Protonation of poly(2-vinyl pyridine-1-oxide) and some analogues in relation to their conformation

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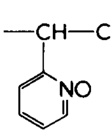
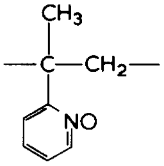
The protonation of poly(2-vinyl pyridine-1-oxide), which is restricted by bonding between the α-hydrogen and the oxygen atom, leads to the formation of a dimer salt in contrast to poly(4-vinyl pyridine-1-oxide) which gives the normal salt. This was supported by a study of the u.v. spectra and viscosity of some derivatives of this polymer. In poly[(2-propene)-2-pyridine oxide], replacement of the α-hydrogen with a methyl group enhances the protonation of the *N*-oxide and increases the basicity markedly. In poly[(1-propene)-2-pyridine oxide], the β-methyl group restricts the close packing of the pyridine oxide rings and hinders the formation of a dimer salt.

INTRODUCTION

Poly(2-vinyl pyridine-1-oxide) has attracted attention since it was found to inhibit the fibrogenic effect of silica in animals[1], and more recently when some of its derivatives were tested for their carcinolytic activity[2]. Holt and Nasrallah[3], in an exploratory work investigated the chemistry of poly(2-vinyl pyridine-1-oxide) compared with poly(4-vinyl pyridine-1-oxide) in an attempt to explain its mode of action against silica toxicity. Since then, many analogues of these polymers with a methyl group at different positions of the ring have been synthesized[4] and tested, and it was found that some of them possess some activity but that poly(2-vinyl pyridine-1-oxide) [I] was outstanding[5]. It was suggested[6] that the activity of poly(2-vinyl pyridine-1-oxide) is related to its conformation in aqueous solution which is attributed to hydrogen bonding between the oxygen atom and the α-hydrogen. However, this suggestion remained unproved. We prepared two derivatives of the polymer: poly[(2-propene)-2-pyridine-1-oxide] (II) and poly[(1-propene)-2-pyridine-1-oxide] (III). In the first polymer a methyl group replaces the α-hydrogen on the chain; and the second, a methyl group replaces the β-hydrogen. We studied the basicity of these polymers in relation to their conformation, by examining the u.v. spectrum and the viscosity of the aqueous solutions on protonation in hydrochloric acid.


(I)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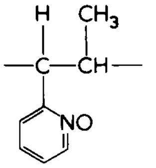
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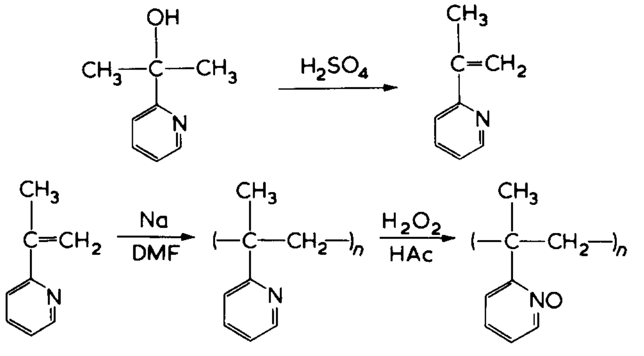
The ease of protonation (pK_a) was determined from the spectra, and the mode of change in conformation was observed from the viscosity/pH curves.

EXPERIMENTAL

Preparation of poly[(2-propene)-2-pyridine-1-oxide]



Freshly prepared (2-pyridyl)-α,α-dimethyl methanol[7] was mixed gradually with an equal volume of concentrated sulphuric acid while cooling in an ice–water bath. The mixture was then heated to 140°C and kept at this temperature, with stirring, for 30 min. Then it was cooled to room temperature, and neutralized with 50% sodium hydroxide while cooling. The 2-(2-pyridyl propene) monomer was extracted with ether and purified by fractional distillation under reduced pressure (b.p. 60°–63°C, 10mmHg).

2-(2-Pyridyl)-propene (20 g), which was distilled twice under reduced pressure, was dissolved in *N*,*N*-dimethyl formamide (30 ml) which had been distilled over phosphorous pentoxide. The solution was poured quickly into a two-necked polymerization flask under a stream of dry oxygen-free nitrogen, then sodium metal (1g) was added at room temperature while stirring, and the polymerization continued for 3 h. Water was added until the dark red colour of the 'living' polymer disappeared. After removal of solvent by evaporation the residue was dissolved in a minimum of methanol and the solution poured over acetone with vigorous stirring. The white solid polymer was dried *in vacuo* at 70°C (m.p. 210°–235°C).

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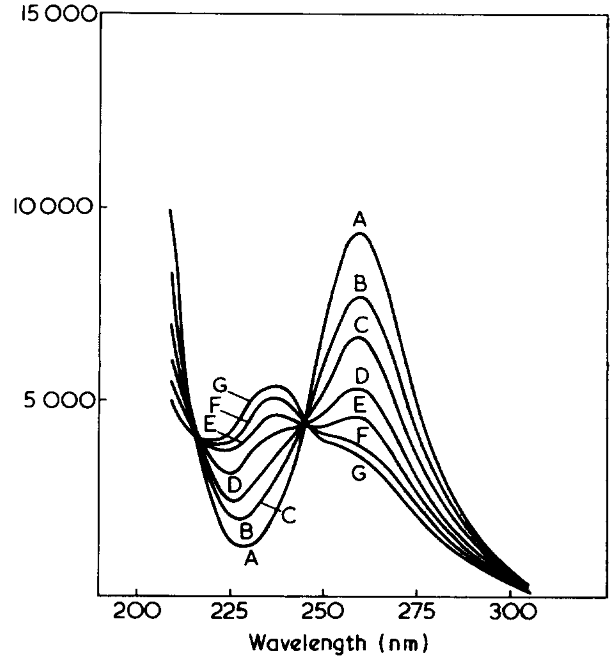
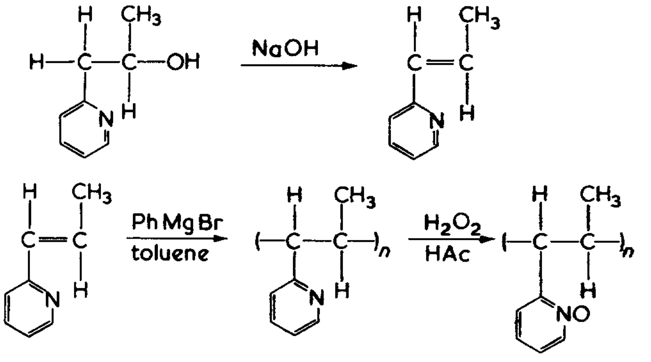


Figure 1 Spectra of poly(4-vinyl pyridine-1-oxide) in: A, H_2O; B, 0.125N HCl; C, 0.250 N HCl; D, 0.500N HCl; E, 0.875N HCl; F, 1.250N HCl; G, 1.87N HCl

The polymer was oxidized with hydrogen peroxide in glacial acetic acid at 75°–80°C, using the method described for poly(2-vinyl pyridine)[3]. The product is a yellow hygroscopic powder (m.p. 215°–220°C with decomposition) soluble in alcohols and water. Elemental analysis (C_8H_9NO): calculated C 71.6%, H 6.66%, N 10.36%: found, C 70.11%, H 6.60%, N 10.3%.

PREPARATION OF POLY[(1-PROPENE)-2-PYRIDINE-1-OXIDE]



Freshly prepared 1-(2-pyridyl)-2-propanol[8] (6 ml) was refluxed over sodium hydroxide for 10 min. This gave a better yield than dehydration with concentrated sulphuric acid. The product, 1-(2-pyridyl)-propene was distilled under reduced pressure and collected at 65°C, 9 mmHg.

Freshly prepared monomer, 1-(2-pyridyl)-propene (8 ml) was dissolved in toluene (8 ml) previously dried over sodium metal. Phenyl magnesium bromide (1.5 g) was prepared in a two-necked 250 ml flask under a stream of nitrogen, dry toluene (20 ml) was added to this catalyst and the temperature brought up to 45°C. Then the monomer solution was added with vigorous stirring. The mixture was stirred for 4 h at 45°C, then enough water was added until the red colour due to the 'living' polymer disappeared. The solvent was evaporated, the white solid residue was dissolved in a minimum of 5% hydrochloric acid, and reprecipitated by the addition of 5% ammonium chloride to pH 6. The polymer was dried *in vacuo* at 70°C (m.p. 245°–270°C).

The *N*-oxide of the polymer was prepared with hydrogen peroxide in glacial acetic acid at 75°–80°C by the same method used for the oxidation of poly(2-vinyl pyridine)[3]. The hygroscopic yellow solid (m.p. 160°–190°C) was soluble in alcohols, chloroform and water. Elemental analysis (C_8H_9NO): calculated, C 71.06%, H 6.66%, N 10.36%; found, C 70.48%, H 6.47%, N 10.30%. Poly2-vinyl-pyridine-1-oxide) and poly(4-vinyl pyridine 1-oxide) were prepared by oxidation of the corresponding poly(vinyl pyridines)[3].

U.v. spectra were obtained on a Perkin–Elmer 202 spectrophotometer. The pK_a values (±0.02) were calculated from the spectra by the method used by Kubota[9].

Viscosities were determined with a modified suspended-level viscometer: a glass tube, wide enough to insert the combined electrode, was sealed into the viscometer bulb so that the pH is measured immediately after each flow-time reading. The viscosities were measured at 25° ± 0.1°C on aqueous solutions containing 0.4 g/100 ml polymer. The pH of the solution in the viscometer was adjusted by the dropwise addition of acidic or basic solution of the polymer at the same concentration as that in the viscometer, with solution mixing until the pH reading was constant. The flow-time readings were within ± 0.2 sec which corresponds to η_{sp}/c ± 0.005. A radiometer M 65 Research pH meter was used.

RESULTS AND DISCUSSION

U.v. spectra.

Poly(4-vinyl pyridine-1-oxide), like 4-ethyl pyridine-1-oxide, protonates normally in HCl solution since its spectra shows clear isosbestic points indicating a simple acid–base equilibrium (*Figure 1*). However, in the spectra of poly(2-vinyl pyridine-1-oxide) no isosbestic points were observed (*Figure 2*), and the pH_a value calculated from the spectra

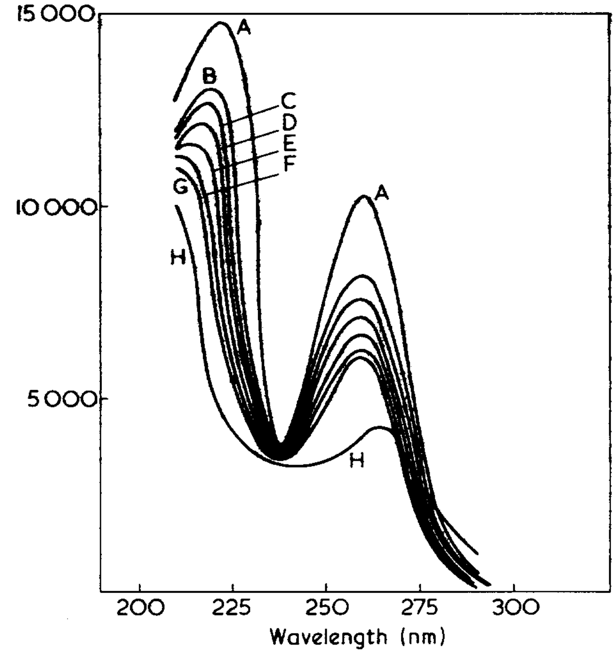
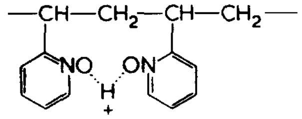


Figure 2 Spectra of poly(2-vinyl pyridine-1-oxide) in: A, H_2O; B, 0.125N HCl; C, 0.250N HCl; D, 0.500N HCL; E, 0.875N NCl; F, 1.250N HCl; G, 1.875N HCl; H, 5.000N HCl

Table 1 λ_{max} (nm) and ϵ of the longest wavelengths band, and pK_a values of the polymers and their monomer analogues

	Absorbtion in basic solution		Absorbtion in acid solution		
Sample	λ_{max}	(10^3 ϵ)	λ_{max}	(10^3 ϵ)	pK_a
Poly(2-vinyl pyridine oxide) (I)	260	(5.1)	265	(2.2)	0.48
Poly[(2-propene)-2-pyridine oxide] (II)	265	(5.3)	272	(2.3)	1.12
Poly[(1-propene)-2-pyridine oxide] (III)	262	(1.6)	265	(4.0)	1.35
2-methyl pyridine oxide	252	(10.7)	265	(1.4)	1.02
2-ethyl pyridine oxide	253	(10.1)	266	(1.9)	1.17

was much lower than expected, compared to 2-ethyl pyridine-1-oxide (*Table 1*). If we assume an intramolecular bonding between the α-hydrogen and the oxygen atom in poly(2-vinyl pyridine 1-oxide), then an orientation of the rings can take place so that the oxygen atoms are close to one another and on one side of the polymer chain. Thus, in strongly acidic solution a proton can be shared with two adjacent oxygen atoms to form a dimer salt (IV) whereas 2-ethyl pyridine-1-oxide forms the normal salt (V).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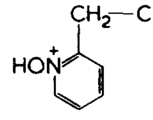

(V)

The formation of such a dimer salt is less probable in the case of the monomer analogue, 2-ethyl pyridine-1-oxide, particularly in dilute solution (1×10^{-4} M/residue) which was used for our u.v. measurements. However, it was reported that 2-methyl pyridine-1-oxide hydrochloride is a dimer salt only in the solid state[10,11].

We also found that isotactic poly(2-vinyl pyridine-1-oxide) (pK_a 0.56) has lower basicity than syndiotactic poly(2-vinyl pyridine-1-oxide) (pK_a 0.78). This supports our hypothesis that when the oxygen atoms are on the same side of the chain, dimer salts are more favourable, as in the case of the isotactic form.

When the α-hydrogen is replaced with a methyl group (polymer II), the basicity increases markedly (pK_a changes from 0.48 to 1.12 as shown in *Table 1*). This increase in basicity cannot be due only to the increase in the inductive effect of one methyl group since the pK_a of 2-ethyl pyridine-1-oxide is 1.17 and the pK_a of 2-methyl pyridine-1-oxide is 1.02. (Also, the pK_a of 2-ethyl pyridine is 5.83, and the pK_a of 2-isopropyl pyridine[12] is only 5.97.) Therefore, the increase in the basicity of polymer II must also be due to the absence of bonding between the α-hydrogen and the oxygen atom, unlike poly(2-vinyl pyridine-1-oxide), which renders polymer II easier to protonate. Moreover, a molecular model shows that the α-methyl group in polymer II restricts the orientation of the rings about the chain, so that close packing of the polymer is more difficult and hence the formation of a dimer salt is less probable.

When the β-hydrogen is replaced with a methyl group (polymer III), the basicity also increased ($pK_a = 1.35$). This increase in basicity compared to polymer I, cannot be due only to the inductive effect of one methyl group. This can be explained if we assume that in polymer III the presence of a methyl group between the two rings restricts the close packing of the rings, and the formtion of a dimer salt is unlikely. Thus, the polymer behaves as a stronger base compared with polymer I, and protonates in the normal way.

Viscosity – pH curves

The viscosities of our polymer solutions conform to those of non-electrolytes since a plot of intrinsic viscosity, η_{sp}/c *versus* concentration, *c*, was linear; thus a change in the viscosity of the solution is related to the degree of coiling of the polymer molecule.

The shape of the viscosity/pH curve (*Figure 3*) of poly(2-vinyl pyridine-1-oxide) (I) was generally similar to that reported before[13]. However, the peak at about pH 4 was not shown. This can be explained if we assume that when the adjacent N–O groups are protonated, the repulsion between them leads to an orientation of the rings so that some intramolecular crosslinking through hydrogen bonding takes place and the viscosity drops. Further protonation, in stronger acid, leads to more repulsion of the N–O groups, the polymer chain expands again, approaching a rod shape, and the viscosity increases.

When the α-hydrogen was replaced with a methyl group as in polymer II three major differences were observed: firstly, in polymer I there was a minimum over a relatively wide pH range (6–8.5) where the bonding between the α-hydrogen and the adjacent oxygen is not affected, but in polymer II the minimum was only at pH 6. Thus the viscosity of polymer II was more sensitive to the pH change since it went up sharply both above and below pH 6, probably because the oxygen atom is no longer shielded by the α-hydrogen. Secondly, the viscosity of polymer II increased continuously in acidic solution, in contrast to polymer I. This indicates that it protonates in the normal way, and that

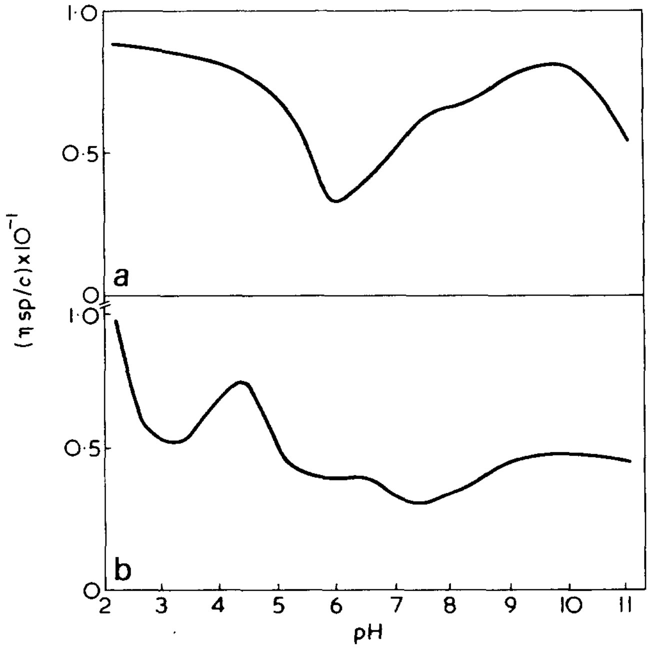
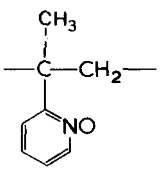
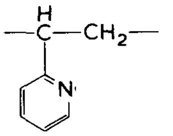


Figure 3 Viscosity *versus* pH curves for: (a),



(b)



its protonation is not accompanied by any change in conformation due to orientation of the rings. Thirdly, above pH 10–11 the water molecules associated with polymer II are more easily replaced by OH ions and the polymer coil contracts due to crosslinking so the viscosity drops.

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