Zarine Mehta for technical assistance and Professor K. Mislow for suggesting the use of ref 34. This research has been supported in part by Grants ES-00537 from the National Institutes of Health, U.S. Public Health Service, and F-440 from the Robert A. Welch Foundation. D.T.G. is a USPHS Career Development Awardee, 1 K04 ES-70088.

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Poly(vinylamine hydrochloride). Synthesis and Utilization for the Preparation of Water-Soluble Polymeric Dyes

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Abstract: A simple and practical route to poly(vinylamine hydrochloride) has been developed. Ethylidene bisacetamide was prepared by condensing (sulfuric acid catalyst) acetaldehyde with 2 equiv of acetamide. After neutralization of the acid with calcium carbonate, the intermediate was directly pyrolyzed (175–195 °C) in the presence of a surface catalyst (Celite) to *N*-vinylacetamide. Polymerization of the unpurified product, followed by acid hydrolysis of the resulting poly(*N*-vinylacetamide), afforded poly(vinylamine hydrochloride) in an overall yield of greater than 80% from acetaldehyde. A series of water-soluble, polymeric azo dyes was prepared from poly(vinylamine hydrochloride) by a sequence of reactions which consisted of: (1) a Schotten–Baumann reaction of the polymer with *p*-acetamidobenzenesulfonyl chloride in aqueous tetrahydrofuran; (2) hydrolysis of the *p*-acetamido function in hydrochloric acid to afford a polymeric sulfanilamide; (3) diazotization; (4) reaction of the resulting diazonium salt with sulfonated coupling agents. Some of the physical properties of these polymeric dyes are briefly discussed.

In the past few years chemists have become increasingly interested in preparing and using functionalized polymers.[1] Materials of this type have been shown to have numerous advantages over their monomeric counterparts. Polymeric reagents,[2] which consist of a reactive functional group attached to an insoluble support, are receiving a growing amount of

attention because of their nonpolluting and recyclable nature.[3] Biologically active molecules, such as drugs[4] and enzymes,[5] have been immobilized on polymers advantageously for a number of uses. Polymeric organometallics have been shown to have excellent semiconducting properties.[6] Polymerically insolubilized chelating agents,[7] supports for organic synthesis,[8] and catalysts[9] are all of considerable commercial interest because of the mechanical and operational advantages inherent in solid–liquid systems.

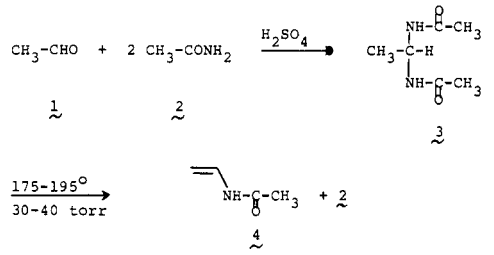
Only limited attention has been given to functionalized soluble polymers even though materials of this type could be extremely useful in a variety of applications. Polymeric water-soluble dyes, which are of great biological interest because of their inability to cross cell membranes, are an example of a material in this class which has been little studied. One reason for this is the lack of suitable "reactive" polymers which can serve as a starting point for their preparation. As a consequence, polymeric dyes have been prepared almost exclusively by the polymerization of difficultly obtained dye monomers.[10]

Poly(vinylamine) is a linear polymer which has the potential of affording a wide variety of soluble functionalized polymers by the attachment of various functional units. Three prominent syntheses of this material appear in the literature.[11-13] Our studies indicated that these routes were not satisfactory for the large-scale preparations of homogeneous poly(vinylamine) necessary for its use as a primary synthetic intermediate. We report here a new, high-yield synthesis of this polymeric amine and detail its multistep conversion into water-soluble polymeric dyes.

Poly(vinylamine hydrochloride)

Synthesis of *N*-Vinylacetamide. By analogy to poly(vinyl alcohol), it was reasoned that the polymerization of *N*-vinylacetamide, followed by acid hydrolysis, would afford poly(vinylamine).[14] The route (Scheme I) to the key intermediate,

Scheme I



N-vinylacetamide (**4**), was based upon literature precedent. Acetaldehyde was reported to condense with 2 equiv of acetamide under the catalytic influence of perchloric acid to afford ethylidene bisacetamide (**3**) in 40% yield.[16] The thermal cracking (220 °C) of **3** into *N*-vinylacetamide and acetamide had been achieved in a yield of 50%.[17]

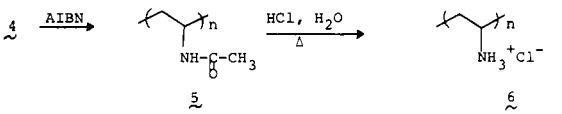
Upon investigation of the aldehyde–amide condensation it was found that the low yield reported was primarily caused by an acid-catalyzed reversal of the reaction. This reversal was found to take place upon attempted isolation–purification or upon direct pyrolysis of the ethylidene bisacetamide. The use of sulfuric acid as the catalytic agent followed by the addition of calcium carbonate immediately upon completion of the condensation solved this problem and allowed the intermediate bisacetamide to be pyrolyzed directly.

Study of the second reaction revealed that the yield was scale sensitive. As the reaction size increased, the time required for complete pyrolysis increased and the yield decreased. Suspicions that the pyrolysis was surface-catalyzed were confirmed when the addition of powdered glass caused a considerable increase in both the yield and rate of product formation. A number of potential catalysts (powdered soft glass, powdered Pyrex, silica, alumina, amphoteric metal oxides, Celite) were investigated in conjunction with a variety of pyrolysis temperatures. As expected, the catalysts which improved the yield also permitted a lower pyrolysis temperature. Using the best catalyst (Celite) and pyrolysis temperatures of 175–195 °C, acetaldehyde was converted into *N*-vinylacetamide in yields of 85–90% in a one-pot reaction sequence.

The *N*-vinylacetamide produced by this method was a crude distillate containing at least 1 mol equiv of acetamide. Complete purification could be accomplished either by fractional distillation, fractional crystallization, or silica-gel chromatography. Because each of these methods involved some degradation of this sensitive intermediate, best results were obtained by removing only a portion of the acetamide by crystallization, followed by polymerizing the mixture and purifying the resulting poly(*N*-vinylacetamide).

Polymerization and Hydrolysis. *N*-Vinylacetamide underwent free-radical polymerization in a variety of solvents (water, alcohols, ether, ketones) in the absence of oxygen with 2,2′-azobis(2-methylpropionitrile) (AIBN) as initiator (Scheme II). A concentrated solution of the crude *N*-vinylacetamide

Scheme II



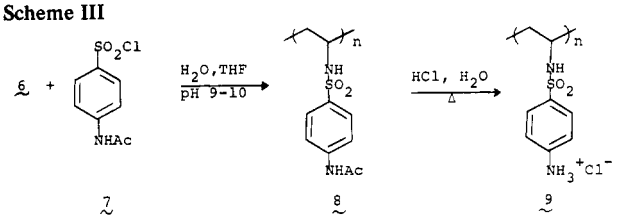
distillate in methanol routinely provided poly(*N*-vinylacetamide) (**5**) with a gel permeation chromatography peak molecular weight of 6×10^4. The use of slightly purified methanolic solutions resulted in a polymer peak molecular weight of 2×10^5. Lower molecular weight preparations (3×10^4) were obtained by using the more active chain-transfer solvent isopropyl alcohol. Polymeric amide **5** proved soluble in water and the lower alcohols, but was insoluble in nonhydroxylic solvents. Isolation and purification were therefore readily accomplished by precipitation from acetone. The yield of polymeric amide **5**, as a white powder, was found to be in the 80–85% range based on acetaldehyde.

As might be expected, the acid hydrolysis of all the *N*-acetyl groups of poly(*N*-vinylacetamide) was much more difficult than for a simple monomeric amide. As hydrolysis progresses, an increasing positive charge density is formed on the polymer backbone. Further hydrolysis becomes thermodynamically unfavorable and kinetically slow because the hydronium ions are electrostatically repelled from the vicinity of the polymer. Nevertheless, essentially total hydrolysis of the amide groups was accomplished without destruction of the polymer backbone by refluxing **5** in concentrated aqueous hydrochloric acid for 1–2 days. Because the hydrochloride salt of poly(vinylamine) is insoluble in organic solvents, the product could be isolated in yields of over 90% by precipitation of the acidic reaction mixture from a water-miscible organic solvent such as isopropyl alcohol. Polymeric hydrochloride **6** showed no more than 3% of residual *N*-acetyl groups when examined by ^1H and ^{13}C NMR spectroscopy.

Dye Preparation

Synthesis of a Polysulfanilamide. The first step in the conversion of poly(vinylamine hydrochloride) into polymeric anionic dyes involved a Schotten–Baumann reaction with *p*-acetamidobenzenesulfonyl chloride (Scheme III). The key to

Scheme III

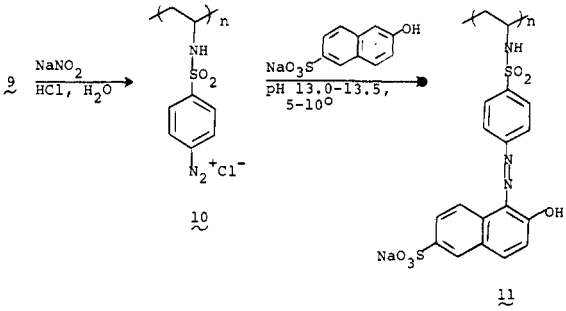


the successful execution of this reaction was the development of a suitable aqueous solvent system. Polymeric hydrochloride **6** is soluble only in aqueous media, while the Schotten–Baumann product, poly(*p*-acetamido-*N*-vinylbenzenesulfonamide) (**8**), is insoluble in dilute aqueous base. Thus, carrying out the reaction under classical conditions afforded, because of premature precipitation, a very poorly substituted product. The precipitation problem was overcome when it was determined that polymeric sulfonamide **8** was soluble in several wet organic solvents. Precipitation was avoided and essentially complete substitution was obtained by adding sulfonyl chloride **7** to a water–tetrahydrofuran (THF) solution of polymer **6** at pH 9–10. Using 1.1 equiv of sulfonyl chloride, a quantitative weight yield of the Schotten–Baumann product was obtained. The product was precipitated as a hard, granular, tan solid by evaporating the THF. Isolation and removal of water-soluble impurities were accomplished by filtration and washing.

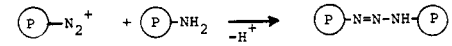
Polysulfanilamide hydrochloride (**9**) was prepared by the hydrolysis of Schotten–Baumann product **8** with 6 equiv of hydrochloric acid at reflux. The isolation of polysulfanilamide **9** was not necessary prior to diazotization, but the solvent could be removed to afford the polymer as a stable hydrochloride salt. Samples prepared in this manner were further purified by either dialysis or precipitation. Titration of the purified polymer for aromatic amine content (see Experimental Section) afforded values of 3.9–4.1 mequiv/g (theoretical value 4.26). Dried samples of polysulfanilamide **9** will redissolve in dilute hydrochloric acid, but not in neutral or alkaline media.

Diazotization and Coupling. Solutions of polysulfanilamide **9,** prepared as described above, already contained the requisite amount of acid and could be directly diazotized by the rapid addition of sodium nitrite solution (Scheme IV). Slow addition

Scheme IV



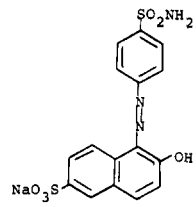
of sodium nitrite afforded a gel. This phenomenon was caused by the coupling of polymeric diazonium ions with polymeric aryl amines to form a triazine crosslink.[18] The rapid addition



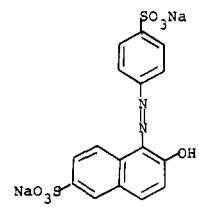
of sodium nitrite solution avoided this problem, apparently because the polymeric sulfanilamide was completely diazotized before triazine formation could take place. When prepared in this manner, solutions of the diazonium salt were clear and pale yellow in color.

Polymeric diazonium salt **10** was found to couple rapidly and completely with sodium 2-naphthol-6-sulfonate in cold aqueous alkali to produce orange dye **11.** Removal of the salts and monomeric impurities was accomplished by aqueous dialysis with either 20 000 or 30 000 molecular weight cutoff membranes and isolation was carried out by freeze drying. Reductive titration (see Experimental Section) of the polymeric dye revealed 2.1–2.2 mequiv of azo groups per gram (theoretical value 2.2). This indicates the material is essentially a homopolymer of structure **11.**

Dried samples of **11** rapidly redissolve in water to afford completely clear solutions with a λ_{max} of 475 nm and an absorptivity of 34.0 $(g/l.)^{-1}$ cm^{-1}. Aqueous solutions of **11** are visually indistinguishable from those of its monomeric counterparts **12**[19] and **13.** Spectroscopically, the visual absorption



12



13

band of polymer dye **11** is slightly broader than that of the two monomers. This phenomenon might be caused by interaction between the chromophores stacked along the backbone. The polymeric dye is far more soluble in water than **13,** but will precipitate in solutions of high ionic strength.

Water-soluble polymeric dyes containing other chromophores were readily prepared by treating diazonium salt **10** with various coupling agents. These materials and the properties of the dyes afforded were (absorption maxima and absorptivity values in $(g/l.)^{-1}$ cm^{-1} were obtained in water): sodium 2-naphthol-4-sulfonate[20] (λ_{max} 498 nm, *a* 44.5, orangish red); disodium 1-acetamido-8-naphthol-3,6-disulfonate[21] (λ_{max} 510 nm, *a* 28.9, bluish red); disodium 1-amino-8-naphthol-2,4-disulfonate[22] (λ_{max} 530 nm, *a* 41.5, reddish purple); disodium 1-(*p*-sulfophenyl)-5-pyrazolone-3-carboxylate (λ_{max} 430 nm, *a* 38.6, yellow).

In summary, we emphasize that a convenient and straightforward synthesis of poly(vinylamine) is now available. A high-yield, one-pot reaction sequence converts acetaldehyde into *N*-vinylacetamide. This key intermediate can be converted, via polymerization and hydrolysis, into poly(vinylamine hydrochloride) in greater than 80% yield based on acetaldehyde. This valuable chemical intermediate has been converted into a series of sulfonated azo dyes by a sequence of four clean reactions. This sequence is indicative of the facility with which synthetic manipulations can be carried out on soluble functionalized polymers, provided the reagents are chosen judiciously and the reaction conditions are carefully developed.

Experimental Section

Melting points are uncorrected. Ultraviolet and visible spectra were obtained with a Cary Model 118 spectrophotometer. Elemental analyses were performed by the Microanalytical Laboratory, Stanford University, Stanford, Calif. Direct functional analysis of the polymers was conducted in Dynapol's analytical laboratories as follows: the amine content of poly(vinylamine hydrochloride) was determined by titration with tetrabutylammonium hydroxide in dimethyl sulfoxide; the amine content of polysulfanilamide **9** was measured by titration with $NaNO_2$ solution in acid using a Pt vs. Ag/AgCl electrode pair to detect the end point; the azo bond content of the dyes was ascertained by reductive titration with aqueous $TiCl_3$ solution. Molecular weights were characterized in Dynapol's polymer sciences department. Gel permeation chromatography techniques were employed and molecular weights, as determined from peak elution volumes, were recorded relative to polystyrene standards (M_p^{PS}) using 0.01 M LiBr in dimethylformamide on silanized glass columns.[23]

Small-scale preparations of soluble polymers were purified by bag dialysis (regenerated cellulose, average pore radius 24 Å, estimated molecular weight cut-off 2×10^4) against 0.1% saline solution for 96 h (dialsate changed every 12 h) followed by dialysis against pure H_2O for 12 h. Large-scale dye preparations were purified and concentrated using a Bio-Fiber 80 cellulose acetate hollow-fiber dialysis unit (*nominal molecular weight cut-off* 3×10^4) purchased from Bio-Rad Laboratories, Richmond, Calif. This device was operated at 10 psi in conjunction with a peristaltic pump.

***N*-Vinylacetamide (4).** A 2-l., three-neck flask, equipped with an overhead stirrer, thermometer, and dry-ice condenser, was charged with 532 g (9.0 mol) of technical acetamide. With stirring, 12.4 ml of 6 M H_2SO_4 and 134 g (3.0 mol) of acetaldehyde were added sequentially and the reaction vessel was heated with a 100 °C oil bath. After the reaction had stirred for 10 min, the internal temperature (T_i) was 75 °C and the mixture was homogeneous. The condenser was

removed as an exotherm began, which raised T_i to 100 °C within 2 min. Ethylidene bisacetamide crystallized rapidly from the mixture, causing a further increase in T_i to 108 °C. After 7 min at or above 100 °C, the heating bath was turned off and 60 g (0.60 mol) of $CaCO_3$ (precipitated chalk) was carefully added, followed by 30 g of Celite 503.

The reaction vessel was fitted with a wide-bore, vacuum-distillation apparatus equipped with a Vigreux column and the pressure was slowly decreased to 30–40 mmHg. The bath was heated to 200 °C and the mixture was distilled to dryness (~4 h).[24] Three fractions were taken: fraction 1 (114 g, bp 130–138 °C (31–32 mm)) was identified as water and acetamide by NMR; fraction 2 (33 g, bp 138–148 °C (32–41 mm)) was identified as acetamide; fraction 3 (480 g, bp 148 °C (41 mm)–74 °C (27 mm)) was a reddish-orange semisolid consisting (by NMR in CD_3OD) of 230 g (90%) of *N*-vinylacetamide (**4**) and 250 g of acetamide.

The crude distillate was melted, diluted with 250 ml of isopropyl alcohol, and cooled to 5 °C for 18 h. Filtration afforded 125 g of acetamide and a filtrate which was 38.7 wt % *N*-vinylacetamide by bromine titration. This solution was subjected to polymerization without further purification.

In a separate experiment, an analytical sample was obtained by preparative thin-layer chromatography on silica gel with ethyl acetate elution followed by recrystallization from benzene–cyclohexane: mp 54–55 °C (lit.[25] mp 53 °C); ir ($CHCl_3$) 3480, 1700, 1650, 1480, 1390, 1360, and 980 cm^{-1}; NMR ($CDCl_3$) δ_{Me_4Si} 9.23 (br s, 1, –NH–), 6.60–7.17 (m, 1, –CH═), 4.30, 4.43, 4.55, 4.82 (maxima of AB portion of ABX system, $J_{AX} = 8$, $J_{BX} = 16$ Hz, 2, ═CH_2), and 2.10 (s, 3, –CH_3); uv λ_{max} (EtOH) 225 nm (ϵ 16 000).

Anal. Calcd for C_4H_7NO: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.06; H, 8.38; N, 16.31.

Poly(*N*-vinylacetamide) (5). A 5-l., four-neck flask, equipped with an overhead stirrer, thermometer, reflux condenser, Ar inlet, and heating mantle, was charged with 1165 g of an *N*-vinylacetamide solution (451 g, 5.30 mol) prepared as described in the preceding step. After isopropyl alcohol addition (1.3 l.), the reaction mixture was thoroughly deoxygenated and heated to a vigorous reflux under Ar. A solution of 22.3 g (0.14 mol) of AIBN in 83 ml of acetone was added in one portion (gas evolution) and the reaction was refluxed for 3 h.

After cooling, most of the solvent was removed in vacuo and the resulting thick orange oil was precipitated by slow addition to 10 l. of rapidly stirred acetone. The solid was filtered, washed with acetone (3 × 2 l.), and dried in vacuo at 50 °C to afford 431 g (96%) of poly(*N*-vinylacetamide) as a white powder, M_p^{PS} 3.4×10^4. An analytical sample was obtained by aqueous dialysis.

Anal. Calcd for $(C_4H_7NO)_n$: C, 56.45; H, 8.29; N, 16.46. Found: C, 55.84; H, 8.51; N, 16.01.

Drying the filter cake is unnecessary and need not be performed prior to the next reaction provided solvent residues are distilled before acid addition.

Poly(vinylamine hydrochloride) (6). A 5-l., four-neck flask, equipped with overhead stirrer, thermometer, distillation head, and heating mantle, was charged with 1 l. of H_2O and stirring was begun. The H_2O was boiled as 1412 g of an acetone-wet filter cake of polymer **5** (424 g, 4.98 mol as determined by drying a sample, M_p^{PS} 3.4×10^4) was added along with 200 ml of H_2O. After the acetone had been removed by distillation (maximum distillate temperature 100 °C), the mixture was cooled and treated with 522 ml of 12 N HCl (6.26 mol). Reflux was resumed under Ar. After 20 and 25 h, the incompletely hydrolyzed product had begun to precipitate. In each case the addition of 50 ml of H_2O clarified the solution. At 40 h, the cloudy solution was treated with 100 ml of H_2O and precipitated, while still warm, into 14 l. of rapidly stirred isopropyl alcohol. The product was filtered, washed with isopropyl alcohol (6 l.), and dried in vacuo at 100 °C for 14 h to afford 415 g of an off-white powdery solid.

Proton titration (calcd: 12.6 mequiv/g; found: 11.5) and elemental analysis showed the material to consist of 91% poly(vinylamine hydrochloride) (378 g, 95%) and 9% of residual isopropyl alcohol. A small sample was further purified by dialysis, followed by precipitation of an aqueous solution (10 ml/g) into 25 vol of 12 N HCl.

Anal. Calcd for $(C_2H_6NCl)_n$: C, 30.20; H, 7.60; N, 17.61. Found: 30.75; H, 8.26; N, 16.89.

Poly(*p*-acetamido-*N*-vinylbenzenesulfonamide) (8). A 1-l. flask was fitted with an overhead stirrer, a 100-ml dropping funnel containing 8 N NaOH, a pH probe, and a gas inlet tube. The vessel was charged with 14.0 g (176 mmol) of poly(vinylamine hydrochloride) (prepared from **5** of M_p^{PS} 4.7×10^4), 140 ml of H_2O, 15 ml of 8 N NaOH, and 70 ml of THF. After stirring for several minutes, a homogeneous solution of pH 10 was obtained. With vigorous stirring, 15.1 g (64.6 mmol) of powdered sulfonyl chloride **7** was added and the pH was maintained at 9–10 by base addition as necessary for 5 min. A second portion of sulfonyl chloride (15.1 g) was then added followed by 70 ml of THF. After an additional 15 min at pH 9–10, a third equal portion of sulfonyl chloride was added followed by 70 ml of THF and the pH was maintained at 10–11 until no further reaction was observed (stable pH, 60 min).

The flask was equipped for vacuum distillation and the THF was removed (35 °C (20 mm)). Schotten–Baumann product **8** precipitated as an easily filterable, light-tan, brittle solid. The yield was 41.7 g (99%) after thorough water washing and drying. For additional purification, a 1-g sample was finely pulverized, dispersed in 20 ml of THF, and dissolved by the slow addition of 2.5 ml of H_2O. Precipitation from 200 ml of methanol afforded **8** as a white powder: M_p^{PS} 1.2×10^5.

Anal. Calcd for $(C_{10}H_{12}N_2O_3S)_n$: C, 49.99; H, 5.03; N, 11.66; S, 13.34. Found: C, 49.64; H, 5.32; N, 11.48; S, 12.77.

Preparation of Polysulfanilamide 9. To a 1-l. flask, equipped with mechanical stirrer and reflux condenser, was added 40.0 g (167 mmol) of crude **8** (M_p^{PS} 1.2×10^5), 330 ml of H_2O, and 88 ml of 12 N HCl (1.06 mol). The mixture was stirred at reflux for 6 h and the clear solution was cooled. A 10-ml aliquot was withdrawn for purification and analysis, while the remainder was used for diazotization. The aliquot was dialyzed against H_2O and the resulting precipitate was isolated by centrifugation, dried, and titrated for aryl amine content (calcd: 4.26 mequiv/g; found: 3.98).

In a separate experiment, a sample was dialyzed against H_2O–THF (1:1) and precipitated (after evaporation of the THF and reacidification with HCl) by addition to isopropyl alcohol.

Anal. Calcd for $(C_8H_{11}N_2O_2SCl)_n$: C, 40.94; H, 4.72; N, 11.94; S, 13.66. Found: C, 41.66; H, 5.13; N, 12.05; S, 13.37.

Preparation of Polymeric Orange 11. A 1-l., three-neck flask, fitted with an overhead stirrer, was charged with a solution of 41.2 g (175 mmol) of polysulfanilamide **9** (prepared from a sample of **8** with M_p^{PS} 1.2×10^5) as obtained directly from the preceding step. The flask was fitted with a funnel which extended below the surface of the solution and with a gas exit tube. With vigorous stirring, 42.2 ml of 5 N $NaNO_2$ solution (211 mmol) was added as rapidly as possible. A positive KI starch test was obtained after 5 min.

The solution of diazonium salt was added over 20 min to a mechanically stirred solution of 47.6 g (dry basis, 194 mmol) of sodium 2-naphthol-6-sulfonate in 540 ml of 0.6 N aqueous NaOH. Throughout the addition, the pH was maintained at 13.0–13.5 by the addition of 8 N NaOH and the temperature was kept at 5–10 °C by the addition of ice. The dark red solution (2 l. in vol) was stirred for 45 min at pH 13.0 with no additional cooling and the pH was lowered to 10 by the addition of 12 N HCl.[26] The slurry was redissolved by the addition of H_2O (8 l.) and the product was purified, neutralized, and concentrated with the hollow-fiber dialysis unit. The resulting orange solution (1.5 l.) was passed through a 0.8 μm filter and freeze dried to afford 67 g (84%) of the polymeric orange dye **11**: vis λ_{max} (H_2O) 475 nm, a 34.0 $(g/l.)^{-1}$ cm^{-1}; azo bond titration (2.2 mequiv/g calculated) was 2.2 after correction for the H_2O content of the dye. A number average molecular weight of 8.2×10^4 was calculated from membrane osmometry data.

Anal. Calcd for $(C_{18}H_{14}N_3O_6S_2Na)_n$: C, 47.47; H, 3.10; N, 9.23, S, 14.08. Found: C, 46.80; H, 4.05; N, 9.27; S, 13.09.

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The Formation of Cyclic Peroxides from Unsaturated Hydroperoxides: Models for Prostaglandin Biosynthesis[1,2]

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Abstract: Several unsaturated hydroperoxides were synthesized by reaction of alkenyl mesylates with hydrogen peroxide and potassium hydroxide in methanol/water. These hydroperoxides were treated with di-*tert*-butyl peroxyoxalate in oxygenated benzene. Following reduction of the product mixture with triphenylphosphine, cyclic peroxides were isolated and purified by chromatographic methods. Acetophenone-initiated photodecomposition of unsaturated hydroperoxides also led to cyclic peroxide products. Another route to the same cyclic peroxides generated by peroxy radical cyclization (vide supra) was via bifunctional oxirane hydroperoxides. Unsaturated hydroperoxides were epoxidized by *m*-chloroperbenzoic acid. Treatment of the oxirane hydroperoxides prepared in this way with trichloroacetic acid led in most cases to cyclic peroxides. The mechanism of the free radical cyclization and the oxirane hydroperoxide reaction are discussed with reference to the proposed mechanism for prostaglandin biosynthesis.

The universal presence of prostaglandins in mammalian tissues coupled with their high potency in a divergent set of biological functions has prompted a comprehensive investigation into the nature of these compounds. While the functions in which prostaglandins have thus far been identified include reproduction, blood pressure regulation, inflammation, plasma electrolyte regulation, and platelet aggregation, the mechanism of their formation and action remains a matter of great research interest.[3-7]

A peroxy radical cyclization mechanism leading to intermediate endoperoxides has been proposed for the biosynthesis[8] (Scheme I). The intermediacy of endoperoxides has, in fact, been concretely established by the isolation of two such compounds, PGG and PGH.[9] Not only have these compounds been identified as intermediates in prostaglandin formation, they have also been shown to exhibit strong and independent physiological effects as well.[10,11]

In light of the potential importance of peroxy radical cyclization as outlined in Scheme I, it is remarkable that little information is available about this class of reaction. Cyclization of peroxy radicals has been proposed in order to account for the autoxidation products formed from a variety of different hydrocarbons. Anet,[12] for example, has proposed a peroxy radical cyclization in the autoxidation of α-farnesene. Similarly, Nugteren[13] and Haverkamp-Begeman[14] have suggested peroxy radical cyclization steps in the autoxidation of lipid. More recently, Pryor[15] has studied the autoxidation of methyl α-linolenate and has reported the isolation and identification of cyclic peroxide products.

Due to the complex and random nature of the autoxidation reaction, a different, more specific, method for the study of unsaturated peroxy radicals would appear to be desirable. We describe herein a method of generation of specific peroxy radicals from unsaturated hydroperoxides. Simple unsaturated