglobulin (Ig).[2] When drugs were substituted on the Ig unit, its physiochemical properties were changed and the directing and antibody activities were lost. As more drug was substituted on the Ig unit, the less water soluble the Ig unit became. These problems were overcome by using a polyanion polymer carrier, polyglutamic acid (PGA). The chemotherapeutic drug was p-phenylenediamine mustard (PDM) which has a free amino group. The drug carrier was prepared by reacting PGA in water with 1-ethyl-3(3-dimethylaminopropyl)carbodiimide and PDM at room temperature. After isolation, the PDM-PGA was linked to Ig unit (rabbit antiserum to mouse lymphoma cells). The linkage of the PDM-PGA to the Ig unit was effected by a carbodiimide reaction between the free carboxyl group of the drug

carrier and the free amino group of the Ig unit. The new drug acted as one entity in dialysis, ion-exchange chromatography and immunoelectrophoresis. [2] The effectiveness of the drug was checked for any synergistic effect. The PDM-PGA complex plus the unlinked Ig had less effect than did the PDM-PGA-Ig complex which provided strong evidence that the PDM-PGA-Ig was indeed working on a homing mechanism. [2]

The subject of biomedical polymeric drugs has been reviewed with extensive consideration as to their problems and advantages. [9, 10] The medical field has not accepted polymeric drugs with much enthusiam, but as time and research continues, their importance and usefulness will become evident. The papers and research in this field have grown rapidly. [9] Several models have been proposed for polymeric drugs. [3, 9] One model has been reproduced in Figure 1. [3] The logic and construction of a chemotherapeutic polymer was exemplified in the work at Searle Research Laboratories by G. F. Rowland and coworkers. [2]

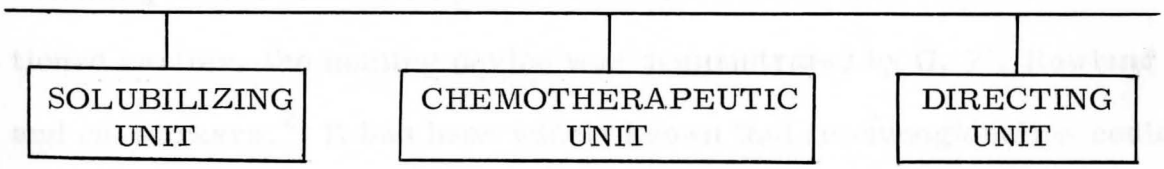


Figure 1. Schematic representation of a chemotherapeutic copolymer which contains several specific functional units. [3]

As mentioned before, the drug could be insoluble after synthesis making it necessary for a solubilizing group to be attached. [9] The type of organ or tissue in which the drug was to be used would have

an influence over the type of solubilizing group.[9] A solubilizing group should not be toxic, and the best ones appear to be vinylpyrrolidones,[9] vinylpyridine-N-oxides,[9, 11] sulfoxide derivatives,[9, 12] and esters of β-hydroxyethyl acrylates and acrylamides.[9] However, if it was desirable for the drug to be lipid soluble, then long chain alkyl systems would be used.[9]

The chemotherapeutic group theoretically could be any drug which had biomedical activity. The important factor is the conditions under which it was attached. Harsh conditions could destroy the drug completely, while even mild conditions which react with an important functional group of the drug could render it useless.[9] There have been various coupling methods used in order to keep the drug active. Some of these coupling methods use esters of N-hydroxysuccinimide, N-hydroxybenztriazole, imidazole and trichlorophenol to fix the drugs on the polymer chain.[9, 13]

The transport system could work on two different principles: a homing device and a nonspecific resorption enhancer.[9] As mentioned earlier, the homing device was demonstrated by G. F. Rowland and co-workers.[2] It has been widely known that immunoglobulins could be produced which have a high degree of specificity with little cross-over precipitation with extraneous proteins. Nonspecific resorption enhancers which would act by inducing a variation in the distribution of polymers in the body could be made of sulfoxide and formamide compounds.[9] Based on the fact that DMSO solutions can absorb through the

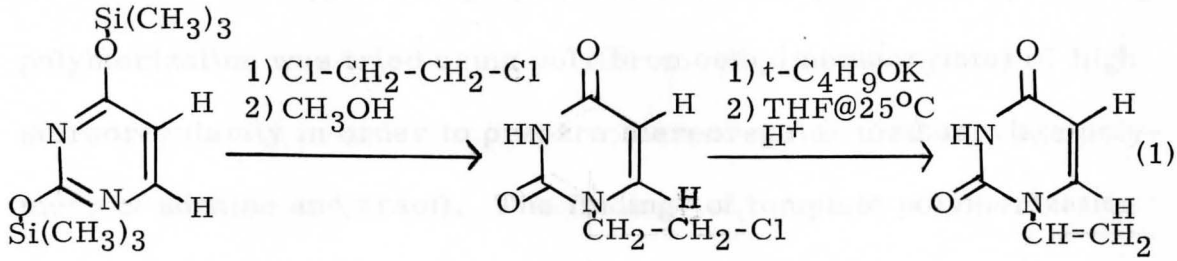
skin, a series of sulfoxide containing polymers were synthesized and apparently are able to carry drugs through the skin.[9, 12]

Polymers have been synthesized with biologically active groups attached in a pendant arrangement or incorporated into the chain of the polymer.[7, 16, 17] C. Pinazzi and co-workers have synthesized polymers containing the biologically active compounds cholesterol and testosterone.[7] The backbone of the polymer was (2-hydroxyethyl)methacrylate, the 2-hydroxyethyl group being a spacer group[9] to move the biologically active compound away from the backbone.[7] The polymers were made via two different routes: 1) synthesizing the polymerizable monomer then polymerizing and 2) polymerizing (2-hydroxyethyl)methacrylate then attaching the cholesterol and testosterone by a carbonate linkage.[7] The biological activity of these polymers were not examined. However, an important experiment was performed demonstrating the importance of degradable spacer groups which release the drug when placed in the body.[9] Two polymers containing testosterone were synthesized. One polymer contained testosterone directly fixed via ester linkage to the polymethacrylate backbone.[9] The other polymer separated testosterone from the polymethacrylate backbone by a degradable spacer group which incorporated an alkylated quaternary ammonium salt.[9] Both polymers contained a sulfoxide solubilizer group.[9] The polymer with the spacer group showed almost the same activity in rats as the free testosterones while the polymer with testosterone attached directly to the backbone showed no activity.[9]

Histamine was fixed on a macromolecular chain of polyisoprene in which by altering reaction conditions, the histamine could be dangling from the backbone or could be a crosslink between two polyisoprene chains. The type of linkage that histamine or any drug has with the polymer backbone determines the ease of release of that drug into the body.[16]

The field of biomedical polymer research has grown rapidly in Italy where numerous works have been started and completed.[15] A few of these research projects should be mentioned briefly. Several new synthetic polymers for preventing silicosis have been studied at the Industrial Chemistry Department of Polytechnic Institute in conjunction with the Institute of Labour Medicine at the University of Milan.[15] Salicylic and other acids were esterified to polyvinyl alcohol at the University of Naples.[15] The recent work in the area of heparin complexation has led to a new polymer of the poly(amido-amine) structure. When this polymer was crosslinked and placed in an aqueous media, it swelled and became a strong and selective heparin adsorber without any side effect on the blood.[15] Later, the crosslinked poly(amido-amine) blocks were coupled to inert blocks which made the deheparinizing polymer fixation permanent.[15]

More closely related to the nature of this study was the work and review of Kiichi Takemoto which dealt with functional monomers and polymers containing nucleic acid bases.[17] The compound 1-vinyluracil and 1-vinylthymine were prepared by the method shown on the following page.[17, 18]



In 1971, Kaye reported that the free radical polymerization of 1-vinyluracil resulted in a back-biting cyclopolymerization.[19] However, in 1974 Kaye successfully homopolymerized 1-vinyluracil without cyclopolymerization by gamma-irradiation at temperatures of -190° to -78° C.[20] Derivatives of N-vinylpyrimidines were reported to have been homopolymerized and copolymerized with acrylamide, maleic anhydride, and N-vinylpyrrolidone using AIBN.[9]

When polymers of uradylic acid and 9-vinyladenine were mixed together, a based paired complex formation took place that was assumed to be a triple-stranded structure.[9, 17, 21] The chromatographic use of a polymer resin of 1-vinyluracil separated a mixture of thymine and adenine.[17, 22]

Template polymerization is a process whereby polymerization takes place on a polymer strand which is complementary to the new polymer forming. Just as DNA replication takes place (only enzymatically) with complementary strands, template polymerization first lines up the polymerizable monomeric derivatives of adenine or uracil on poly-uradylic acid or poly-9-vinyladenine strands respectively. Once the

monomers are in position, polymerization takes place readily. Template polymerization was tried using poly(bromoethylmethacrylate) of high stereoregularity in order to prepare stereoregular methacrylate polymers of adenine and uracil. The findings of template polymerization using the stereoregular polymers containing adenine and uracil was that the complement polymers were polymerized much faster with the template than without. In addition, polymerization with an isotactic template polymer was much faster than with a syndiotactic template polymer.[17]

To date, polymeric biomedical drug research at Youngstown State University has brought forth unique compounds which have great potential in the chemotherapy field.[23-30] New potential polymerizable drugs were synthesized using 5-fluorouracil and 6-methylthiopurine as their chemotherapeutic drug. The drugs synthesized were 5-fluoro-N-(ethylcarbamoyl)uracil (not polymerizable), 5-fluoro-N-(N-allylcarbamoyl)uracil, 5-fluoro-N-(N-isopropylidenecarbamoyl)uracil, 5-fluoro-N-(N-vinylcarbamoyl)uracil.[23, 24, 28] The yield of 5-fluoro-N-(N-vinylcarbamoyl)uracil was improved during further research by T. Ryan who performed a study on the effect different reaction solvents had on the yield of desired product.[26] Potentially polymerizable analogues of a purine were first synthesized at Youngstown State Univsity. These new chemotherapeutic purine monomers were 6-methylthio-9-(N-allylcarbamoyl)purine,[25] 9-acrylyl-6-methylthiopurine[25] and 6-methylthio-9-(N-vinylcarbamoyl)purine.[27, 29, 30] Of these new potentially polymerizable monomers, homopolymers were made of

5-fluoro-N-(N-vinylcarbamoyl)uracil,[23, 24, 26, 28] 9-acrylyl-6-methylthiopurine[25, 29] and 6-methylthio-9-(N-vinylcarbamoyl)purine.[27, 29] These compounds contain the chemotherapeutic units of 5-fluorouracil or 6-methylthiopurine. Much work has been done in the way of turning nucleic acid bases into chemotherapeutic or antiviral drugs by a slight modification of the nucleic acid base or the ribose portion of uridine analogues.[31-40]

Methods and reaction mechanisms of 5-substituted pyrimidine nucleosides and nuclelotides were reviewed by T. K. Bradshaw and D. W. Hutchinson.[40] Bradshaw and Hutchinson dealt with the subject of the reaction mechanisms of halogenation, hydroxymethylation, hydrogen isotope exchange, nitration, thiolation and mercuration. They discussed the hydroxymethylation of uridine and proposed that the influence of the 5'-OH of ribose may facilitate the reaction.[40]

In 1969, Swierkowski and Shugar prepared 5-ethyl-2'-deoxyuridine (Figure 2) which was investigated for its possible mutagenic and antiviral activity.[39] The 5-ethyl-2'-deoxyuridine did not exhibit any mutagenic activity, but it did have a potent antiviral activity as great as 5-iodo-2'-deoxyuridine and 5-bromo-2'-deoxyuridine.[39] Also, in 1969, Gauri and co-workers examined 5-ethyl-2'-deoxyuridine for its possible immunosuppression effect.[32] The findings of such studies led to the belief that 5-ethyl-2'-deoxyuridine would not exhibit an immunosuppressive activity in man when used in therapeutic doses as a virostatic drug.[32] In 1970, Muraoka reported on the synthesis and antiviral

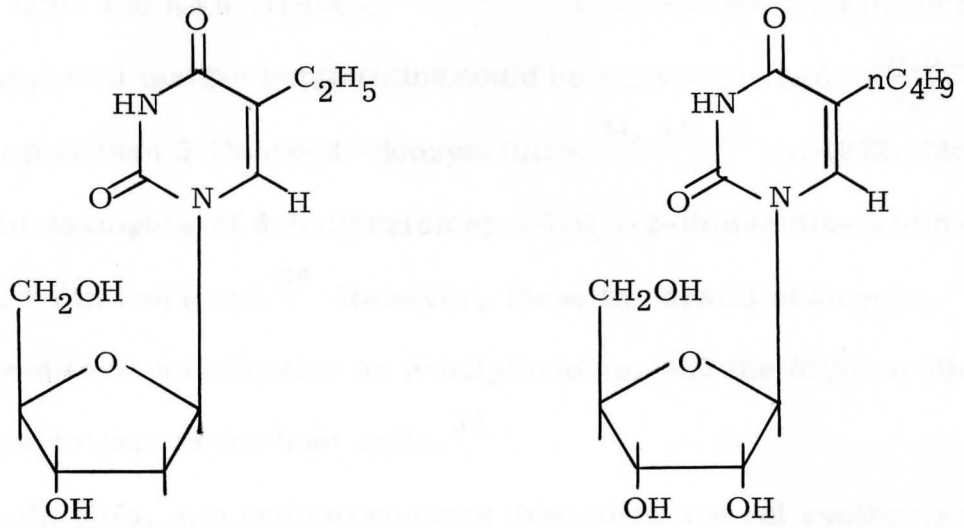


Figure 2. Structure of: a) 5-ethyl-2'-deoxyuridine; b) 5-n-butyluridine

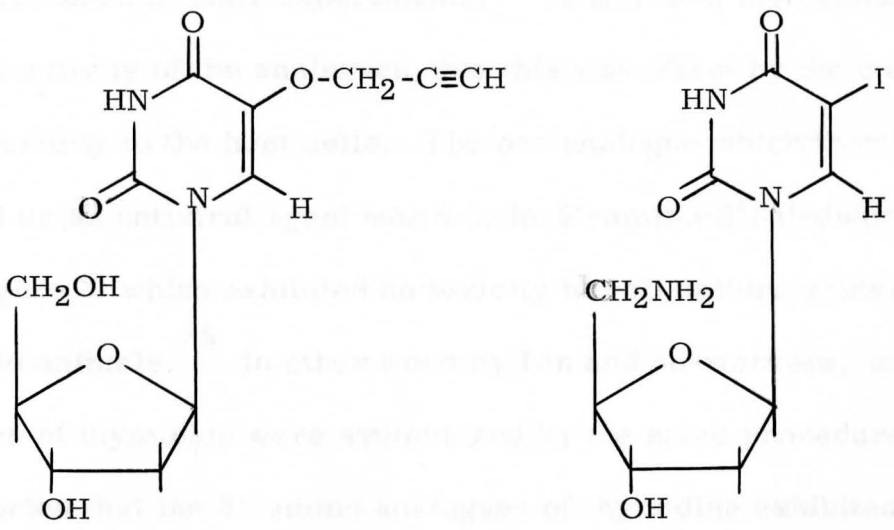


Figure 3. Structure of: a) 5-(2-propynyloxy)-2'-deoxyuridine;
b) 5-iodo-5'-amino-2',5'-dideoxyuridine

activity of 5-butyluridine (Figure 2) which exhibited antiviral activity against DNA and RNA viruses.[34, 41, 42] Muraoka and co-workers even suggested that 5-n-butyluridine could be a stronger and broader antiviral agent than 5-fluoro-2'-deoxyuridine.[34, 41, 42] In 1972, Moffatt produced analogues of 5-butyluridine; 5-butyl-2-thiouridine and 5-butyl-2,4-dithiouridine.[34] However, these thiouracil analogues proved not to be as effective as 5-butyluridine, and the dithiouridine became cytotoxic to the host cells.[34]

In 1978, Lin and co-workers described a novel synthesis and the biological activity of analogues of 5-halo-5'-amino-2',5'-dideoxyribosepyrimidine nucleosides.[35] It was hoped that these new analogues could be used as antiviral agents but would not be as toxic as the 5'-hydroxy analogues.[35] The results of their research showed a complete loss of toxicity to the host Vero cells and the sarcoma 180 cells which were used in their experiments.[35] There was also some loss in antiviral activity of the analogues, but this was offset by the complete loss of toxicity to the host cells. The one analogue which they felt had potential as an antiviral agent was 5-iodo-5'-amino-2',5'-dideoxyuridine (Figure 3) which exhibited no toxicity to cell culture systems as well as to animals.[35] In other work by Lin and co-workers, amino analogues of thymidine were synthesized by the same procedure.[35, 38] Lin reported that the 3'-amino analogues of thymidine exhibited only 62% inhibition and that 3',5' amino analogue had no effect at all.[38] The reasons for the decrease in activity were reported to be under

investigation.[38]

In 1974, a rapid method for the preparation of 5-vinyluracil was reported.[31] Chelton and co-workers demonstrated that 5-vinyluracil could be used by a thymine deficient mutant of Escherichia coli when no thymine was provided in the medium.[31, 43] It has been stated that when 5-vinyluracil is polymerized, it could be used for selective chromatography.[31, 44] In 1975, Bobek used 5-vinyluracil to make 5-vinyluridine and 5-vinyl-2'-deoxyuridine.[33] The antiviral activity of these nucleosides was not investigated, but could be similar to 5-ethyl-2'-deoxyuridine.[33, 39] In 1977, Torrence and co-workers studied the relation of antiviral activity to the steric bulk and configuration of 5-O-alkylated derivatives of 2'-deoxyuridine.[36] In their studies, they found that 5-(2-propynyloxy)-2'-deoxyuridine(Figure 3) was a potent inhibitor of herpes simplex virus.[36]

In light of all the aforementioned compounds, the uniqueness of 5-hydroxymethyluracil (5-HMU) and its derivatives might also prove to be a useful chemotherapeutic drug as a monomer or as a polymer. The nearness of the 5-HMU structure to some of these derivatives might also suggest possible use as an antiviral drug.

The first high-yield synthesis of 5-HMU was reported in 1958 by R. E. Cline and co-workers.[45] The abundance and relative cost to synthesize 5-HMU encouraged the use of the uracil analogue in this study. It has been reported that 5-HMU has been identified in the DNA of a bacteriophage of Bacillus subtilus.[46] It could be possible that such

an analogue of uracil could have use as an antiviral or virostatic drug. The use of 5-HMU as a chemotherapeutic drug could be possible if vital metabolic enzymes would be adsorbed on the polymeric drug while trying to hydrolyze 5-HMU from an ester linkage. Some of the reactions of 5-HMU are shown in Figure 4. Some 5-HMU esters could be readily hydrolyzed by boiling them in water.[45] The hydrolysis of 5-acetoxymethyluracil was rapidly completed in a solution of sodium methoxide and methanol at room temperature.[47] The biological activity of 5-HMU had been examined by incubating radioactive 5-HMU with rat liver slices.[45] In the liver 5-HMU was found to be metabolized to 5-carboxyuracil, 5-hydroxymethyluridine and one other unknown product thought to be a condensation product of 5-HMU and an amino acid.[45]

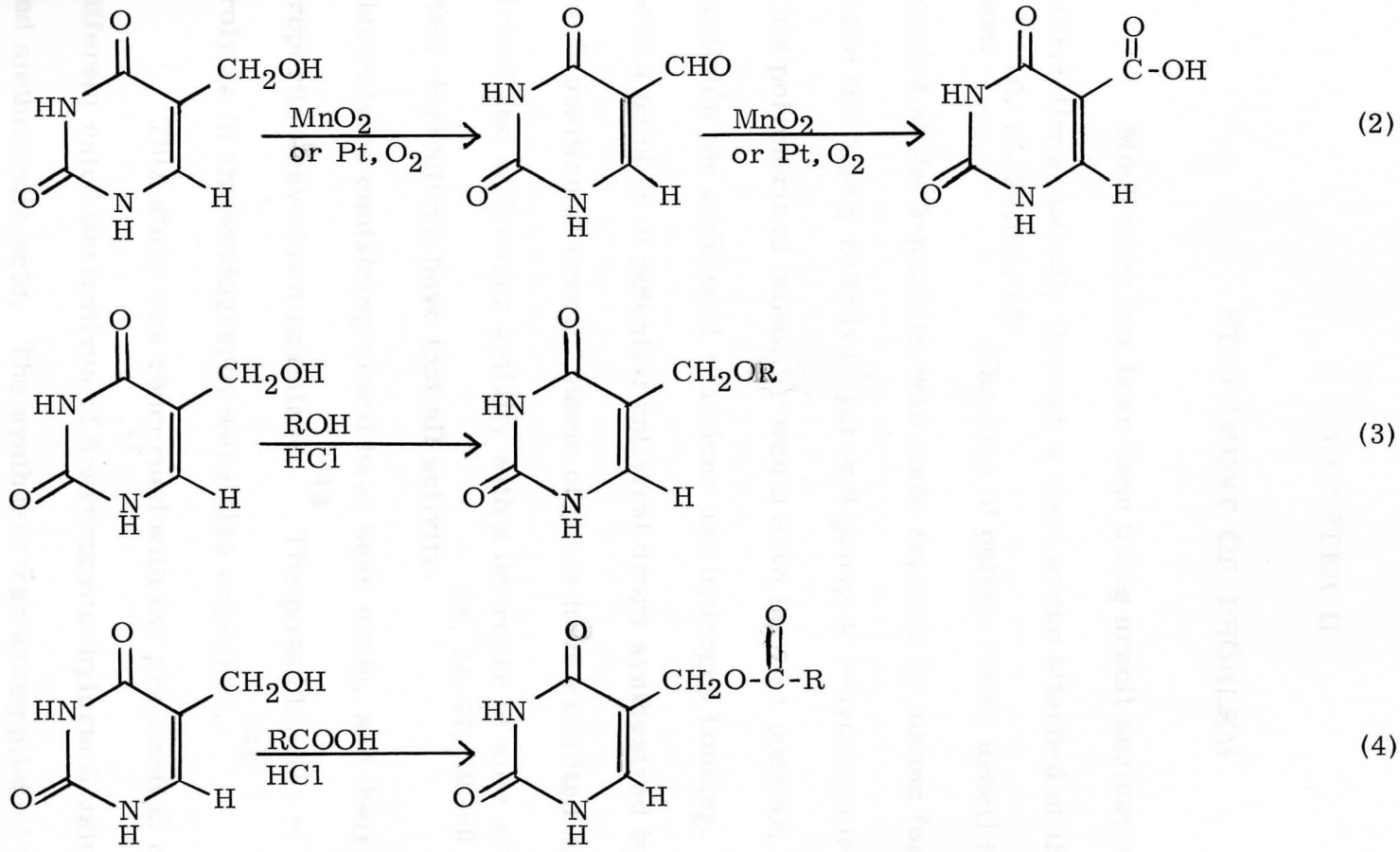


Figure 4. Reactions of 5-HMU: 2) oxidation reactions, 5-HMU, 5-formyluracil and 5-carboxylic acid uracil; 3) etherification and 4) esterification.

CHAPTER II

STATEMENT OF PROBLEM

Much work has been done using uracil derivatives in polymerizations, usually through a vinyl group attached at the N-1 position.[10, 17, 24, 26, 48] The idea of polymerizing uracil through an extension at the 5-position was made feasible by adding formaldehyde to make the highly reactive hydroxyl group of 5-hydroxymethyluracil.[45] This polymerized monomer would have the N-1 position of uracil available for additional reactions and hydrogen bonding. There have been a number of potential antiviral drugs synthesized by reaction at the 5-position of uracil. Some of these have exhibited an increased antiviral and anticancer activity with a decrease of side effects while other derivatives have lost all activity.[31, 34-37, 39, 40] Synthetic polyelectrolytes containing uracil have been made, and their physical properties have been examined.[48] The possible uses of the polyelectrolytes in chromatography were also examined.[48]

This study was concerned with the preparation of two new and different ester derivatives of 5-hydroxymethyluracil using acrylic acid and methacrylic acid. The synthesis was accomplished by condensing water from the alcohol and acid functions. Hydrochloric acid was used as a catalyst to facilitate the condensation esterification reaction. The

two new monomers are shown below in Figure 5.

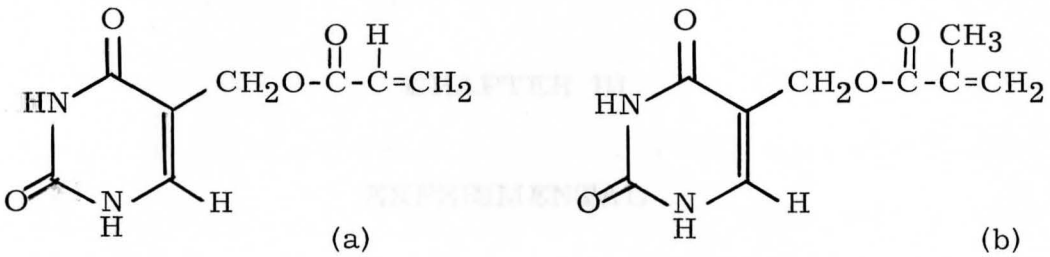


Figure 5. Structure of: a) 5-hydroxymethyluracil acrylate; b) 5-hydroxymethyluracil methacrylate.

The two new monomers were then polymerized in DMSO by free radical polymerization. The catalyst α, α'-azobisisobutyronitrile was used as the free radical initiator.

The synthesis and polymerization of the two new monomers may lead to new uses in treatment of viral disease, cancerous disease and in chromatography as a polyelectrolyte.

CHAPTER III

EXPERIMENTAL

Reagents

The reagents used in this study were of technical grade or better. The ethyl acetate was the only chemical that needed purification. The chemicals used, the grade of the reagent and the manufacturer are shown in Table 1.

Equipment

Most of the equipment used in this study was made of glass with standard 24/40 tapered joints, unless otherwise stated. The cleaning of the glassware was done with soap, rinsed thoroughly with distilled water, then cleaning solution and again rinsed thoroughly with distilled water.

A Buchler flash evaporator was used to evaporate the water from the 5-hydroxymethyluracil and the ethyl acetate from the derivates of 5-hydroxymethyluracil. A Sartorius top-loading balance was used in determining weights of reagents and products. A Sartorius analytical balance was used to determine weights of the polymers used for the dilute solution viscosity studies. The melting points were uncorrected and run on a Mel-Temp melting point apparatus which was made by

Laboratory Devices.

Infrared spectra of the monomers were obtained as KBr discs on a Beckman IR-12. The infrared spectra of uracil, 5-hydroxymethyl-uracil (as KBr discs) and the polymers from films cast on salt plates were obtained using the Beckman IR Acculab-4. NMR spectra were run on a Varian EM360. The viscometer used in dilute solution viscosity studies was a series 100 Cannon-Fenske viscometer. The stopwatch used to time the efflux times for the dilute solution viscosity studies was a Sargent-Welch stopwatch, model S-77440.

TABLE 1

Reagents Used

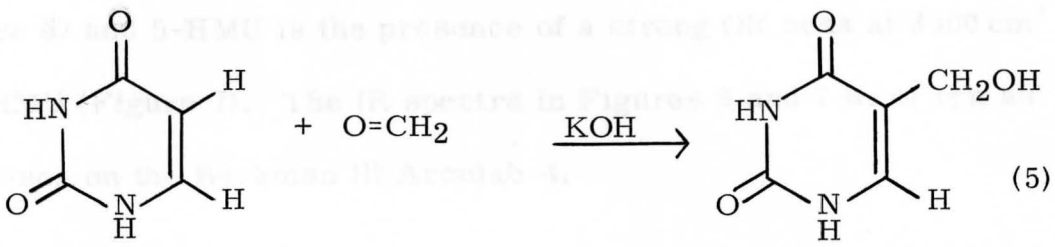
Material	Formula	Grade of Reagent	Manufacturer
Glacial Methacrylic Acid	$H_2C=C(CH_3)COOH$	Technical	Rohm and Haas
Glacial Acrylic Acid	$H_2C=CHCOOH$	Technical	Rohm and Haas
Hydroquinone	$C_6H_6O_2$	Technical	Stansi Scientific Co.
Anhydrous ether	$(C_2H_5)_2O$	A.C.S.	Fisher
Acetone	$(CH_3)_2C=O$	Technical	Baker
Uracil	$C_4H_4N_2O_2$	Practical	Aldrich
Paraformaldehyde	$(CH_2O)n$	Technical	Mallinckrodt
Hydrochloric Acid	HCl	Analytical	Mallinckrodt
Sulfuric Acid	H_2SO_4	Reagent Grade	DuPont
Ethyl Acetate	$CH_3COOCH_2CH_3$	Technical	Baker and Adamson
Potassium Hydroxide	KOH	Analytical	Mallinckrodt
DMSO	$(CH_3)_2S=O$	Spectrophotometric	Eastman
DMSO	$(CH_3)_2S=O$	Analytical	Mallinckrodt

TABLE 1 cont.

Reagents Used

Material	Formula	Grade of Reagent	Manufacturer
Acetic Anhydride	$CH_3CH_2COOC(O)CH_2CH_3$	Reagent Grade	Fisher
AIBN	$(CH_3)_2C(CN)N{=}NC(CN)(CH_3)_2$	Analyzed	Aldrich
Sodium Carbonate	Na_2CO_3	Technical	Fisher
Petroleum Ether		A.C.S.	Fisher
Dowex 50W x 8, H^+form		Analyzed	Baker
Silica Gel 60			EM Reagents
Molecular Sieves			Baker

The Preparation of 5-Hydroxymethyluracil (5-HMU)



(5)

Uracil Formaldehyde 5-HMU

The method of synthesis of 5-HMU used was reported by R. E. Cline, R. M. Fink and K. Fink in 1958.[45] Their procedure utilized base catalyzed formaldehyde addition to uracil as shown in the equation above.[45]

A volume of 500 ml of 0.42 N KOH, 36 g (0.32 moles) of uracil, and 12 g (0.4 moles) of paraformaldehyde were added to a 1000-ml round-bottomed flask and incubated at 50° C for 73 hours. After incubation, the 500 ml solution was diluted with 1400 ml of distilled water. The diluted solution was mixed with 120 g of Dowex 50 (H^+form 100-200 mesh, freshly washed) and filtered to remove the resin. The now slightly acidic filtrate was flash evaporated to a volume of approximately 100 ml from an initial volume of 2000 ml. The concentrated solution was refrigerated to crystallize the crude product which was then filtered off. A volume of 200 ml of water was used in the first recrystallization which yielded 35.3 g (0.25 moles) (78% of theory) crude product. The final recrystallization with acetone and water (2:1) yielded 25.2 g (0.18 moles) (55.5% of theory) microcrystals which decomposed from 260° to

300°C.

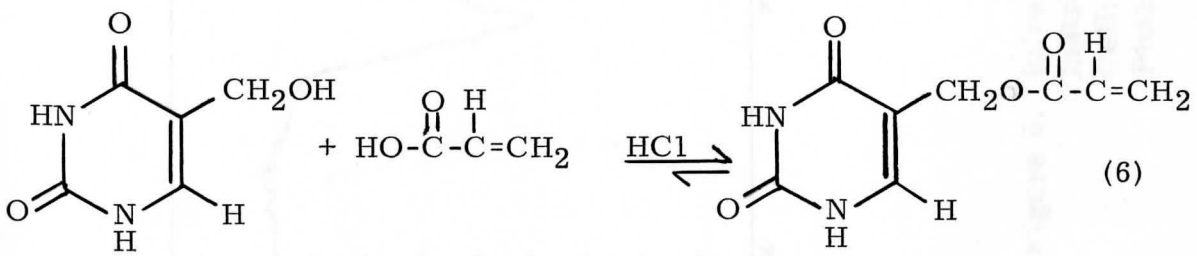
The major difference between the infrared spectra of uracil (Figure 6) and 5-HMU is the presence of a strong OH peak at 3500 cm^{-1} in 5-HMU (Figure 7). The IR spectra in Figures 6 and 7 were run as KBr discs on the Beckman IR Acculab-4.

Purification of Ethyl Acetate

A volume of 500 ml of acetic anhydride and 2 ml of concentrated sulfuric acid was added to 5000 ml of ethyl acetate. The mixture was refluxed overnight and then fractionally distilled the next morning. The collected fraction (76-78°C) was shaken with 20 g/liter of anhydrous Na_2CO_3, then filtered, redistilled and stored over molecular sieves.[49] Ethyl acetate prepared by this procedure was reported to have a purity of 99.7%.[49]

The Preparation and Purification of 5-Hydroxymethyluracil Acrylate (5-HMUA)

The method of preparation of 5-HMUA was esterification catalyzed by concentrated hydrochloric acid as shown in the equation below.



(6)

5-HMU Acrylic Acid 5-HMUA

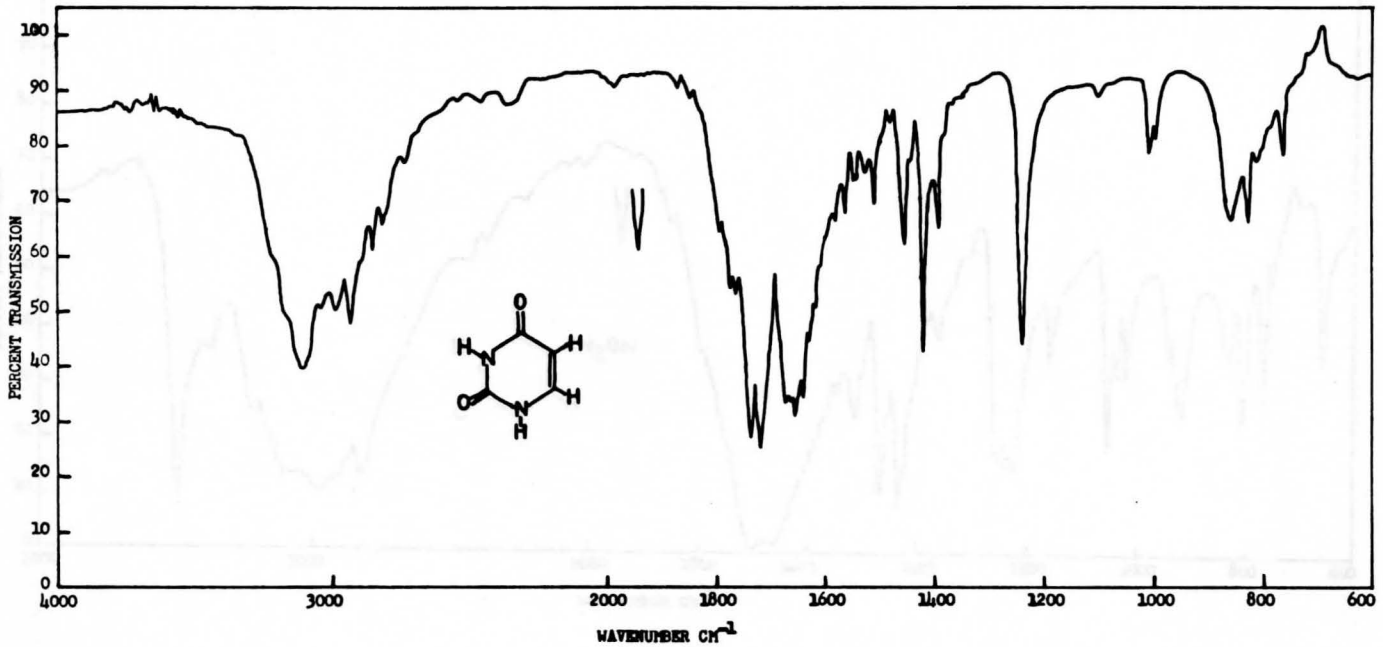


Figure 6. Infrared Spectrum of Uracil
Instrument: Beckman IR Acculab-4
Cell: KBr disc (concentration 1 mg/100 mg KBr)
Phase: Solid

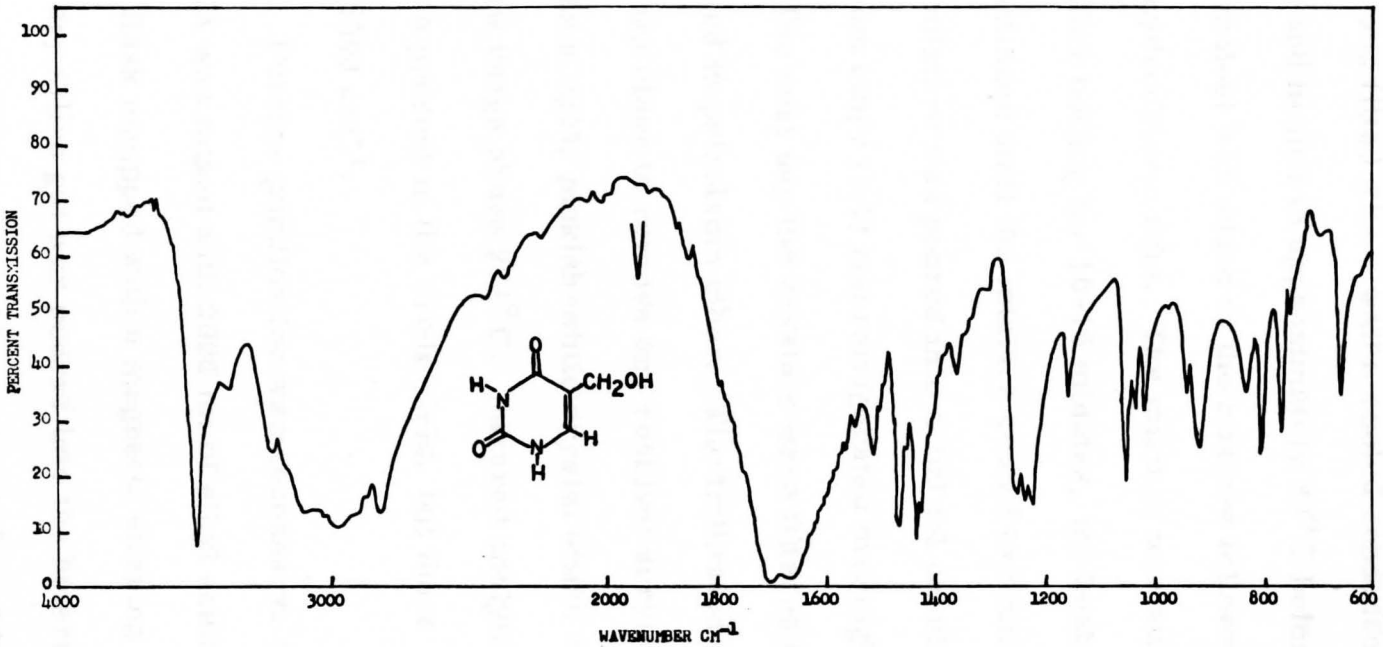


Figure 7. Infrared Spectrum of 5-Hydroxymethyluracil
Instrument: Beckman IR Acculab-4
Cell: KBr disc (concentration 1 mg/100 mg KBr)
Phase: Solid

A volume of 70 ml of acrylic acid (1.02 moles) and 0.13 g hydroquinone(0.0012 moles)(a free radical polymerization inhibitor) were placed in a 250-ml round-bottom flask equipped with a magnetic stirring bar. The flask was placed in a Glas-col heating mantel on a magnetic stirrer and fitted with a water-cooled condensor. The mixture was stirred and heated to approximately 80°C before 3.0 g of 5-HMU (0.021 moles) was added to the mixture followed by 0.1 ml of concentrated hydrochloric acid. The mixture was stirred and heated to boiling. After boiling for 10-15 minutes, the heating was halted and stirring continued until the mixture cooled to room temperature. The cooled mixture was poured into a 700 ml solution of diethyl ether and petroleum ether (1:1) and refrigerated overnight to crystallize the product. The next day the crystals were filtered from the solution and triturated in petroleum ether. The triturated crystals were boiled in petroleum ether to remove any residual acrylic acid. The crude product was a light, pinkish-white crystal which melted over broad temperature range above 284°C. Infrared analysis indicated that the product was present in the crude yield, but there was a small broad shoulder at 3500 cm^{-1}.

Further purification was necessary; therefore, 1.0 g of crude 5-HMUA was mixed with 2000 ml of ethyl acetate in a 2000-ml Erlenmeyer flask equipped with a magnetic stirring bar. After mixing overnight, dry silica gel was poured into the heterogeneous mixture and stirred for no more than 30 minutes before filtration. The filtered

ethyl acetate solution was concentrated to a volume of 100 ml which now contained fine white crystals. These white crystals were dried at 80°C under vacuum and over P_2O_5 overnight. The white crystal product melted from 198°-203°C.

Crude yields were high at 83-95% while recovery of pure product was approximately 65% of the crude product mass. Spectral data of infrared spectroscopy (Figure 8) indicated that the product was formed in that: 1) the OH peak of 5-HMU at 3500 cm^{-1} disappeared; 2) the appearance of a CH in plane deformation of $R_1CH=CH_2$ at 1310 and 1275 cm^{-1}; 3) the appearance of a CH out of plane deformation of $R_1CH=CH_2$ at 995 cm^{-1}.

NMR spectra of a deuterated DMSO solution of the acrylate derivative of 5-hydroxymethyluracil showed similar chemical shifts as the NMR spectra of a CCl_4 solution of methyl acrylate and ethyl acrylate with TMS as the reference. Protons attributed to the uracil portion of the derivative were matched with NMR spectra of uracil and 5-HMU ran in deuterated DMSO with TMS as the reference.

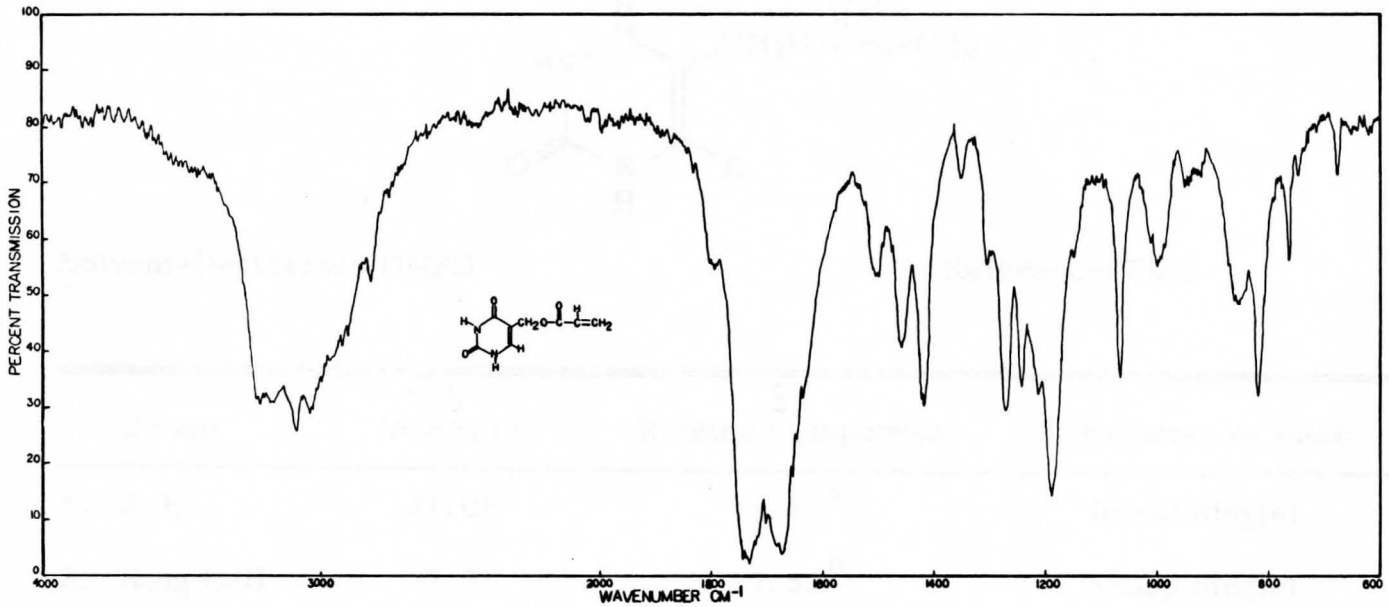
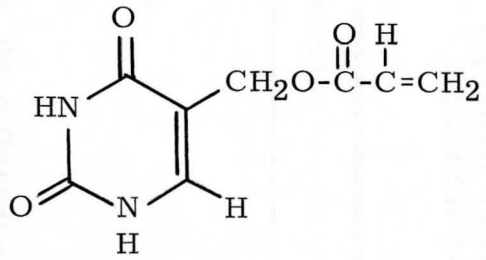


Figure 8. Infrared Spectrum of 5-Hydroxymethyluracil Acrylate
Instrument: Beckman IR-12
Cell: KBr disc (concentration 1 mg/100 mg KBr)
Phase: Solid

Table 2

NMR Data for 5-HMUA



Solvent-Deuterated DMSO Reference-TMS

Group	δ Monomer	δ Related Compounds	Character of Peak	Integral
1. N-H	11.08	11.08 [a]	broad singlet	2
2. Ring C-H	7.52	7.52 [b]	sharp singlet	1
3. $-CH_2O-$	4.70	4.10 [c]	sharp singlet	2
4. $-C(H)=C(H)H$	6.13 5.83	6.20 [c] 5.80 [c]	triplet doublet	3

a=uracil; b=5-HMU; c=ethyl acrylate

In Table 3 the observed elemental analysis (C, H, N, O) of this monomer was compared with the theoretical values for 5-hydroxymethyluracil acrylate and showed good agreement with the theoretical values. The elemental analysis results by M. H. W. Laboratories, Phoenix, Arizona, in conjunction with IR (Figure 8) and NMR spectral data substantiated that the desired product was synthesized.

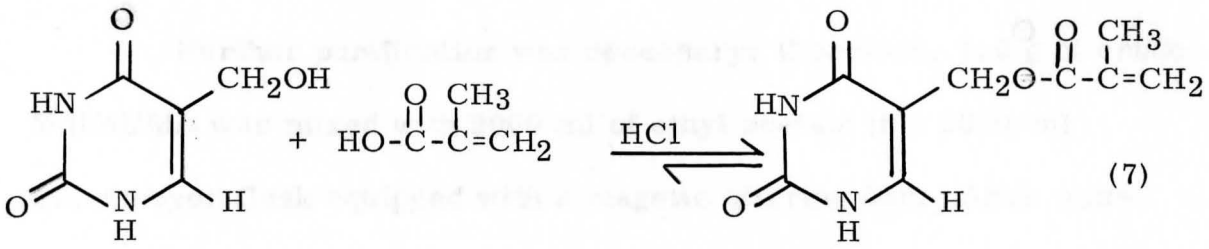
TABLE 3

Elemental Analysis of 5-Hydroxymethyluracil Acrylate
$C_8H_8N_2O$ Calculated versus Elemental Analysis
Found for 5-Hydroxymethyluracil Acrylate

Element	Calculated (%)	Found (%)
C	48.98	48.43
H	4.08	4.26
N	14.29	14.34
O (by difference)	32.65	32.97

The Preparation and Purification of 5-Hydroxymethyluracil Methacrylate (5-HMUMA)

The method of preparation of 5-HMUMA was esterification, catalyzed by concentrated hydrochloric acid, as shown in the equation on the following page.



5-HMU Methacrylic Acid 5-HMUMA

(7)

A volume of 70 ml of methacrylic acid (0.83 moles) and 0.13 g of hydroquinone (0.0012 moles) (a free radical polymerization inhibitor) were added to a 250-ml round-bottomed flask equipped with a magnetic stirring bar. The flask was placed in a Glas-col heating mantle on a magnetic stirrer and fitted with a water-cooled condensor. The mixture was stirred and heated to approximately 80°C; 3.0 g of 5-hydroxymethyluracil (0.021 moles) was then added to the mixture followed by 0.1 ml of concentrated hydrochloric acid. The mixture was stirred and heated to boiling. After boiling 10-15 minutes, heating was discontinued and stirring continued until the mixture cooled to room temperature. The cooled mixture was poured into a 700 ml solution of diethyl ether and petroleum ether (1:1) and refrigerated overnight to crystallize the product. The next day the crystals were filtered from the solution and triturated in petroleum ether. The triturated crystals were boiled in petroleum ether to remove any residual methacrylic acid. The crude product was pinkish-white crystals which melted over a broad temperature range above 280°C. Infrared analysis indicated that the product was present in the crude yield, but there was a small

broad shoulder at 3500 cm^{-1}.

Further purification was necessary; therefore, 1.0 g of crude 5-HMUMA was mixed with 2000 ml of ethyl acetate in a 2000-ml Erlenmeyer flask equipped with a magetic stirring bar. After mixing overnight, dry silica gel was poured into the heterogeneous mixture and stirred for no more than 30 minutes before filtration. The filtered ethyl acetate solution was concentrated to a volume of 100 ml which now contained fine white crystals. These white crystals were dried at 80° C under vacuum and over P_2O_5 overnight. The white crystal product melted from 194°-200° C.

Crude yields were moderately high at 70 to 87% while recovery of pure product was approximately 40% of crude product mass. Spectral data of infrared spectroscopy (Figure 9) indicated formation of desired product by: 1) disappearance of OH peak of the 5-HMU at 3500 cm^{-1}; 2) appearance of peaks at 1425-1403 cm^{-1} of $R_1R_2C{=}CH_2$, CH_2 in plane deformation and 3) the appearance of a peak at 870 cm^{-1} for the out of the plane deformation of the $R_1R_2C{=}CH_2$ group. Nuclear magnetic resonance spectra of a deuterated DMSO solution of the methacrylated derivative of 5-HMU showed similar chemical shifts as the NMR spectra of a CCl_4 solution of butyl methacrylate and methyl methacrylate. Protons attributed to the uracil portion of the derivative were matched with NMR spectra of uracil and 5-HMU in deuterated DMSO with TMS as reference.

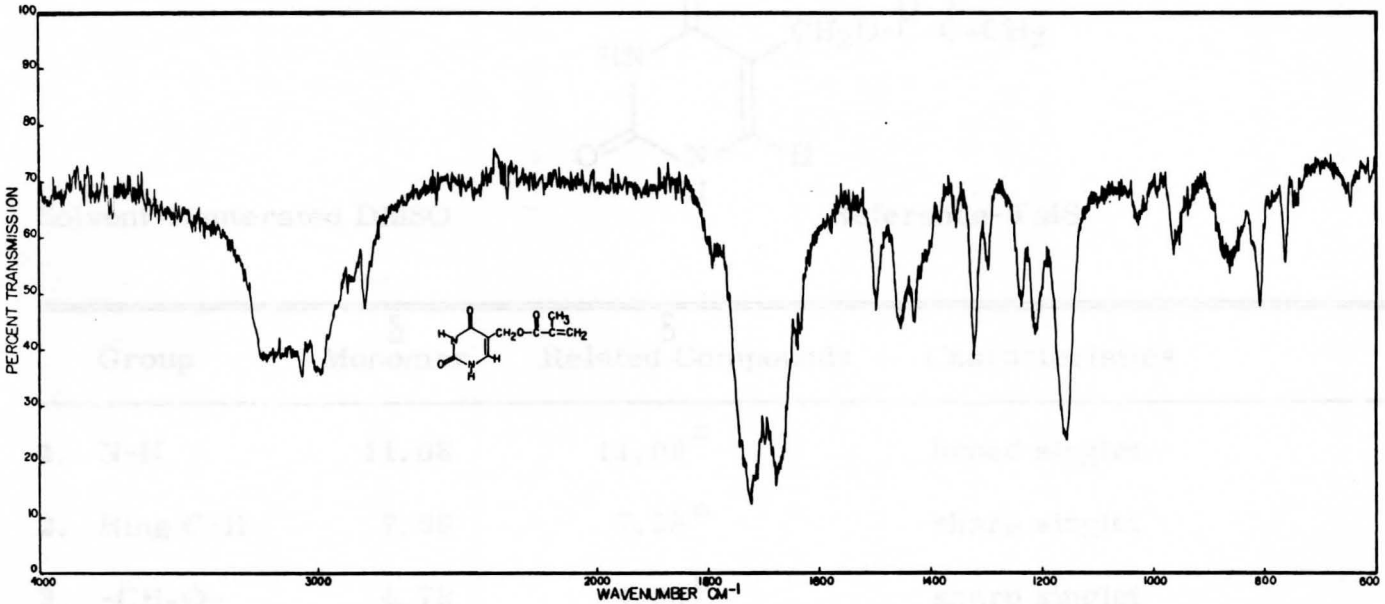
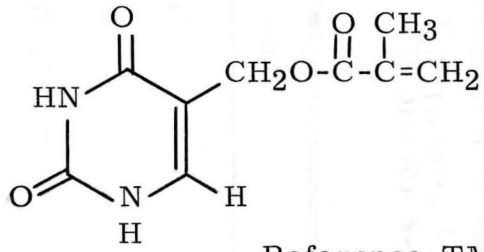


Figure 9. Infrared Spectrum of 5-Hydroxymethyluracil Methacrylate
Instrument: Beckman IR-12
Cell: KBr disc (concentration 1 mg/100 mg KBr)
Phase: Solid

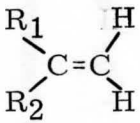
TABLE 4

NMR Data for 5-HMUMA



Solvent-Deuterated DMSO

Reference-TMS

	Group	δ Monomer	δ Related Compounds	Characteristics	Integral
1.	N-H	11.08	11.08 [a]	broad singlet	2
2.	Ring C-H	7.58	7.58 [a]	sharp singlet	1
3.	$-CH_2O-$	4.78	4.30 [b]	sharp singlet	2
4.	$-CH_3$	1.77	1.88 [c]	sharp singlet	3
5.		5.97	5.96 [c]	doublet J value 2 cps	1
		5.66	5.45 [c]	doublet J value 2 cps	1

a=uracil; b=5-HMU; c=butyl methacrylate

In Table 5 the observed elemental analysis (C, H, N, O) of this monomer was compared with the theoretical values for 5-hydroxymethyluracil methacrylate and showed good agreement. The elemental analysis results by M. H. W. Laboratories, Phoenix, Arizona, in conjunction with IR and NMR spectral data substantiated that the desired product was synthesized.

TABLE 5

Elemental Analysis of 5-Hydroxymethyluracil Methacrylate
$C_9H_{10}N_2O_4$ Calculated versus Elemental Analysis
Found for 5-Hydroxymethyluracil Methacrylate

Element	Calculated (%)	Found (%)
C	51.43	50.90
H	4.80	4.96
N	13.33	13.38
O (by difference)	30.44	30.76

Procedure for Free Radical Polymerization of 5-HMUA

A volume of 10 ml of DMSO was pipetted into the reaction vessel. The reaction vessel was then placed in an oil bath at 80° C and purged with dry N_2 to remove any O_2. The 5-HMUA monomer was added to make a 10% by weight of DMSO solution (1.0 g 5-HMUA, 5.1×10^{-3} moles). The α,α'-azobisisobutyronitrile (AIBN) was then

added (1.0 mole% based on the monomer) (0.0084 g AIBN, 5.1×10^{-5} moles). The reaction vessel was sealed and allowed to stand at 80°C for 24 hours after which polymerization was halted by removing the reaction vessel from the oil bath.

The reaction solution was poured into 500 ml of methanol which precipitated white powdery crystals from the solution. Infrared spectroscopic studies (Figure 10) showed the absence of absorbance bands at 1310, 1275 and 995 cm^{-1}, thus indicating no sign of the monomer. By the disappearance of these bands, the polymer was assumed to be pure. The polymer softened and decomposed from 242° to 336°C.

Procedure for the Free Radical Polymerization of 5-HMUMA

A volume of 10 ml of DMSO was pipetted into the reaction vessel. The reaction vessel was then placed in an oil bath at 80°C and purged with dry N_2 to remove any O_2. The 5-HMUMA monomer was added to make a 10% by weight of DMSO solution: (1.0 g 5-HMUMA, 4.9×10^{-3} moles). AIBN was then added (1.0 mole% based on the monomer) (0.0080 g AIBN, 4.9×10^{-5} moles). The reaction vessel was sealed and allowed to stand at 80°C for 108 hours after which polymerization was halted by removing the reaction vessel from the oil bath.

The reaction solution was poured into 500 ml of methanol which precipitated white powdery crystals from solution.

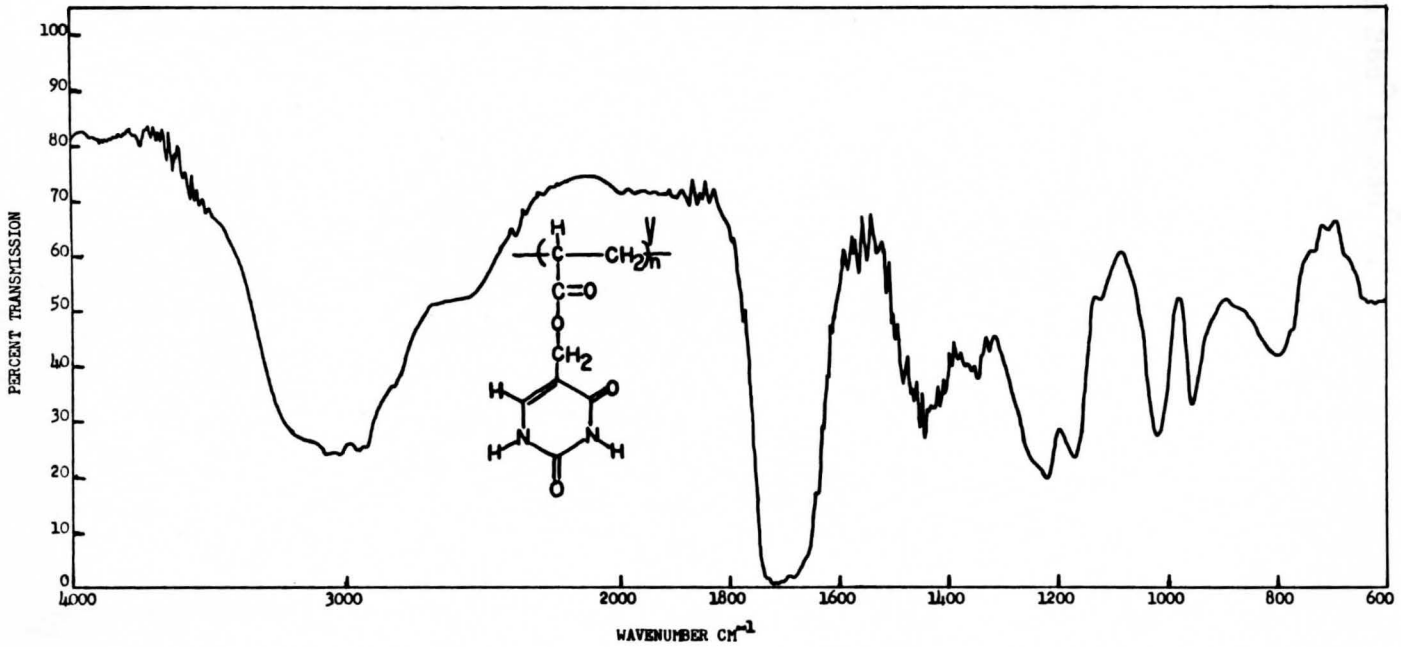


Figure 10. Infrared Spectrum of Poly-5-Hydroxymethyluracil Acrylate
Instrument: Beckman IR Acculab-4
Cell: Film cast on salt plate
Phase: Solid

Infrared spectroscopic studies (Figure 11) showed the absence of peaks at 1425, 1403 and 870 cm^{-1}, thus indicating no sign of monomer presence. By the disappearance of these absorption bands, the polymer was assumed to be pure. The polymer softened and decomposed from 266° to 336° C.

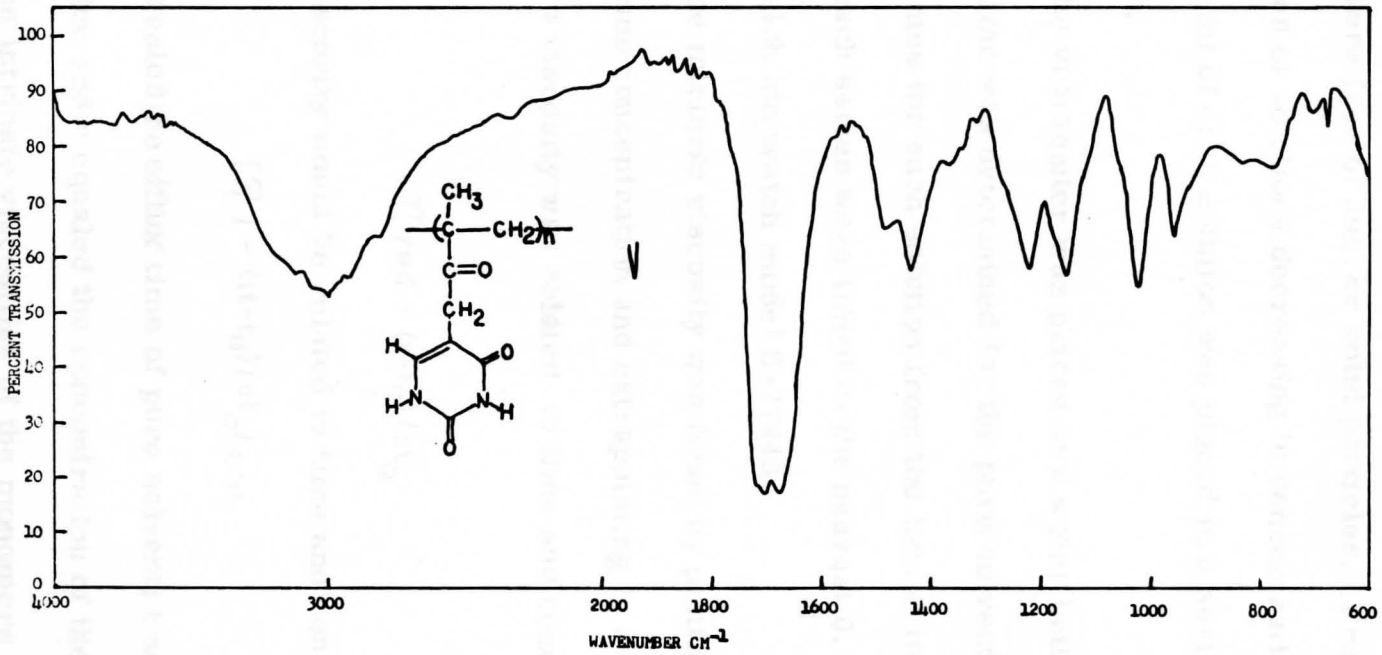


Figure 11. Infrared Spectrum of Poly-5-Hydroxymethyluracil Methacrylate
Instrument: Beckman IR Acculab-4
Cell: Film cast on salt plate
Phase: Solid

Intrinsic Viscosity by Dilute Solution Viscosity Studies

Dilute solution viscosity studies were performed on the monomers and polymers. A stock solution was made for each monomer and polymer using DMSO as the solvent. Care was taken to insure that solutions were free of dust or solid particles. From each stock solution a series of solutions decreasing in concentration was prepared. Exactly 10 ml of each solution was placed in a series 100 Cannon-Fenske viscometer.

The viscometer was placed in a water bath at $30.0^{\circ}C \pm 0.1^{\circ}C$. The eflux time was determined for the pure solvent before each run. The flow times for each solution from the lowest to the highest concentration in each series were timed to the nearest 0.1 second using a Sargent-Welch stopwatch model S-77440.

The intrinsic viscosity was found by plotting reduced viscosity (ηred) versus concentration and extrapolating to zero concentration. The reduced viscosity was related to time and concentration by the equation

$$\eta \text{ red} = (t-t_o)/ct_o \qquad (8)$$

Intrinsic viscosity would be related to time and concentration by the equation

$$[\eta] = ((t-t_o)/ct_o)_{c=o} \qquad (9)$$

where t_o equaled the efflux time of pure solvent; t equaled efflux time of the solution and c equaled the concentration of the solution.

The intrinsic viscosities of the monomers and polymers were

found and have been reported in Table 6. The reduced viscosities for the monomers and polymers were calculated and have been reported in Tables 7-10.

TABLE 6

Intrinsic Viscosity

Compound	$[\eta]$
5-HMUA	3.2
5-HMUMA	3.3
Poly-5-HMUA	8.9
Poly-5-HMUMA	15.0

TABLE 7

Reduced Viscosity by
Dilute Solution Viscosity Studies of
5-HMUA

Concentration g/ml x10^4	Efflux Time in Seconds	η_{red}
0	115.9	----
11.1	116.7	6.20
22.1	116.9	3.90
36.6	117.4	3.54
55.3	118.9	4.68
74.2	118.7	3.26
88.6	119.6	3.60
108.5	121.7	4.61

TABLE 8

Reduced Viscosity by
Dilute Solution Viscosity Studies of
5-HMUMA

Concentration g/ml x10^4	Efflux Time in Seconds	η_{red}
0	116.8	----
10.8	117.8	7.93
21.8	118.0	4.71
35.9	118.4	3.82
72.9	120.1	3.88
87.0	121.1	4.23
107.4	122.1	4.23

TABLE 9

Reduced Viscosity by
Dilute Solution Viscosity Studies of
Poly-5-HMUA

Concentration g/ml x10^4	Efflux Time in Seconds	η_{red}
0	117.2	----
9.76	117.4	17.5
19.4	118.9	7.5
31.7	120.6	9.2
48.4	122.6	9.5
65.2	124.3	9.3
76.8	126.4	10.2

TABLE 10

Reduced Viscosity by
Dilute Solution Viscosity Studies of
Poly-5-HMUMA

Concentration g/ml x10^4	Efflux Time in Seconds	η_{red}
0	117.1	----
11.2	119.1	15.2
21.9	121.2	16.0
36.7	124.3	16.8
54.7	128.4	17.6
73.3	132.8	18.3
86.5	135.1	17.8

CHAPTER IV

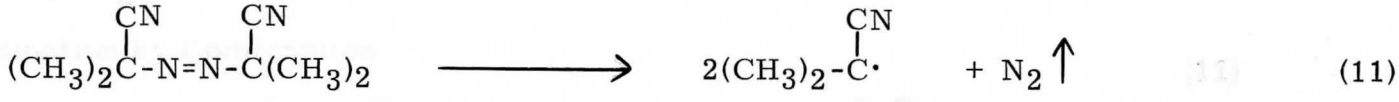
RESULTS AND DISCUSSION

The first step in this work was to make 5-HMU by the method described by R. E. Cline and co-workers.[45] The method was very easily followed and led to modest yields of 5-HMU. The confirmation of structure for 5-HMU was by infrared spectroscopy and melting point. It was felt that since the original experiments confirmed the synthesis of 5-HMU by elemental analysis, IR, UV, and chromatography, the confirmation of our synthesis of 5-HMU by IR and melting point was sufficient.[45] The next step was to esterify the 5-HMU with acrylic or methacrylic acid. Hydrochloric acid was used as the catalyst for these reactions. The acrylic and methacrylic acids would polymerize quite readily under the conditions of the esterification reaction; therefore, hydroquinone was added which effectively cut down on free radical polymerization. The results of the esterification yielded two different esters whose structures were confirmed by IR, NMR, and elemental analysis. However, the crude product yielded a melting point that was not in line with our estimation of what it should be. Infrared analysis indicated that the product was present in the crude yield, but there was a small broad shoulder at 3500 cm^{-1}. A slight pinkish tint also indicated that the product was not pure. A literature search[33]

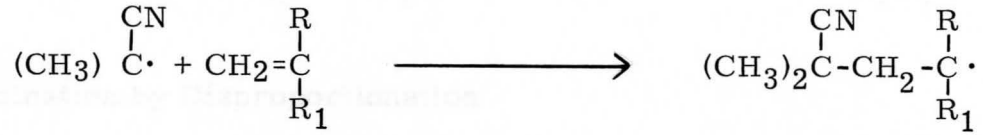
and solvent study indicated that ethyl acetate might be a desirable solvent for purification in that: 1) during flash evaporation low boiling temperatures were obtained; 2) 5-HMU was held stationary in silica gel TLC studies using ethyl acetate as the moving solvent; 3) ethyl acetate was available in large quantities; and 4) ethyl acetate was used to purify a compound very similar to ours.[33] The acrylic and methacrylic acids were removed in the first steps of purification by the wash with petroleum ether. The method of purification of the monomer was then developed which called for the 5-HMU impurities to be removed from the ethyl acetate solution by adsorbing them on silica gel. The monomer was then crystallized from the ethyl acetate solution after flash evaporation of most of the solvent. Where there once was a small shoulder at 3500 cm^{-1} in the IR spectrum of the crude products, there was now essentially no indication of a shoulder on the scan at 3500 cm^{-1} thus indicating that the unreacted 5-HMU was removed.

Once the monomers were purified, successful polymerization was accomplished using the free radical initiator, α,α'-azobisisobutyronitrile (AIBN). The mechanism for polymerization and termination can be seen in Figure 12. The polymerization of 5-HMUMA ran for 108 hr. while the polymerization of 5-HMUA only ran for 24 hr. which probably accounted for the difference in intrinsic viscosity of the two polymers. The longer the polymerization the higher the intrinsic viscosity which is directly proportional to average molecular weight by the

Initiation:

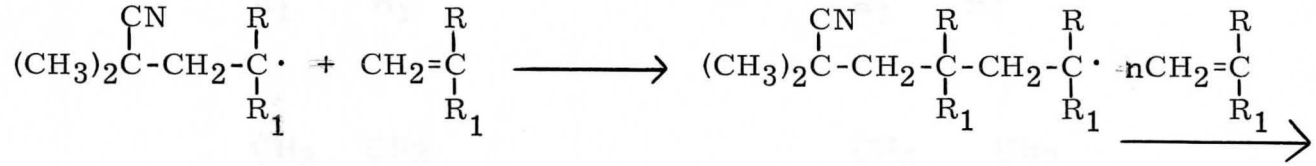


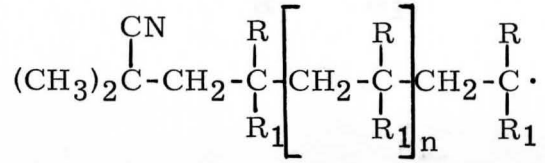
(11)



(12)

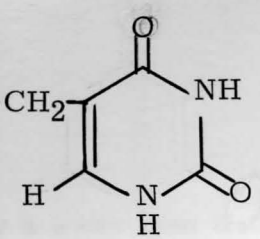
Propagation:





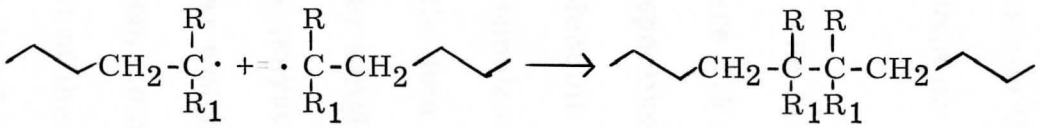
(13)

Figure 12. Mechanisms for Polymerization and Termination: R=-H, $-CH_3$; R_1=



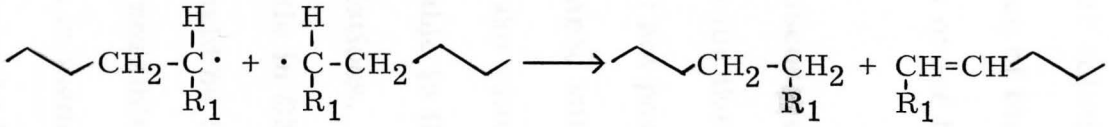
Chain Termination:

A) Termination by Combination

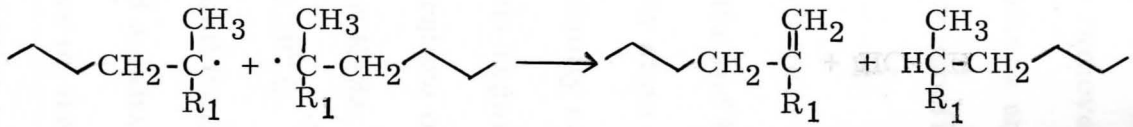


(14)

B) Termination by Disproportionation



(15)



(16)

Figure 12. (continued) To simplify the diagram, the polymer chain was represented by a wave line with only the portions taking part in the reaction shown.

Mark-Houwink equation:

$$[\eta]=K\overline{M}^{a} \qquad (10)$$

where K and a are constants.[50] The dilute solution viscosity studies indicated that the monomers had actually polymerized. It was necessary to filter the polymer solutions to remove solid particles in the solution since the solution of the monomers and the polymers had to be free of dust or solids in order for the viscosity efflux times to be correct.

The intrinsic viscosities which were observed for these polymers were 8.9 and 15.0 for the acrylate and the methacrylate derivatives respectively. It is not possible to state with absolute certainty to what molecular weight these values actually correspond, but we can make estimates if we make assumptions regarding the values of K and a. Very little data is available in the literature on DMSO solution viscosity-molecular weight correlations. Values $K=32.1\times10^{-5}$ and a=0.75 are given for polyacrylonitrile in DMSO at 20^{o}C.[51] Table 11 shows the molecular weight that could be calculated from these K and a values. In addition, some other possible K and a values are used here to indicate the effect of the changes in these values on the molecular weight. The actual molecular weights could be anywhere between 7.3×10^{5} and $230,000\times10^{5}$ but clearly, the materials are polymeric.

TABLE 11

Molecular Weight Approximations With
Some Estimated Values of K and a

$[\eta]$	K x 10^5	a	M x 10^{-5}
8.9	32.1	.75	8.4
8.9	20.0	.75	16
15.0	60.0	.75	7.3
15.0	32.1	.75	17
15.0	20.0	.75	32
15.0	10.0	.75	80
15.0	10.0	.50	230000
15.0	5.0	.85	28
15.0	5.0	.80	70
15.0	5.0	.75	200
15.0	5.0	.70	670
15.0	5.0	.65	2700
15.0	1.0	.75	1700

CHAPTER V

SUMMARY

In this study two new polymerizable derivatives of 5-hydroxymethyluracil were synthesized and viscosity studies were made on the polymers. The compounds synthesized were 5-hydroxymethyluracil acrylate and 5-hydroxymethyluracil methacrylate. It was hoped that the new compounds and polymers would find use in the chemotherapeutic polymer field due to the unique structure of the compounds and polymers.

Uracil was reacted with formaldehyde to yield 5-hydroxymethyluracil because the reactions with acrylic and methacrylic acid would be a very straight-forward simple esterification. The ester derivatives were polymerized in DMSO under a nitrogen atmosphere using AIBN at a concentration of 1 mole percent based on moles of monomer. Both the acrylate and methacrylate monomers polymerized well and the degree of polymerization appears to be related to the time of polymerization. Both polymers were easily recovered from DMSO by precipitating them with methanol. The dilute solution viscosity studies were performed using DMSO as the solvent and a Cannon-Fenske viscometer.

The ester derivatives were analyzed by IR, NMR, and elemental analysis. The polymers were analyzed by IR which showed no

presence of the acrylate or methacrylate double bond, while the N-H bands (3200 to 3000 cm^{-1}), the C=O (1720 cm^{-1}) and the amide-I band of secondary amines (1675 cm^{-1}) were clearly visible in both polymers. The melting points of the product polymers increased and became more of a decomposition range rather than the sharp melting point which the monomers exhibited. Infrared spectroscopic data of the monomers was discussed earlier in the experimental section.

The solubility of the monomers and polymers were surprisingly low in ethyl acetate which necessitated large volumes of ethyl acetate in the purification procedure. The solvents in which the monomers were soluble were highly polar with high boiling points.

Future studies should consider the copolymerization of these monomers with monomers containing solubilizing and/or directing groups. In addition, the biological activity of these materials should be studied.

REFERENCES

1. "Polymers Put Cancer Drugs on Target," Chemical Week, April 26, (1978), 45.
2. G. F. Rowland, G. J. O'Neill and D. A. L. Davies, Nature, 255, 487 (1975).
3. C. G. Gebelein, Polymer News, 4, 163 (1978).
4. H. G. Batz, "Polymeric Drugs," Advances in Polymer Science, 23, 25, Springer-Verlag, New York, 1977.
5. C. A. Nichol, Cancer, 40, 519 (1977).
6. V. Chytrý, A. Vrána and J. Kopeček, Makromol. Chem., 179, 329 (1978).
7. C. Pinazzi, J. C. Rabadeau and A. Pleurdeau, European Polymer J. ,14, 205 (1978).
8. W. L. Chick, J. J. Perna, V. Lauris, D. Low, P. M. Galletti, G. Panol, A. D. Whittemore, A. A. Like, C. K. Colton and M. J. Lysaght, Science, 19, 780 (1978).
9. H. Ringsdorf, J. Polymer Sci., Symposium No. 51, 135 (1975).
10. L. G. Donaruma and Otto Vogl, Polymeric Drugs, Academic Press, New York, N. Y., 1978.
11. M. Lieflander and F. J. Strecker, Hoppe-Seylers, Z. Physiological Chem., 347, 268 (1966).
12. H. G. Batz, V. Hoffmann and H. Ringsdorf, Makromol. Chem., 169, 323 (1973).

13. H. G. Batz, G. Franzmann and H. Ringsdorf, Angew. Chem., 24, 1189 (1972).

14. H. G. Batz, G. Franzmann and H. Ringsdorf, Makromol. Chem., 172, 27 (1973).

15. F. Danusso and P. Ferruti, J. Polymer Sci.: Polymer Letter Ed., 15, 17 (1977).

16. C. Pinazzi, J. C. Rabadeux and A. Pleurdeau, J. Polymer Sci.: Chem. Ed., 15, 1319 (1977).

17. K. Takemoto, J. Polymer Sci.: Symposium, No. 55, 105 (1976).

18. H. Kaye, J. Polymer Sci.: Polymer Letter Ed., 1, 7, 1 (1969).

19. H. Kaye, Macromolecules, 4, (2), 147 (1971).

20. H. Kaye, U. S. Patent 3,824,225. July 16, 1974. Chem. Abstract, 81, P170236W (1977).

21. H. Kaye, J. Amer. Chem. Soc., 92, 5777 (1970).

22. N. Udea, K. Nakatatani, K. Kondo, K. Takemoto and M. Imoto, Makromol. Chem., 134, 305 (1970).

23. C. G. Gebelein and R. M. Morgan, Polymer Preprints, 18, 811 (1977).

24. C. G. Gebelein, R. M. Morgan and R. Glowacky, Polymer Preprints, 18, 513 (1977).

25. C. G. Gebelein and R. Glowacky, Polymer Preprints, 18, 806 (1977).

26. C. G. Gebelein and T. M. Ryan, Polymer Preprints, 19, 538 (1978).

27. C. G. Gebelein and M. W. Baig, Polymer Preprints, 19, 543 (1978).

28. R. M. Morgan, Preparation of Some Potentially Polymerizable Derivatives of Uracil and 5-Fluoruracil, Master's Thesis, Youngstown State University, August, 1976.

29. R. Glowacky, The Synthesis and Attempted Polymerization of a Potential Antineoplastic Agent, Master's Thesis, Youngstown State University, June, 1976.

30. M. W. Baig, The Synthesis and Polymerization of a Vinyl Derivative of 6-Methylthiopurine, Master's Thesis, Youngstown State University, June, 1978.

31. A. S. Jones, G. P. Stephenson and R. T. Walker, Nucleic Acid Research, 1, 105 (1974).

32. K. K. Gauri, G. Malorny and W. Schiff, Chemotherapy, 14, 129 (1969).

33. R. A. Sharma and M. Bobek, J. Org. Chem., 40, 2377 (1975).

34. E. H. Hamamura, K. Sato and J. G. Moffatt, J. Medicinal Chem., 15, 1061 (1972).

35. T. Lin and W. H. Prusoff, J. Medicinal Chem., 21, 106 (1978).

36. P. F. Torrence, J. W. Spencer, A. M. Bobst, J. Descamps and E. De Clerq, J. Medicinal Chem., 21, 228 (1978).

37. C. K. Chu, U. Reichman, K. A. Wantanebe and J. J. Fox, J. Medicinal Chem., 21, 96 (1978).

38. T. Lin and W. H. Prussoff, J. Medicinal Chem., 21, 109 (1978).

39. M. Swierkowski and D. Shugar, J. Medicinal Chem., 12, 533 (1969).

40. T. K. Bradshaw and D. W. Hutchinson, Chem. Soc. Revs., 6, 43 (1977).

41. M. Muraoka, A. Takada and T. Ueda, Chem. Pharm. Bull., 18 (2), 26 (1970).

42. M. Muraoka, Y. Seto and T. Ueda, Chem. Pharm. Bull., 18 (2), 269 (1970).

43. E. T. J. Chelton, C. H. Evans, A. S. Jones and R. T. Walker, Biochim. Biophys. Acta., 312, 38 (1973).

44. J. D. Fissekis and F. Sweet, J. Org. Chem., 38, 264 (1973).

45. R. E. Cline, R. M. Fink and K. Fink, J. Amer. Chem. Soc., 81, 2521 (1959).

46. A. White, P. Handler and E. L. Smith, Principles of Biochemistry. 5th Ed. p. 205, McGraw-Hill Book Company. New York, 1973.

47. D. V. Santi and A. L. Pogolotti, Jr., Tetrahedron Letters, 1968, 6159.

48. T. Okubo and N. Ise, "Synthetic Polyelectrolytes," Advances in Polymer Science, 25, 135, Springer-Verlag, New York, 1977.

49. A. I. Vogel, A Textbook of Practical Organic Chemistry. 3rd Ed., p. 174, John Wiley and Sons Inc., New York, 1966.

50. M. C. Stevens, Polymer Chemistry an Introduction. Addison-Wesley Publishing Company, Inc. Reading, Mass., 1975.

51. J. Brandrup and E. H. Immergut, Polymer Handbook. John Wiley and Sons. New York, 1966. p. IV-23.