

Copolymerization of Vinylene Carbonate with Vinyl Thiolacetate and *N,N,N*-Triethyl-*N*-[2-(Methacryloxy)ethyl]ammonium Iodide with 4-Vinylpyridine*†

C. G. OVERBERGER, H. BILETCH,‡ and R. G. NICKERSON, *Department of Chemistry, The Polymer Research Institute, Polytechnic Institute of Brooklyn, N. Y.*

INTRODUCTION

A study of the reactions of polymers which contain nucleophilic groups with phosphorus halides such as diisopropyl phosphorofluoridate has been initiated. Copolymers with thiol and hydroxy groups and amine and quaternary nitrogen sites have been prepared. The reaction of these polymers with phosphorus halides and the related question of their ability to reactivate the enzyme acetylcholinesterase, which has been inactivated by reaction with a phosphorus halide of the above type, is of major interest.¹⁻³ Accordingly, vinyl thiolacetate was copolymerized with vinylene carbonate and *N,N,N*-triethyl-*N*-[2-(methacryloxy)ethyl]ammonium iodide with 4-vinylpyridine and the reactivity ratios determined.

The vinyl thiolacetate-vinylene carbonate copolymer was hydrolyzed to give a copolymer (with sulfhydryl groups) which was found to be readily converted to a crosslinked structure in the presence of air. The soluble sulfhydryl polymer has given promising results as a prophylactic for ionizing radiation. This phase of the study is being extended and will be reported elsewhere.

EXPERIMENTAL

Purification of Reagents

Benzene, acetone, and methanol (C. P. grades) were dried and distilled before use. Ether (C. P., Mallinckrodt Co.) was used without further purification. Methyl methacrylate (Rohm and Haas Co.) was distilled and the fraction of b.p. 100–101°/757 mm. was used. 4-Vinylpyridine (Reilly Tar Corp.) was fractionally distilled and a middle fraction of b.p. 40–41°/1.4 mm., n_D^{25} 1.5551, was taken.

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† This is the fifteenth in a series of papers on new monomers and polymers. For the previous paper in this series, see C. G. Overberger and F. W. Michelotti, *J. Am. Chem. Soc.*, in press.

‡ Present address: Central Research and Engineering Division, Continental Can Company, Chicago, Illinois.

Preparation of Monomers

Vinylene Carbonate. The procedure of Newman and Addor⁴ was followed. Chlorination of ethylene carbonate (300 g., 3.41 moles), controlled by a Fisher-Porter flowmeter (5 ml./min.), using a 3650 Å. ultraviolet light source afforded a reaction temperature of 63–70° and an uptake of 117 g. of chlorine in 44 hours. Fractional distillation gave 273 g. (65%) of monochloroethylene carbonate, b.p. 93–94°/8 mm., n_D^{25} 1.4537, in agreement with the previously reported results.⁴

Monochloroethylene carbonate (273 g., 2.23 moles) was allowed to react with 226 g. (2.24 moles) of triethylamine in a liter of ether,⁴ giving 59.5 g. (31%) of vinylene carbonate, b.p. 74°/33 mm., n_D^{25} 1.4218, after a second fractionation (one distillation 59%, b.p. 73–74°/32 mm., n_D^{25} 1.4190).⁴

Vinyl Thioloacetate. To 150 g. (1.92 moles) of 2-mercaptoethanol in 303.6 g. (3.84 moles) of pyridine was added 304.5 g. (3.84 moles) of acetyl chloride, dropwise, over 6 hours according to a procedure similar to that of Rojahn and Lemme,⁵ while the temperature was kept below 40°. After 15 hours, 1500 ml. of water was added cautiously to the mass, the mixture was stirred for 15 minutes, and the yellow oily layer was separated, washed with two 200-ml. portions of water, dissolved in 250 ml. of ether, and dried over anhydrous magnesium sulfate. From the ether solution was obtained 179 g. (58%) of 2-acetoxyethyl thioloacetate, b.p. 92–93°/9 mm., n_D^{25} 1.4706, d_4^{25} 1.142, molecular refraction 39.54 (calculated) and 39.70 (found) (b.p. 102–104°/15 mm., no refractive index)⁶ (no yield reported, d_4^{25} 1.140, n_D^{25} 1.4700).⁵

According to a modified procedure of Brubaker,⁷ 179 g. (1.10 moles) of 2-acetoxyethyl thioloacetate was pyrolyzed at 508–514° in a 1.4 × 30 cm. tube packed with cut glass tubing (5 mm. inner diameter) under an atmosphere of nitrogen at the rate of 60 g./17 min. The condensate was flash distilled at atmospheric pressure and the fraction b.p. 98–183° was separated. The residue was again pyrolyzed by the same procedure. The condensate was again flash distilled and the fraction b.p. 98–138° was combined with the similar fraction from the first distillation. The combined fractions, impure vinyl thioloacetate, were dissolved in 150 ml. of ether and shaken cautiously with a 10% sodium carbonate solution until neutral. This was followed by successive washings with 10% sodium chloride solution and two portions of water. After drying with magnesium sulfate the ether solution was fractionated at atmospheric pressure. A second distillation gave 21.3 g. (21% based on starting material and not including recovered diester), n_D^{25} 1.4908, b.p. 115°/760 mm., (35% based on conversion, b.p. 120–122°, n_D^{25} 1.4901).⁷

***N,N*-Triethyl-*N*-[2-(methacryloxy)ethyl]ammonium Iodide.** The desired 2-(*N,N*-diethylamino)ethyl methacrylate was prepared as previously described by ester interchange except that a Dean-Stark trap was used to remove the methanol-methyl methacrylate azeotrope.⁹

To 63.0 g. (0.34 mole) of 2-(*N,N*-diethylamino)ethyl methacrylate in a one-

neck flask fitted with a condenser was added 265 g. (1.70 moles) of ethyl iodide and 0.20 g. of hydroquinone. After refluxing two hours, 100 ml. of benzene was added to the precipitated product and the mixture was allowed to stand overnight. The solid was filtered, washed several times with 100 ml. portions of dry ether, and dissolved in 100 ml. of dry methanol. The solution was made faintly cloudy by the addition of ether and was stored in the ice box for 24 hours. The white platelets that had precipitated (84 g.) were filtered off and recrystallized in the same manner to yield 76 g. (65.5%) of product, m.p. 103–104° (dec).

ANALYSIS: *Calcd.* for $C_{12}H_{24}O_2NI$: I, 37.19. *Found*: I, 36.98.

Copolymerization Experiments

Vinylene carbonate and vinyl thiolacetate were copolymerized at 60.0° in benzene solution at monomer concentrations of 5–10 moles per liter using 0.1–0.2 mole per cent concentration of 2,2'-azobisisobutyronitrile as catalyst. The polymerizations were carried out in sealed glass tubes that had been degassed to remove oxygen. Table I summarizes these experiments.

N,N,N-Triethyl-*N*-[2-(methacryloxy)ethyl]ammonium iodide and 4-vinylpyridine were polymerized under similar conditions, in acetone, at monomer concentrations 1–2 moles per liter and at 0.2–0.3 mole per cent catalyst concentrations. Table II includes these data.

Hydrolysis of Vinyl Thiolacetate-Vinylene Carbonate Copolymers

In initial experiments alkali-water in combination with a variety of solvents such as dimethyl formamide, acetone, methanol, or dioxane was heated in a nitrogen atmosphere with the vinyl thiolacetate-vinylene carbonate copolymer for periods of time extending from 3 hours to 4 days. In all cases products were obtained which rapidly became insoluble in all organic solvents and alkali on standing. Reductive hydrolysis conditions did not give different results. Ultimately aqueous alkali with extensive precautions against air oxidation gave products that could be redissolved in base. Typical experiments will be described.

(1) Use of Potassium Hydroxide-Water-Dimethyl Formamide

To 0.100 g. of vinylene carbonate-vinyl thiolacetate copolymer (0.40 mole per cent vinylene carbonate) in 25 ml. of dimethyl formamide was added a solution of 0.310 g. (0.005 mole) of potassium hydroxide in 10 ml. of water and 10 ml. of dimethyl formamide. The solution was heated at 110° for 3 hours but solid precipitated soon after heating began. After filtration the solid was washed with water and dried giving 0.060 gram of polymer which was insoluble in all solvents. It could not be starting material which was acetone soluble.

The initial combined filtrate was evaporated to dryness at 40° and 1 mm. and the inorganics washed away in 5 ml. of water by filtration leaving 0.008 g. of polymer which was found to be insoluble in all solvents.

Complete hydrolysis of the copolymer would yield 0.074 g. The 0.068 g. of insoluble polymer was approximately 92% of theory.

(2) *Use of Sodium Sulfite-Water-Acetone*

To 0.100 g. of vinylene carbonate-vinyl thiolacetate copolymer (0.40 mole per cent vinylene carbonate) in 30 ml. of acetone was added 1.26 g. (0.005 mole) of sodium sulfite in 10 ml. of water. After refluxing under nitrogen 24 hours 0.61 g. of inorganic salt was filtered and the filtrate concentrated to one-third its volume causing the precipitation of 0.028 g. of a yellow solid. This proved to be predominantly starting material by its softening point, 112–116° (starting material 115–118°), solubility and infrared spectrum (3.45 μ (w), 5.75 μ (m), 5.9 μ (s), 7.37 μ (m), 8.8–9.0 μ (s), 10.45 μ (m) as compared to starting material in which all bands were identical except at 5.75 μ , which is at 5.52 μ in the starting material).

The filtrate from isolating the 0.028 g. of polymer was taken to dryness and the solid triturated with 20 ml. of benzene. By the frozen benzene technique, 0.060 g. of solid was obtained, softening point 76–82°, soluble in acetone, dimethyl formamide, and pyridine. The sulfhydryl group was present as indicated by color bleaching when 5 mg. of the polymer in 2 ml. of benzene was tested with a 1% solution of iodine in benzene. The infrared spectrum indicated extensive hydrolysis (3.41 μ (s) characteristic of –SH, 3.5 μ (m), 5.75 μ (s), 5.90 μ (m), 8.6–9.0 μ (m)). After standing exposed to air a few days the polymer was found to be insoluble in the organic solvents mentioned above and in base.

A repetition of this experiment except for the period of heating, which was extended to four days, gave an insoluble polymer which was nearly completely hydrolyzed as indicated by the infrared spectrum (2.85–3.1 μ (s) broad –OH, 3.45 μ (m), sharp –SH, 5.88 μ (w), 6.98 μ (m), 8.25–9.75 μ (v.s.)).

Attempts to reduce the oxidized insoluble polymer with basic thiolacetic acid did not give a base-soluble material. This result may be due to the heterogeneous nature of the reaction mixtures, and a failure to exercise all the precautions later found to be necessary to prevent oxidation.

(3) *Use of Sodium Hydroxide-Water*

In a nitrogen atmosphere (converted dry box) 0.300 g. of vinylene carbonate-vinyl thiolacetate copolymer (36.5 mole per cent of vinylene carbonate) was heated at 85–95° for 3 hours with 0.50 g. of sodium hydroxide in 5 ml. of distilled water. (All water used in this experiment was distilled water, boiled vigorously for 30 minutes just before use and stored under nitrogen. All operations were carried out in the nitrogen box.) The resulting tan solution was filtered and by use of a citric acid solution (2.00 g. in 5 ml. of water) was adjusted to pH 9, the lower limit for solubility. In a more acid solution solid separated but could be redissolved by adding dilute sodium hydroxide. A portion of the basic solution was removed from the nitrogen atmosphere and made acidic with dilute hydrochloric

acid causing precipitation of the polymer, which was separated by centrifuging. The solid was washed exhaustively with water (centrifuge), then filtered and dried. The infrared spectrum was identical to that of the polymer obtained in the four-day heating period mentioned above.

The carefully prepared citrate solution of polymer at pH 9 was tested as a prophylactic for ionizing radiation in animals and found to be of special interest. These interesting results will be described elsewhere.

RESULTS AND DISCUSSION

Copolymers of vinylene carbonate and vinyl thiolacetate were prepared and the reactivity ratios determined by the method of Fineman and Ross.¹⁰ The reactivity ratios of the vinyl thiolacetate (monomer 1)-vinylene carbonate (monomer 2) system were $r_1 = 12.9 \pm 1.1$ and $r_2 = 0.04 \pm 0.01$. The preferred reactivity of vinyl thiolacetate radical with its monomer may indicate that resonance stabilization is greater for this radical than for the vinylene carbonate radical. Forms involving "d-orbital" expansion for

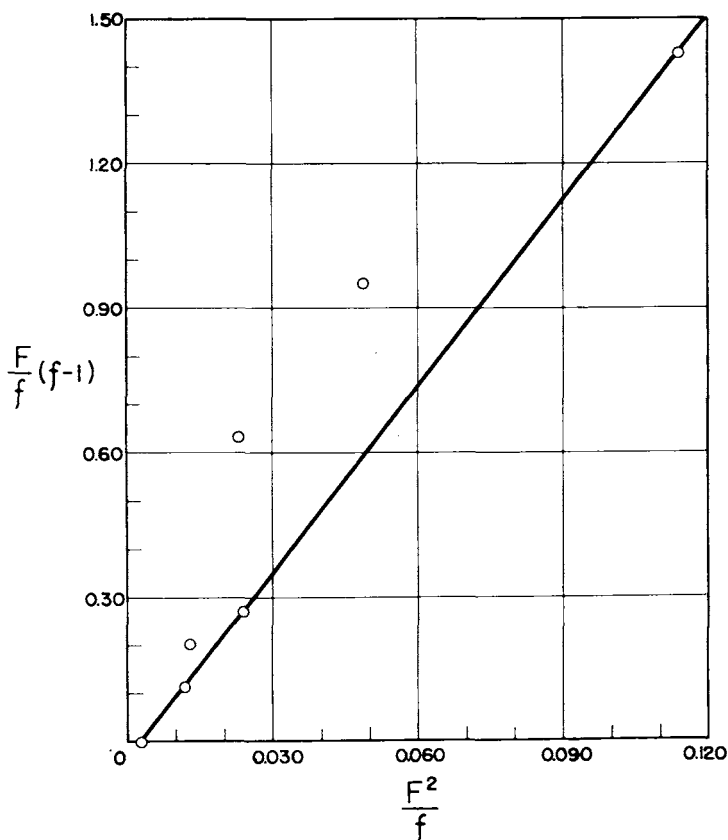


Fig. 1. Fineman and Ross plot for vinyl thiolacetate and vinylene carbonate copolymerization.

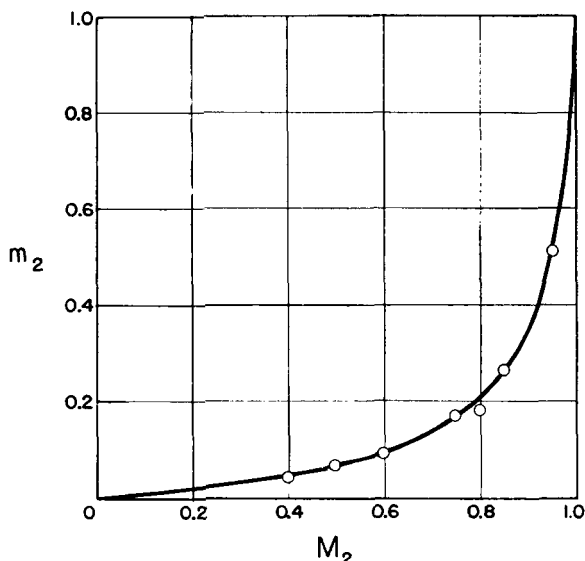


Fig. 2. Copolymer composition plot for vinyl thiolacetate and vinylene carbonate.

sulfur may contribute to the stabilization.¹¹ The small value for r_2 is also consistent with this argument. In addition, steric factors probably would not favor the addition of the 1,2-disubstituted monomer, vinylene carbonate, to the vinylene carbonate radical.

Table I summarized the copolymerization and the Fineman and Ross data. Figure 1 represents the Fineman and Ross plot and Figure 2 the copolymer composition diagram.

TABLE I. Vinyl Thiolacetate and Vinylene Carbonate Copolymerization at 60°C.^{a,b}

Expt. No.	M_1^c	Polymerization time, hrs.	% Conversion in benzene	Copolymer ^d analysis, % S	m_1^e	Eqs. plotted in Fig. 1 ^f
5.....	0.60	20	7.8	30.09	0.952	$1.425 = r_1(0.114) - r_2$
4.....	0.50	15	9.6	30.10	0.953	$0.952 = r_1(0.049) - r_2$
3.....	0.40	16	8.7	30.05	0.951	$0.633 = r_1(0.023) - r_2$
6.....	0.25	17	1.3	26.58	0.824	$0.261 = r_1(0.024) - r_2$
2.....	0.20	15	4.5	26.79	0.831	$0.199 = r_1(0.013) - r_2$
7.....	0.15	18.5	1.3	24.02	0.733	$0.113 = r_1(0.012) - r_2$
8.....	0.05	18.5	0.6	16.54	0.484	$-0.004 = r_1(0.003) - r_2$

^a Method of Fineman and Ross.¹⁰ Figure 1 gives plot and r_1 and r_2 values obtained from these data.

^b Catalyst 2,2'-azobisisobutyronitrile in 0.2 mole per cent for experiments 2-5 and 0.1 mole per cent for experiments 6-8.

^c M_1 = initial concentration of vinyl thiolacetate (mole fraction).

^d Sulfur analyses by Dr. F. Schwarzkopf, New York, N. Y., and Dr. K. Ritter, Basel, Switzerland.

^e m_1 = concentration of vinyl thiolacetate in copolymer (mole fraction).

^f Equation used: $(F/f)(f - 1) = (F^2/f) - r_2$, where $f = (m_1/m_2)$ and $F = M_1/M_2$.

TABLE II
4-Vinylpyridine and *N,N,N*-Triethyl-*N*-[2-(methacryloxy)ethyl]ammonium Iodide Copolymerization at 60°C.^{a,b}

Expt. No.	$M_1^c \times 10^3$	$M_2 \times 10^3$	$m_1^d \times 10^3$	$m_2 \times 10^3$	Polymeri- zation time, min.	% Conversion	Copolymer ^e analysis, % I_2	p^f	r_2^g	r_1^g
1.....	8.00	2.00	7.96	1.82	120	4.3	15.68	30	1.00	0.94
2.....	6.00	4.00	5.48	3.52	135	10.8	28.04	0.3 0.5	4.06 2.71	1.92 1.86
3.....	5.10	5.00	4.16	3.85	210	21.8	29.62	0.7 0.2	10.87 8.63	7.91 2.53
4.....	4.00	6.00	3.57	4.17	210	13.3	32.06	-0.6 0.4	2.57 0.74	0.06 0.90
5.....	2.30	8.00	2.15	7.58	210	5.4	33.44	0.8	0.72	0.78

^a The reactivity ratios were determined by use of the "integrated equation."

^b 2,2'-Azobisisobutyronitrile was catalyst: in 0.2 mole per cent for experiments 1 and 2, and 0.3 mole per cent for experiments 3-5.

^c M_1 = initial concentration of 4-vinylpyridine in moles.

^d m_1 = moles of 4-vinylpyridine in polymer.

^e Analyses were performed by Dr. F. Schwarzkopf, New York, N. Y.

^f p = Arbitrary factor.

^g In Figure 3 the points plotted lie within the coordinates 0-1. These points were determined from the values of r_2 and r_1 listed in this table. Figure 3, therefore, represents an enlargement of the "area of intersection."

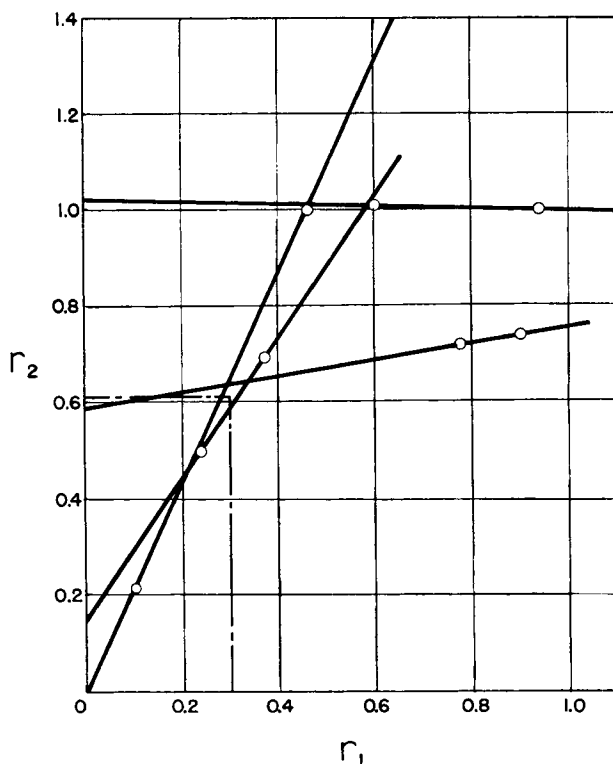


Fig. 3. Determination of reactivity ratios for 4-vinylpyridine and *N,N,N*-triethyl-*N*-[2-(methacryloxy)ethyl]ammonium iodide by the integrated equation method.

N,N,N-Triethyl-*N*-[2-(methacryloxy)ethyl]ammonium iodide was prepared in good yield by quaternizing 2-(*N,N*-diethylamino)ethyl methacrylate in excess ethyl iodide. 2-(*N,N*-Diethylamino)ethyl methacrylate was prepared by the alcoholysis of methyl methacrylate with *N,N*-diethylaminoethanol.

For the copolymerization of 4-vinylpyridine (monomer 1) and the "ammonium iodide" monomer (monomer 2), $r_1 = 0.30 \pm 0.02$ and $r_2 = 0.61 \pm 0.09$. Since both reactivity ratios are less than unity and their product less than 0.25, strong alternation tendencies are indicated. The results are in agreement with considerations of polar factors for this monomer pair since the e value for 4-vinylpyridine is negative and that for the "ammonium iodide" monomer, is positive. The reactivity ratios were determined by use of the "integrated equation" of Mayo and Lewis.¹² Table II summarizes the copolymerization data. Figure 3 is the plot of r_2 vs. r_1 , and Figure 4 the copolymer composition diagram.

Hydrolysis of the vinylene carbonate-vinyl thiolacetate copolymer was accomplished in strong alkali and the resulting sulfhydryl copolymer contained no residual carbonate ring (expected infrared absorption at 5.5–5.6 μ lacking) and only a minor amount of residual acetate (minor absorption

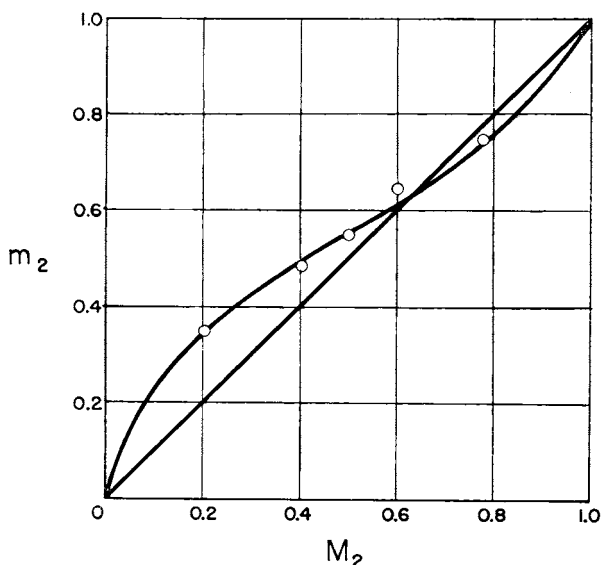


Fig. 4. Copolymer composition plot for 4-vinylpyridine and *N,N,N*-triethyl-*N*-[2-(methacryloxy)ethyl]ammonium iodide.

at 5.88μ). Very strong absorption between 2.85 and 3.1μ coupled with even more intense absorption between 8 and 10μ indicated hydroxyl. The sulfhydryl absorption at 3.45μ would be expected in greater intensity than obtained but hydrogen bonding with residual carbonyl of half hydrolyzed or unhydrolyzed carbonate may account for this observation. A similar explanation may account for the absorption at 5.75μ of the recovered, slightly modified starting material in the hydrolysis using sodium sulfite.

Though a wide variety of hydrolysis conditions was investigated it was found that the exact agent or system for hydrolysis was not so important as the requirement of an inert atmosphere. Crosslinking of the free sulfhydryl groups to give disulfide links led to extremely insoluble products in relatively short time in the presence of air. Solubility in alkali and in organic solvents could not be regained by regeneration of the sulfhydryls in the presence of basic thiolacetic acid.

The hydrolyzed copolymer was soluble in an alkaline solution adjusted with citric acid to pH 9. Below this pH precipitation occurred but addition of base redissolved the polymer. Solutions at pH 9–9.5 have been found to be stable for about a month when stored under nitrogen. From that time precipitation occurs probably because of crosslinking. In the soluble form the sulfhydryl polymer has been found to be of considerable interest in counteracting the lethal nature of ionizing radiation. This property of the copolymer will be discussed more fully elsewhere.

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Synopsis

Copolymerization reactivity ratios for the system vinyl thiolacetate (M_1)-vinylene carbonate (M_2) have been determined to be $r_1 = 12.9 \pm 1.1$ and $r_2 = 0.04 \pm 0.01$ by the method of Fineman and Ross. For the system 4-vinylpyridine (M_1) and N,N,N -triethyl- N -[2-(methacryloxy)ethyl]ammonium iodide (M_2) $r_1 = 0.30 \pm 0.02$ and $r_2 = 0.61 \pm 0.09$ as determined by use of the "integrated equation" of Mayo and Lewis. A base-soluble, easily oxidizable sulfhydryl copolymer has been prepared by hydrolysis of the copolymer of vinyl thiolacetate and vinylene carbonate. The sulfhydryl copolymer is of interest as a successful short lived prophylactic for ionizing radiation.

Résumé

Les rapports de réactivité de la copolymérisation du système thioacétate de vinyle (M_1)-carbonate de vinylène (M_2) ont été déterminés par la méthode de Fineman et Ross: $r_1 = 12.9 \pm 1.1$ et $r_2 = 0.04 \pm 0.01$. Pour le système 4-vinylpyridine (M_1) et l'iodure de N,N,N -triéthyl- N -[2(méthacryloxy)éthyl] ammonium (M_2) $r_1 = 0.30 \pm 0.02$ et $r_2 = 0.61 \pm 0.03$ en utilisant l'équation intégrée de Mayo et Lewis. Une copolymère soluble, porteur de fonctions sulfhydryles facilement oxydables, a été préparé par hydrolyse du copolymère de thioacétate de vinyle et de carbonate de vinylène. Le copolymère sulfhydrylé est intéressant comme substance prophylactique de courte durée de vie: elle est utilisée favorablement contre les radéations ionisantes.

Zusammenfassung

Es wurde durch die Methode von Fineman und Ross bestimmt, dass die Copolymerisations-Reaktivitätsverhältnisse für das System Vinylthiolacetat (M_1)-Vinylencarbonat (M_2) $r_1 = 12,9 \pm 1,1$ und $r_2 = 0,04 \pm 0,01$ sind. Für das System 4-Vinylpyridin (M_1) und N,N,N -Triäthyl- N -[2-(methacryloxy)-äthyl]-ammoniumiodid (M_2) ist $r_1 = 0,30 \pm 0,02$ und $r_2 = 0,61 \pm 0,03$, wie durch Verwendung der "integrierten Gleichung" von Mayo und Lewis bestimmt wurde. Ein basenlöslicher, leicht oxydierbarer Sulfhydrylcopolymer wurde durch Hydrolyse des Copolymers von Vinylthiolacetat und Vinylencarbonat hergestellt. Das Sulfhydrylcopolymer ist als erfolgreich kurzlebenses prophylaktisches Mittel für ionisierende Bestrahlung von Interesse.

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