

# Relationship between pH and viscosity of poly(4-vinylpyrimidine *N*-oxide) in aqueous solution

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(Received 10 October 1977; revised 24 December 1977)

The synthesis and viscosity/pH relationship in aqueous solution of poly(4-vinylpyrimidine *N*-oxide) are described. Below pH 4 viscosity increases sharply. Above pH 4 viscosity rises to a maximum at about pH 7.5, then decreases to a minimum at about pH 10. The viscosity/pH curve is a combination of the curves corresponding to poly(2-vinylpyridine 1-oxide) and poly(4-vinylpyridine 1-oxide).

## INTRODUCTION

Poly(2-vinylpyridine 1-oxide) (I) inhibits the cytotoxicity of quartz dust. Poly(4-vinylpyridine 1-oxide) (II) is much less effective and a study<sup>1</sup> of the effectiveness of various poly(vinylpyridine 1-oxides) on the cytotoxicity of quartz in macrophage cultures has shown that the position of the *N*-oxide group and the presence of alkyl groups affect the activity of the polymer. Detailed studies of the chemistry of these polymers have been made in an attempt to clarify their mode of action<sup>2,3</sup>. By studying the viscosity of aqueous solutions of some of these polymers and copolymers, Holt and Tamami<sup>4-6</sup> attempted to deduce changes in size and conformation at various pH values. Certain characteristic changes appeared to be associated with several polymers.

Holt and Tamami<sup>4,5</sup> reported that atactic poly(2-vinylpyridine 1-oxide) (I) in aqueous solution at different pH values can take up several conformations which are reflected in peaks or troughs in the viscosity/pH curve. (Figure 1). The minimal viscosity between about pH 4–10 has been related to bonding between oxygen and protons of the polymer chains. At higher pH values, the polymer was believed to act as an acid and at lower values as a base, the repulsion between charges on oxygen atoms then increasing the chain length and hence the viscosity. The polymer shows subsidiary peaks at intermediate pH values which were attributed to changes in packing of the syndiotactic and isotactic sequences.

Atactic poly(4-vinylpyridine 1-oxide) (II) shows a very different viscosity/pH curve (Figure 1); the viscosity is maximum at pH 9–10, probably because of crosslinking between molecules by water through oxygens. Fission of hydrogen bonds at higher or lower pH values results in reduced viscosity.

This paper describes the synthesis of, and viscometric studies on, poly(4-vinylpyrimidine *N*-oxide) (III) which were made with the object of extending the biological and chemical investigations.

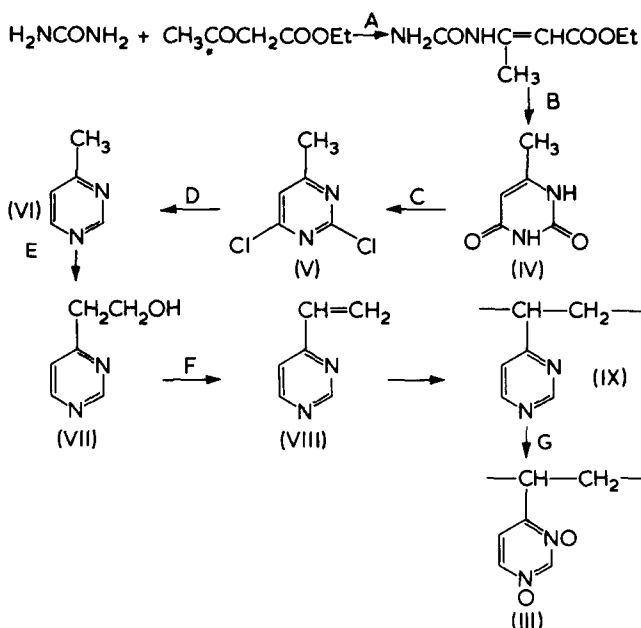
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542 POLYMER, 1978, Vol 19, May

## EXPERIMENTAL

### Preparation of polymers

The polymers were prepared according to the scheme presented below.



Reagents: A, HCl/EtOH; B, (i) NaOH (ii) HCl<sup>7</sup>; C, POCl<sub>3</sub><sup>7</sup>; D, H<sub>2</sub>/Pd<sup>8</sup>; E, (i) C<sub>6</sub>H<sub>5</sub>Br (ii) CH<sub>2</sub>O<sup>9</sup>; F, KOH; G, H<sub>2</sub>O<sub>2</sub>/AcOH<sup>10</sup>.

**6-Methyluracil (IV).** Finely powdered urea (80 g) was stirred into a mixture of ethyl acetoacetate (155 ml), absolute alcohol (25 ml), and concentrated hydrochloric acid (10 drops) and the mixture was dried over concentrated sulphuric acid *in vacuo* (5 to 7 days) to give the crude β-uraminocrotic ester. Yield 203 g (87%).

The crude product was dissolved in a solution of sodium

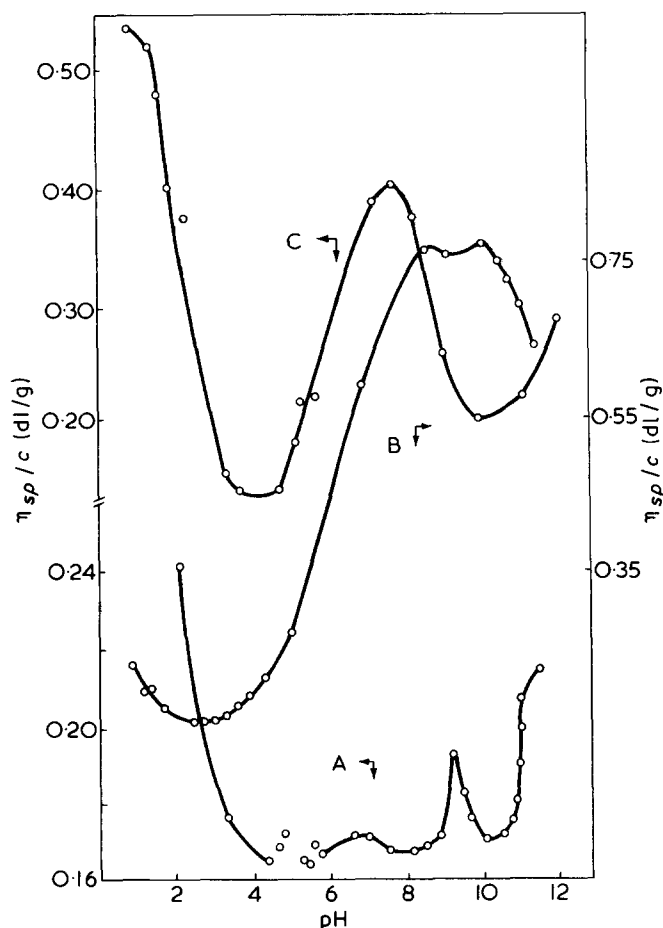


Figure 1 Viscosity/pH curve of poly(2-vinylpyridine 1-oxide). A<sup>6</sup>, poly(4-vinylpyridine 1-oxide); B<sup>6</sup>, poly(4-vinylpyrimidine N-oxide); C, 0.4% solution, 25°C

hydroxide (80 g) in 1.2 l of boiling water, cooled to 65°C and acidified, when (IV) precipitated. The product was washed with cold water, alcohol and ether. Yield 105 g (67%), decomposed above 300°C.

**2,4-Dichloro-6-methylpyrimidine (V).** 6-Methyluracil (IV) (50 g) and phosphorus oxychloride (200 ml) were mixed and refluxed for 30 min. About half of the phosphorous oxychloride was evaporated and the residual solution was poured onto ice, to give (V) as yellow crystals which were recrystallized from petroleum ether. Yield 49 g (75%), m.p. 43°–44°C (lit.<sup>7</sup> 46°–47°C).

**4-Methylpyrimidine (VI).** 2,4-Dichloro-6-methylpyrimidine (V) (20.4 g), magnesium oxide (18 g), methanol (90 ml), and water (180 ml) were shaken together in a hydrogenation apparatus at low hydrogen pressure with palladium on charcoal (5%, 2.4 g) at room temperature. When the theoretical amount of hydrogen had been absorbed, the mixture was filtered and the residue washed with water then dichloromethane. The filtrate was continuously extracted with dichloromethane for 24 h and the extract was dried over anhydrous potassium carbonate. The solution was filtered and evaporated, and the residue distilled *in vacuo* to give a colourless liquid. Yield 3.6 g (30%), b.p. 139°–140°C (lit.<sup>7</sup> 141°–145°C), picrate m.p. 130°–131°C (lit.<sup>8</sup> 131°–134°C).

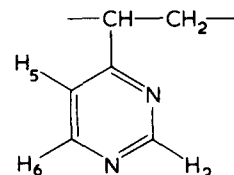
**4-(β-hydroxyethyl) pyrimidine (VII).** A solution of bromobenzene (77.5 g) in dry ether (50 ml) was added to lithium (7 g) in dry ether (100 ml) under nitrogen at a rate sufficient to maintain a gentle reflux. A solution of 4-

methylpyrimidine (VI) (37.6 g) in dry ether (50 ml) was then added during 15 min and the mixture was stirred for 1 h. The flask was cooled and formaldehyde gas passed into the reaction vessel until the intense colour disappeared. The solution was stirred for 45 min, then boiled under reflux for 1 h. The ether layer was separated and extracted 5 times with 15% hydrochloric acid. The acid solution was added to the water phase and poured into aqueous sodium carbonate. The solution was extracted continuously with chloroform for 12 h. The extract was dried, evaporated and the residue distilled at low pressure. Yield 15.1 g (76%) b.p. 125°–126°C.

**4-Vinylpyrimidine (VIII).** 4-(β-hydroxyethyl)pyrimidine (VII) (5 g) was heated with potassium hydroxide (0.5 g, 0.09 mol) and diphenylamine (0.1 g) under nitrogen to give a viscous dark liquid which was extracted several times with chloroform. Evaporation and distillation of the residue under nitrogen at low pressure gave (VIII) as a colourless liquid. Yield 2 g (35%), b.p. 50°–51°C/7 mm, picrate m.p. 115°–120°C.

**Poly(4-vinylpyrimidine) (IX).** A polymerization tube containing a mixture of 4-vinylpyrimidine (3.8 g) and azobisisobutyronitrile (0.037 g) was cooled in liquid nitrogen, flushed with nitrogen, evacuated and sealed. The tube was then heated at 60°C for 2 h. The polymer which formed was purified by dissolution in 5% HCl and precipitation with 5% ammonia and was finally precipitated from a solution of methanol and dimethylformamide with dry ether to give a fluffy white solid, yield 2.9 g. The polymer held a trace of water tenaciously and was slightly soluble in hot water; decomposition occurred at 210°C. Calculated: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.07; H, 6.13; N, 26.18.

N.m.r. (T.F.A.) centred at 1.80 br (S, H<sub>2</sub>, H<sub>6</sub>); 2.8 br (S, H<sub>5</sub>); 7.10 br (S, –CH–); 8.2 br (S, –CH<sub>2</sub>–) ratio of intensities 2:1:1:2



**Poly(4-vinylpyrimidine N-oxide) (III):** Poly(4-vinylpyrimidine) (IX) (6.1 g) was heated with glacial acetic acid (30 ml) and hydrogen peroxide (8 ml, 30%) at 70°C for 6 h. Additional hydrogen peroxide (10 ml) was added and the temperature was maintained at 70°C for 24 h. The solution was evaporated, saturated sodium carbonate solution was added to the residue and the free N-oxide was removed by several extractions with chloroform. The product was precipitated with dry ether. Yield 3.5 g; product decomposed at 260°C. I.r. showed a N–O stretching band at 1230 cm<sup>-1</sup>.

It was impossible to obtain a satisfactory analysis because (III) was extraordinarily hygroscopic.

#### Viscosity determinations

Viscosities were determined with a modified Ubbelohde suspended level viscometer. The modification consisted of replacement of the bulb with a larger bulb carrying a vertical tube wide enough to insert a glass electrode. The bulb carried a second tube through which passed a length of very fine polyethylene tubing, the upper end of which was connected to a micrometer syringe. Through this tubing very small quantities of acid or alkali could be added. Measurements

were made on solutions containing 0.40 g of the polymer in 100 ml water at  $25^{\circ} \pm 0.05^{\circ}\text{C}$ .

## RESULTS

See *Figure 1*. Below pH 4 the viscosity of poly(4-vinylpyrimidine N-oxide) (III) increases sharply with decreasing pH, however at very low pH the rate of increase is reduced. Above pH 4 viscosity rises to a maximum about pH 7.5, then decreases to a minimum about pH 10. There is an increase above pH 10.

## DISCUSSION

The marked differences between the viscosity/pH curves of poly(2-vinylpyridine N-oxide) (I) and poly(4-vinylpyridine N-oxide) (II) was described by Holt and Tamami<sup>4-6</sup>. They studied the viscosity/pH relationship of polymers (I) and (II) (*Figure 1*), and showed that these polymer behave as polyamphlytes. The shape of the viscosity curve of (I) was almost the reverse of that of (II) and the authors suggested that this might have had some relation to the strong activity of polymer (I) and weak activity of polymer (II) against silicosis.

The viscosity/pH curve of poly(4-vinylpyrimidine-N-oxide) (III) (*Figure 1*) has a shape which is a combination of those of polymers (I) and (II). It has the characteristic peak of polymer (II) at about pH 7.5 and the characteristic viscosity increase of polymer (I) at low and high pH values. Apparently the same factors cause changes in viscosity in polymers (I), (II) and (III).

The shape of the viscosity curve of (III) (*Figure 1*) at intermediate pH can be explained if, as previously assumed in the case of polymer (II)<sup>4,5</sup>, polymer chains are associated through water molecules bonded to 1-N-oxide atoms. This is possible since, with the polyvinyl chain attached to the 4-position of the ring, the 1-N-oxide atoms are exposed and free to bond in this manner. The bonds are stable and therefore the viscosity is highest at about pH 7.5. However, above and below this pH these intermolecular bonds are broken and consequently the viscosity decreases. Steric factors would hinder the formation of such intermolecular bonds through water molecules when the polyvinyl chain is in the position 2 as in polymer (I).

Holt and coworkers<sup>2-6</sup> showed by means of n.m.r. and u.v.

spectroscopy and titration curves that oxygen forms a link with the  $\alpha$ -proton of the chain in polymer (I) at intermediate pH values and the polymer has a tightly packed structure as long as this intramolecular bonding exists. They showed by the viscosity/pH curve (*Figure 1*) that at low and high pH values this type of bond is broken, and consequently the molecule expands and viscosity increases. Considering the viscosity/pH curve of polymer (III) below pH 4 and above pH 10 one can conclude that the same type of intramolecular bonding exists between the 3-N-oxides and the  $\alpha$  hydrogen atoms of the chain, and the increase in viscosity below pH 4 and above pH 10 is due to the destruction of these bonds. The increase in viscosity below pH 4 is steeper because the repulsion between the protonated N-oxides causes the molecule to expand even more. At very low pH, when more protons are added than is necessary to protonate the oxygens, ion shielding effects will reduce the repulsion and hence decrease the rate of change of viscosity.

A small peak in the viscosity/pH curve of polymer (I) (*Figure 1*) at pH  $\sim 7$  was interpreted<sup>4</sup> as being due to a change in conformation of the syndiotactic parts of the polymer chain, since the peak was pronounced in the curve relating to the mainly syndiotactic polymer but very small in that of the mainly isotactic polymer. The peak at pH  $\sim 9.5$  in the viscosity/pH curve of polymer (I) was also attributed to change in conformation in the isotactic parts of the polymer chain. However, such small changes at intermediate pH values were not observed in the viscosity/pH curve of polymer (III), presumably because the changes are too small to be detected compared to the main viscosity changes at intermediate pH values due to the intermolecular bondings. The maxima at intermediate pH for polymers (II) and (III) (*Figure 1*) are not at the same pH value, this might be due to the difference in basicity of the two polymers.

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