

Copolymers Prepared by the In-Situ Synthesis of

Maleimide/Maleamic Acid Monomers

Patent Application of Robert B. Login

[0001] This application claims the benefit of United States Provisional Patent Application serial No. 61917500.

Technical Field And Background

[0002] An inexpensive method of producing maleimide/maleamic acid copolymers that are of value as water soluble polycarboxylic acid amides containing copolymers with the potential of being biodegradable replacements for the non-biodegradable polycarboxylic acids now being used as detergent builders, chelating agents, scale inhibitors and flocculants . Additionally, multifunctional primary amines can afford copolymers with other unique properties useful in both cosmetic and pharmaceutical applications. Amines such as dimethylaminopropyl diamine afford cationic and quaternary products useful as hair conditioners and fixatives. Combinations of hydrophilic amines such as ethanolamine and small amounts of long chain primary amines affords surface active copolymers.

[0003] The embodiments of this application illustrate a simple way of handling maleic anhydride by adding it to absolute methanol where under

mild conditions the maleate half ester is formed. The resulting water white, low viscosity solution is safe and easy to handle. A master batch of this solution can be used for multiple reactions avoiding the repeated handling of maleic anhydride. A large investment in equipment to handle molten maleic anhydride can thus be avoided. This would allow smaller chemical companies to manufacture said copolymers. In addition, as will be described, the copolymerization actually is easier to perform with my embodiments.

[0004] The combination of in-situ preparation and polymerization of N-alkylmaleamic acids and maleimides at high temperatures results in copolymers containing significant amounts of polymaleimides. The evidence for this conclusion is based on the deep red color of polymaleimides repeatedly mentioned in the polymaleimide literature and also observed with these polymers.

Prior Art:

[0005] L. E. Coleman et. al. (JOC 24, 185, 1959) trying to obtain high yields of the ring closure of N-alkyl maleamic acids to form the corresponding N-alkyl maleimides monomers, obtained very low yields with the primary product being an ill defined polymer.

[0006] The yield of Coleman's maleimides was in the 15-25% range. Careful removal of the solvent xylene under vacuum at low temperature increased the yield to 50%. Since this publication numerous examples have appeared showing how to increase the yield of the desired maleimide. Yields of the maleimide monomer, even in the 90% plus range have been claimed by utilization of acidic catalysts and azeotropic removal of the water of condensation(P. Y. Reddy et. al. JOC 1997, 62, 2652 and N. B. Mehta et. al. JOC 1960, 25, 1012.).

[0007] The multiple steps required to eventually prepare the desired monomer and subsequent polymaleimide, leaves much to be desired in a commercial process because of the significant expense of all of those steps. No one has investigated the nature of the undesired polymer reported by Coleman. Contrary to Coleman's reported structure, their polymer was probably polymaleimide containing copolymers because of the dehydrating azeotropic conditions during their reaction. My goal therefore was to optimize this "undesired" polymerization to form high yields of polymers in-situ without isolating the corresponding maleimide/maleamic acid monomers or employing azeotroping solvents.

[0008] John M. Weiss and Robert P. Weiss, USP 2,306,18; Feb 15, 1940, is the earliest patent that essentially presents a version of the reaction of

maleic anhydride with primary amines. The problem with this patent is that the inventors employ molten maleic anhydride to which the amine is added. This reaction is exothermic and would be difficult to handle on a large scale. Mixing and temperature control would be a problem; not to mention the handling of the toxic maleic anhydride in molten form. Although they do have examples of adding solid maleic anhydride to amines, this would also presents problems of excess amine in the presence of maleamic acids affording a variety of derivatives such as diamide, Michael addition of amine to the forming adducts, maleic acid, fumaric acid and others.

This patent also indicates that at high temperature used for polymerization that N-alkylmaleimides are formed suggesting that this is actually the polymerizing monomer. However, no mention of the striking red color of these polymers is mentioned which is unlike the literature that will be reviewed showing the connection between said polymers and the red color.

[0009] USP 2,669, 555 to J. Giammaria (Sept.29, 1949) illustrates the reaction of equimolar amounts of primary amines with maleic anhydride in various high bp solvents. The reaction is performed at high temperatures similar to Weiss and Weiss previously mentioned. Subsequent to the formation of the claimed N-alkylmaleimides, a FR initiator is required to generate the polymer. According to this patent, conducting the condensation in a solvent generates

the maleimide monomer.

[0010] Weiss and Weiss conduct the condensation neat and this results in a polymerization that is poorly described but seems to be a mixed polymerization of N-alkylmaleamic and maleimide monomers. As previously mentioned, running the reaction with molten maleic anhydride or adding maleic anhydride to the neat amines is not the way to perform this type of reaction on an industrial scale.

[0011] H. Swartz, USP 3,228,972; Jan.11,1966. The reaction of maleamic acids with low MW alcohols is shown. This is the reverse of my embodiments and said products are not polymerized.

[0012] L.Wood, USP 5,292,858; March 8, 1994. The reaction of maleic anhydride with alcohols first, then followed by amines seems similar to my embodiment but this patent actually adds ammonia and small amounts of primary amines in order to prepare modified polyaspartic acid salts. The structures claimed must contain the ammonia generated amide and no mention is made of the function of the monomaleate ester. Even higher mw alcohols are claimed suggesting no reason for using low or higher mw alcohols is claimed. Furthermore, said patent illustrates the use of secondary amines which would not function in my embodiments.

Comparison to Polyaspartic acid(or its precursor, polysuccinimide):

[0013] Aspartic acid can be readily polymerized by simply heating the powdery aspartic acid to temperatures above 180C at atmospheric. The polymerization can be catalyzed by phosphoric acid and the resulting polymers can have significant MW usually in the 20K range while the uncatalyzed polymerization is usually in the 5K dalton range. The literature concerning polyaspartic acid is quite extensive and has been reviewed several times(M. B. Freeman et. al. Chap. 10 in Hydrogels and Biodegradable Polymers for Bioapplications, 1996 ACS Symposium Series).

[0014] The polymerization produces polysuccinimide which can be hydrolyzed to the corresponding polyaspartic acid salt. Even maleic acid and ammonium hydroxide will polymerized to polysuccinimide. This suggests that however the ammonia initially adds to maleic acid to form aspartic acid or maleamic acid or imide, as the temperature rises eventually only polysuccinimide is formed(Yi. H. Paik et. al. USP 5,463,017, Oct 31,1995 and M. B. Freeman et. al. USP 5,393,868, Feb. 28, 1995). This indicates that the same path will be followed by primary amines. The difference would be that the reaction of primary amines cannot result in the succinimide structure as in the polymerization of aspartic acids(see fig 1).

[0015] Although polyaspartic acid is a useful polymer, its general structure is fixed and contains various amounts of imide, amide and carboxylic acid groups. Only the MW and microstructures can be varied. Post polymerization reactions of amines with the precursor polysuccinimide that opens the imide have been reported; however, this route to derivatives, although useful, is random and cannot be controlled. If related maleimide and maleamic acid monomers could be synthesized in-situ then an inexpensive route to unique polymers would be achieved. This then was a goal of what follows,

Summary:

[0016] A process for preparing copolymers without isolating the corresponding monomers, comprising reacting an equivalent of primary amines with an equivalent of lower alkyl maleate half esters followed by heating to about 150-180C or above under high vacuum of less than 20mmHg for several hours.

[0017] The above process in which a master batch of the methyl half ester is prepared by adding maleic anhydride to an excess of methanol with stirring and subsequent refluxing for about one half hour.

[0018] The above process in which an equivalent of said primary amines

are slowly added to an equivalent containing aliquot of said methanol half ester solution maintaining the temperature at or below 60C.

[0019] The above process in which the excess methanol solvent is removed by distillation at atmospheric or vacuum followed by heating said mixture to 140 to 180C under vacuum of less than 20mmHg.

[0020] The above process in which the primary amines are selected from aliphatic chains of 1-25 carbon atoms, or aromatic amines such as aniline, or aniline derivatives substituted with alkyl groups.

[0021] The above process in which said alkyl chains can contain other functionality such as aromatic moities, and or functional groups such as alcohol, tertiary amines, halides, and so forth as long as such substituted alkyl chains do not react with the terminal mono primary amine.

[0022] A copolymer compound comprising the in-situ formation of N-substituted maleimide and N-substituted maleamic monomers by the addition of an equivalent of primary amines to a solution of an equivalent of methyl maleate half ester in methanol followed by removing excess methanol and subsequently polymerising said intermediate by heating to 140-180C under vacuum of less than 20mmHg for several hours.

Detailed Description:

Monomers:

[0023] One synthetic method for preparing N-alkyl amino acids employs the Michael reaction with maleate diesters or maleate methyl half ester in the presence of tertiary amines such as triethylamine. For example:

C. Lee et. al. Bull. Korean Chem Soc., V8, No6, 1987

C. Abshire and L. Berlinguet, Can. J. Chem., 40, 163(1962).

K. Harada and K. Matsumoto, JOC Sept. 1966, 2985.

A. Zilka and M. Bachi, JOC 24, 1959, 1096.

P. Piispanen et. al. Tetrahedron Lett. 46(2005), 2751.

M. Boros et. al. Amino Acids(2007) 33, 709.

[0024] This reaction requires that the maleate half ester be neutralized with a tertiary amine before the Michael reaction of a primary amine will add to the maleate double bond. However, not using tertiary amines with the methyl half ester results not in the Michael reaction but primary amine neutralization of this maleate half ester. Condensing this neutralized half ester, at high temperatures, leads to the corresponding copolymers. The reason for using lower alkyl maleate half esters is that removal of methyl alcohol for example is more facile than water of condensation, resulting in higher conversion to

maleimide monomer and that holding the primary amine next to the ester also facilitates this reaction. Unlike the polysuccinimides of aspartic acid, this in-situ monomer polymerization can take place at 150C or less (and vacuum) while the later requires temperatures above 180C. It is also easier to handle maleic anhydride as a solution in methanol as the half ester as this results in the desired monomers as the process proceeds to copolymer.

[0025] Bifunctional ethanolamine would be expected to produce even more complicated polymers. Reacting it with the half methyl ester of maleic anhydride and heating to 140-150C and high vacuum (less than 20mmHg) with or without phosphoric acid catalysis, results in a brittle red polymer in nearly quantitative yield. Interestingly, this polymer catalyzed by H₂PO₄ is insoluble in water but gels DMSO, while the uncatalyzed polymer is soluble. This is an indication of ester cross-links. However, both are soluble in dilute caustic, where they form a bright red solution that when acidified with HCl becomes colorless (or various shades of pale orange) below pH 8. This cycle can be repeated several times but eventually the red color does not return as if a chemical change had occurred.

[0026] The polymerization of butyl amine with maleate half esters, resulted in a polymer that was insoluble in water and 1N NaOH where the insoluble polymer turned red. Dissolving this polymer in DMF then adding 1N NaOH

resulted in a deep red solution that lost the red color when acidified. This suggests the same chromophore is in this polymer as that prepared from ethanolamine.

[0027] The actual structure of these polycondensates is a mixture of the various moieties that are reasonably possible with enough polymaleimide repeat units to afford the characteristic red color exhibited by known polymaleimide examples. Figure 3 illustrates possible polymeric structures but said structures are not limiting and are presented to illuminate said polymerization possibilities.

Chromophore:

[0028] The polymerization of ethanolamine or N- butyl amine and maleate half esters results in polymers exhibiting pH color changes. Some of the examples prepared are bright red to begin with and when the pH is raised, even the lightly yellowish examples become soluble and bright red. Lowering the pH as mentioned previously, sharply turns the solution relatively colorless much like phenothalein. Examples of related polymers, containing polymaleimides(prepared by FR or anionic polymerization), show similar red color after polymerization and/or at high pH(see ref. to Hass below). These

polymers are said to contain unsaturation linked to an acidic functionality that cause the red color when this acidic functionality is neutralized. This color change can be repeated several times but in some of samples the red color with time will eventually discharge to a light yellow neutral color as if some type of hydrolysis or other reaction had occurred. The polyaspartic literature contains no specific references to the red color phenomenon. The polyaspartic acids(polysuccinimides) samples I have prepared show very little red color initially that discharges very quickly and must not have been much of an issue to those studying this chemistry. Literature references to polymaleimides prepared by FR or anionic polymerization have significant and numerous mentions of the red color. Several theories of what causes the red color have been put forward by H. C. Haas et. al.

(P. Tawney et. al. JOC 1961 p16.

K. Onimura et. al. Macromolecules V31, No18, 1998.

P. Agarwal et. al. Ind. Eng. Chem. Rev. 2003, 42, 2881.

H. Haas and R. MacDonald, J. Polymer Sci.,V11, No. 2, 327, 1973

H. Haas and R. Moreau, J. Polymer Sci.,V13, 2327, 1975.).

[0029] Other possibilities that might make sense are based on the decarboxylation of any maleamic acid segments along the polymer chain. This type of decarboxylation is observed when maleic anhydride itself is polymerized anionically. The succinimides next to the conjugated

unsaturation have removable acidic protons resulting in an anionic charge at high pH that is reversible in acidic solutions. Whatever causes the color is immaterial to my argument that the red color is the hallmark of the polymaleimides, and that exhibiting this unique red color when formation of polymaleimides is possible; reasonably suggests that the polymaleimide structure is part of said copolymer.

[0030] Not to be limited by a speculation, a new idea for the reversible formation of a chromophore along the polymer backbone is presented in figure 2. Removal of an acidic proton conjugated with the aromatic would afford an extended unsaturation conceivably red in the presence of base.

[0031] These aromatic structures could be red colored in basic solution and acidification interrupts the conjugation only to be reversed upon neutralization to higher pH's. Eventually hydrolysis disrupts irreversibly this proposed chromophore.

[0032] Since the polymers prepared from methyl maleate half esters form deep red solutions sharply above pH 9-10, strongly suggests that this polymer is based on some maleimide polymer segments sufficient to afford the red chromophore. This then is a commercial method of inexpensively preparing polymaleimide copolymers. Although no FR initiator is employed, homolytic

cleavage to form free radicals would not be unexpected at 150C, in addition unreacted amines can polymerize N-alkyl maleimides and/or polyamide condensation can readily occur. Either way it is very difficult to prevent polymerization by FR, anionic and/or condensation polymerization at 140-180C and vacuum.

[0033] Alternative embodiments in addition to the above homo amine copolymers are copolymers based on mixing primary amines of various structures and functionalities. Hydrophilic amines such as ethanolamine amongst other hydroxy derivatised amines affords when copolymerized with alkyl amines especially long chain amines, surface active polymers. This embodiment can be fine tuned to maximize foaming or detergency or lubricity or combinations of desired properties.

[0034] Another embodiment is the use of primary/tertiary amine combinations for example DMAPA(N,N-dimethylpropylendiamine) with other primary amines such as various alkyl amines to afford quaternary containing polymers designed for hair care applications such as conditioners or fixatives.

[0035] These tertiary amines can be easily cross-linked with dialkylating

reagents such as epichlorohydrin to generate a series of hydrogels with uses such drug delivery.

Examples:

[0036] Example 1: (Ethanamine) To a 250ml Erlenmeyer flask equipped with a reflux condenser and magnetic stirrer was charged with 100ml of dry methanol and 36 g maleic anhydride powder. After mixing and refluxing for ½ hour, at which time, 22g of ethanamine (an equivalent) was added drop wise keeping the exotherm temperature between 60-65c. A clear colorless solution was formed. Then most of the methanol was distilled off under modest vacuum which results in a viscous golden colored mush. This intermediate was placed in a suitable polyethylene container in a heated vacuum desiccator, which was evacuated to less than 20mm of Hg and slowly heated to 150C. After 2hrs at 140-150C, the product was removed to reveal 52.3g of a red plastic soluble in water. A pulverized gram sample of which took 2.1ml 1N NaOH to go from a straw colored solution to a red aqueous solution. If only one carboxylic acid is neutralized then the apparent MW is 476 Daltons. This seems unlikely and therefore the MW is some multiple of this.

[0037] The IR of example 1 (referred to as sample 4009) shows significant carboxylic acid bands, this is the result of the polymerization of maleamic acid which does not homopolymerize but as maleimide monomers form in the reaction mixture, then the maleamic acid monomers can condense with

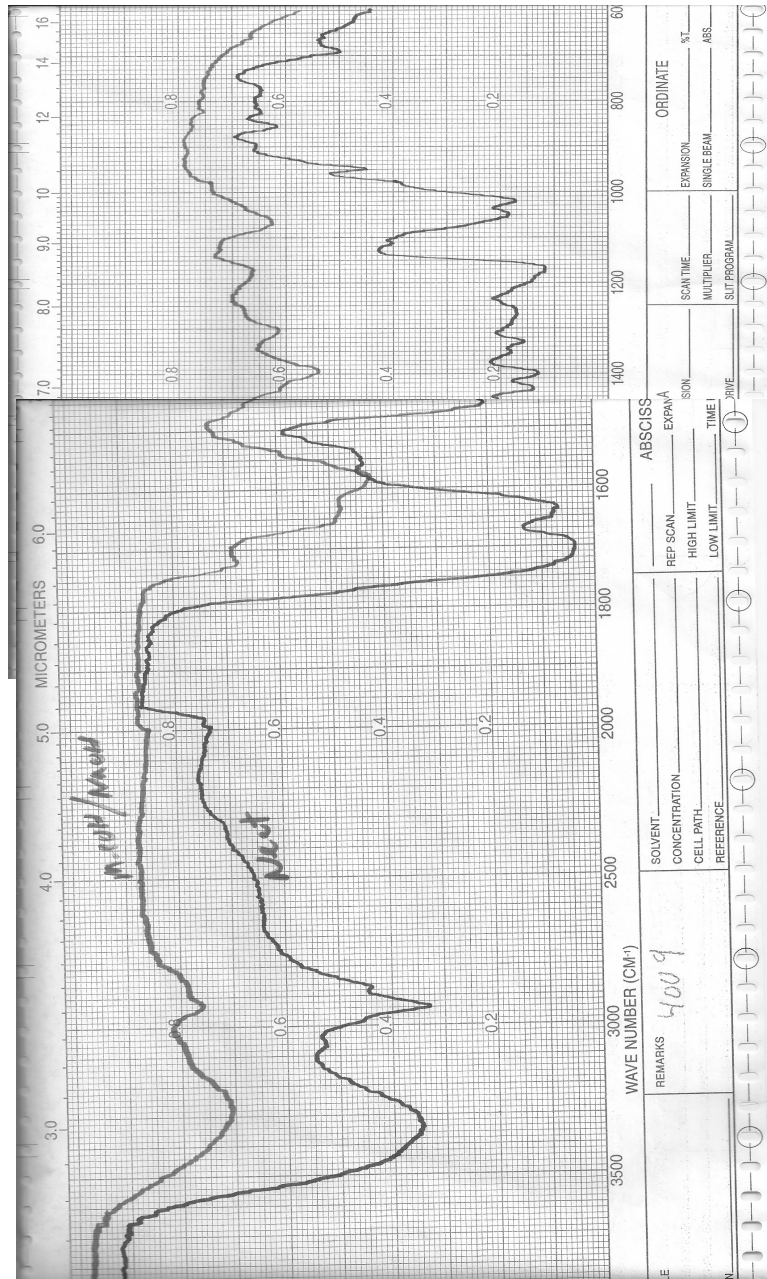
the maleamic acid double bond and or FR copolymerized with them. Eventually one way or another the monomers are incorporated into a polymer.

[0038] Example 2: Maleamic acids are readily synthesized in nearly quantitative yields by simply mixing maleic anhydride with primary amines; however it is much easier to use the methyl half ester as described in this application. Said maleamic acids can be formed from mixed primary amines resulting in unique copolymers. Copolymerization with ethanolamine are illustrated where small amounts of long chain amines can result in surface active polymers with significant utility in a variety of applications such as personal care, cosmetics, and drug delivery. Such large polymeric molecules are expected to notably be non-toxic. Therefore, the same charges as example 1 except that 5% on a molar basis of the ethanolamine is replaced by hexadecylamine. The resulting red plastic was soluble in dilute caustic as a hazy foamy red solution. After vigorous shaking the extensive foam of a 0.1% solution lasts for 30 or more minutes before collapsing indicating surface activity. Eventually the red colored solution becomes more of a yellowish color and pearlescent but still very foamy.

[0039] Example 3: 50/50 polymer of N-butyl amine and ethanolamine. Into

a stirred RB lask is added 100ml of dry methanol followed by 40g of maleic anhydride powder(0.408moles). The maleic anhydride dissolves and initially exotherms but is then heated to reflux for ½ hr at which point, a mixture of ethanolamine and butyl amine (0.204moles each) is added at or below 65C. A clear solution results from which the excess methanol is removed by vacuum stripping. The resulting mush is placed as in example 1, in a heated vacuum dessicator and heated under vacuum as described previously. This results in a nearly quantitative yield of a red plastic insoluble in water but soluble in dilute caustic. A 0.1% soln is red and foamy but much less than example 2. The foam and red color are transitory, resulting in a clear light golden colored solution after several hours.

[0040] Attached are IR's and H-NMR's of an example of the polymer prepared from methyl maleic half ester and ethanolamine(sample 4009). All samples are cast from solvent on salt plates then dried in a vacuum dessicator at 60C for several hours. A Perkin-Elmer 1310 IR was used.



Example 1: top trace neutralized and cast from methanol on salt plates, bottom trace same sample unneutralized cast from dmsu.

[0041] This IR shows significant carboxylic acids either in the polymer to begin with or formed by hydrolysis. Secondary amide can be seen at 1620 and 1550 cm^{-1}

[0042] Figure 4 : illustrates the 400Mhz H-NMR's of the same sample 4009(ethanolamine) and its neutralized version. It was dissolved in water and ppt with methanol twice. The unneutralized sample was also dissolved in water and twice ppt with isopropanol. Both samples were vacuum dried at 60-80C.

[0043] The NMR's show trace unsaturation and aromatic resonances. Even when neutralized these resonances persist in D₂O; however, residual amide resonances are visible around 8-8.5ppm in d₆dmsO but exchange in D₂O. Various unsaturated protons are seen in the 6-7ppm range, and the doublets at 7.1-7.2 are in the aromatic location and were generated in the neutralized basic sample as they do not appear in the d₆dmsO spectrum. The remaining protons associated with the ethanolamine methylenes and other protons are where they would be expected.

Claims:

1. I claim a process for preparing copolymers that form red alkaline solutions or mixtures without isolating the corresponding monomers comprising,
 - a. reacting an equivalent of primary amines with an equivalent of lower alkyl maleate half esters,
 - b. followed by heating to about 150-180C or above under high vacuum of less than 20mmHg for several hours.

2. The process of claim 1 in which said methyl half ester is obtained as an aliquot from a master batch of said ester prepared by adding maleic anhydride to an excess of methanol with stirring and subsequent refluxing for about one half hour.

3. The process of claim 1 in which an equivalent of said primary amines are slowly added to an equivalent containing aliquot of said methanol half ester solution maintaining the temperature at or below 60C.

4. The process of claim 1 in which the excess methanol solvent is

removed by distillation at atmospheric or vacuum followed by heating said mixture to 140 to 180C under vacuum of less than 20mmHg.

5. The process of claim 1 in which the primary amines are selected from aliphatic chains of 1-25 carbon atoms, or aromatic amines such as aniline, or aniline derivatives substituted with alkyl groups.
6. The process of claim 1 in which said alkyl chains can contain other functionality such as aromatic moieties, and or functional groups such as alcohol, tertiary amines, halides, and so forth as long as such substituted alkyl chains do not react with the terminal mono primary amines.
7. A copolymer forming a red alkaline solution or mixture comprising;
 - a. the in-situ formation of a mixture of N-substituted maleimide and N-substituted maleamic acid monomers by,
 - b. the addition of an equivalent of primary amines to a solution of an equivalent of methyl maleate half ester in methanol,
 - c. followed by removing excess methanol and
 - d. subsequently polymerising said intermediate by heating to 140-180C under vacuum of less than

20mmHg for several hours.

8. The copolymer of claim 7 wherein said primary amines contain a plurality of hydroxyl alkyl amines such as ethanolamine and a minor amount of a long chain selected from C8 to C22 alkyl amines.
9. The copolymer of claim 7 wherein said primary amines contain from 1-40% of a tertiary amine such as DMAPA(N,Dimethylpropylamine).
10. The copolymer of claim 7 wherein the primary amine is ethanolamine and 0.1 to 5.0% of phosphoric acid catalyst is added to the monomer mix before polymerization.

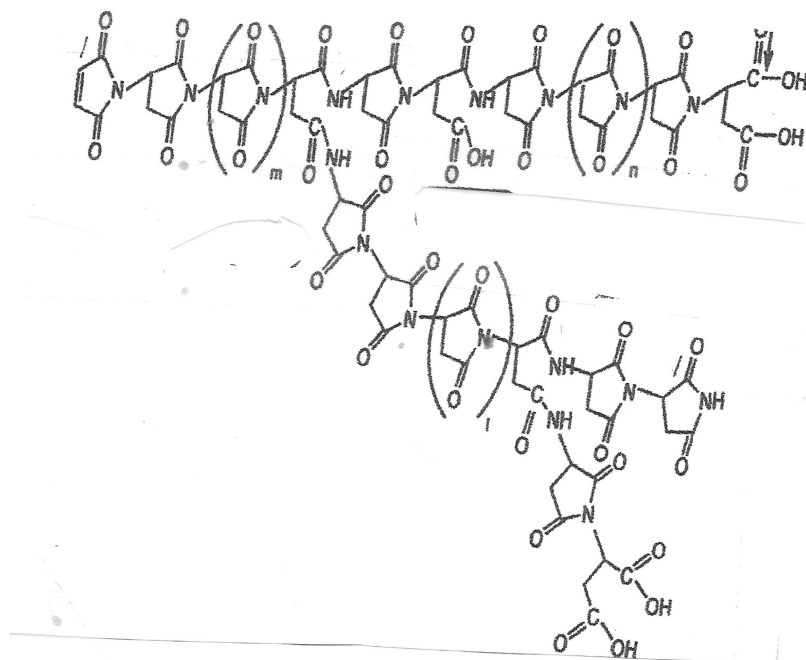


Fig. 1 Proposed general structure of polysuccinimide accounting for all H-NMR protons(Macromolecules, V31, No7, 1998).

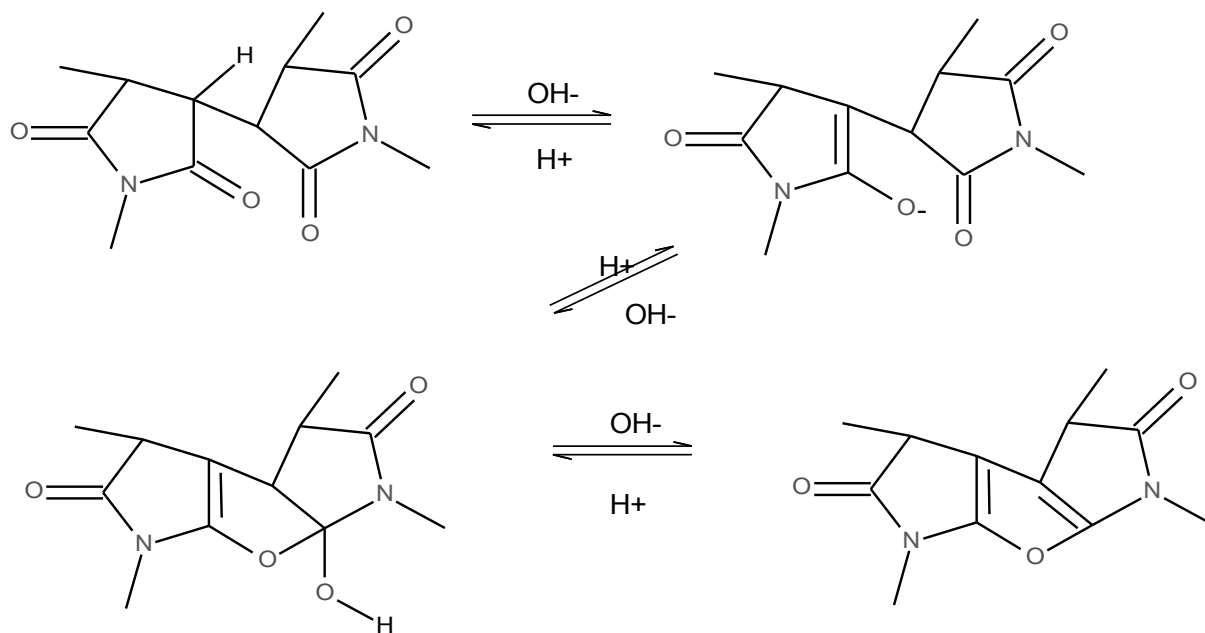


Fig. 2: A new idea for formation of the chromophore. The bonds to the rest of the polymer are shown by straight lines. The IR has a band at 850cm⁻¹

associated with furans.

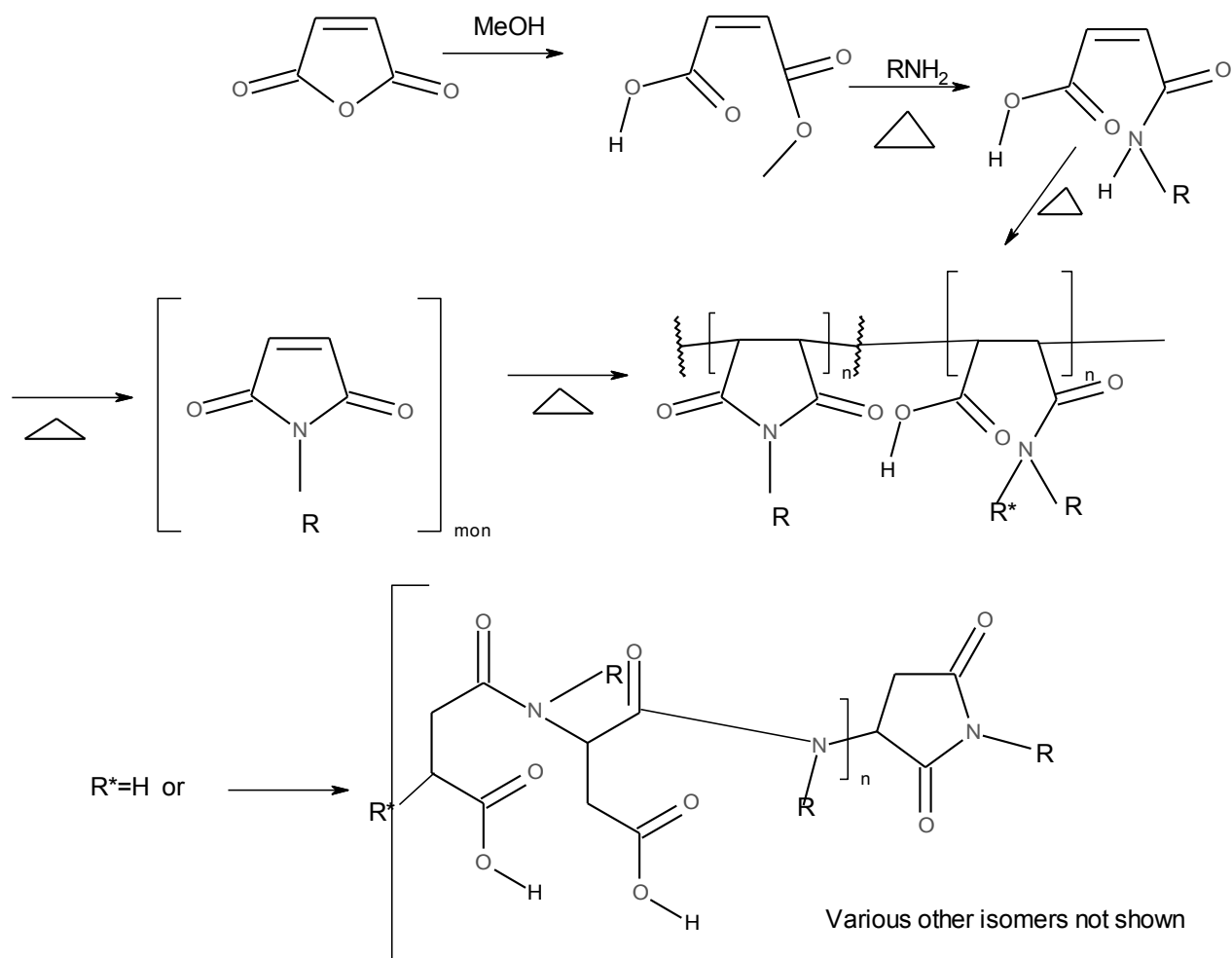


Figure 3: One proposed structure of the copolymer.

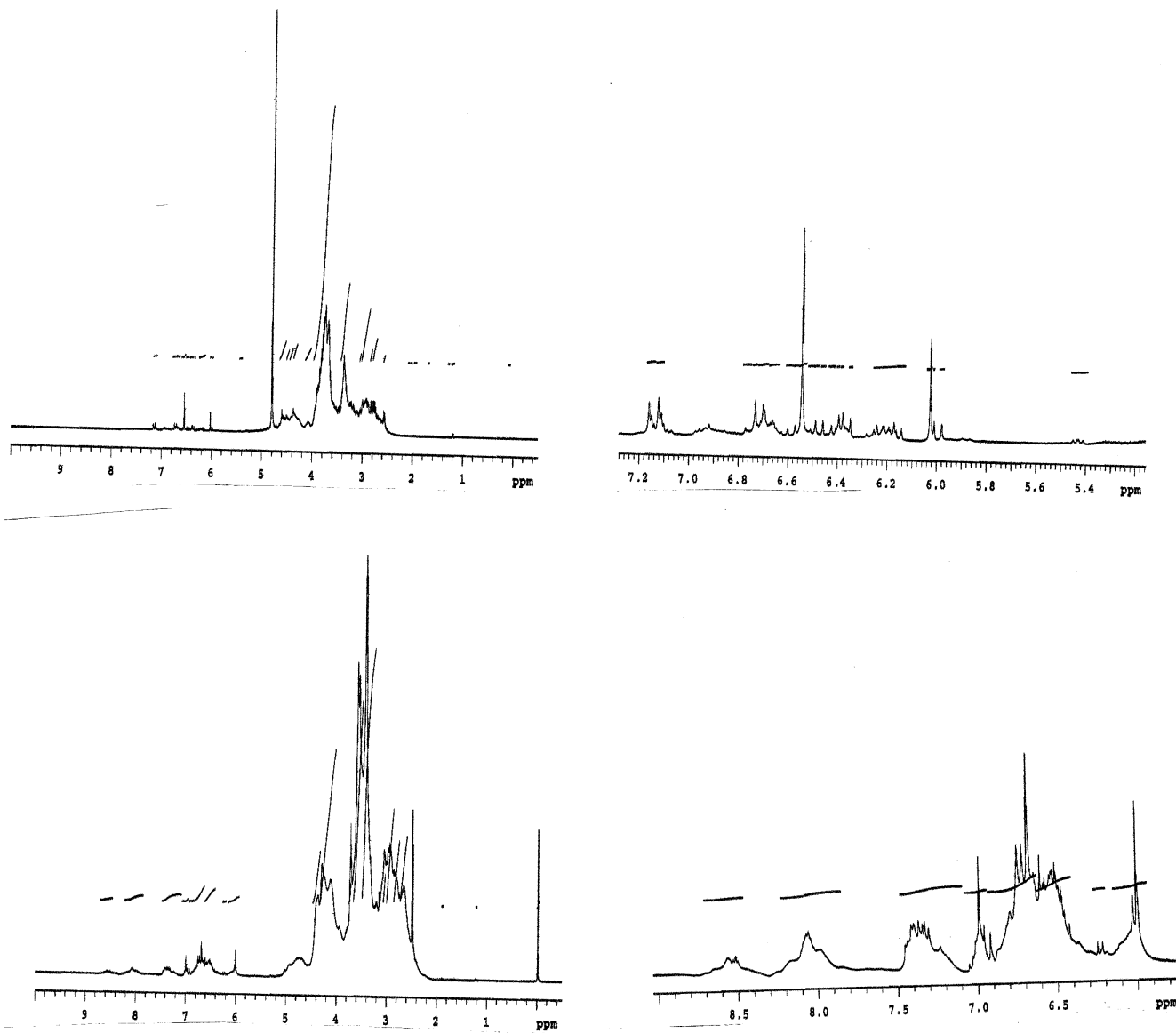


Fig 4: NMR 400Mhz spectrums. Top left in d20 is sample 4009 neutralized with NaOH and ppt from water with IPA 2x. On its right is an expansion from 7.2-5.0ppm. Below is the d6 DMSO unneutralized sample ppt with MeOH 2X. and an expansion from 9.0-6.0ppm.

Abstract:

The reaction of mono primary amines with methyl maleate half ester results in a maleamic monomer containing mixture that can be polymerized in-situ to copolymers containing polymaleimides segments. The evidence for this conclusion is based on the deep red color of neutralized polymaleimides repeatedly mentioned in the polymaleimide literature and also observed with these polymers. A variety of amines are described resulting in several useful embodiments.