Mode of crosslinking of degradable poly(vinylpyridine *N*-oxide) gels

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The degradation mechanism of gels from poly(vinylpyridine *N*-oxide) was investigated by differential scanning calorimetry , C, H, N analysis, infra-red spectroscopy and degradability tests. It was found that poly(2-vinyl pyridine *N*-oxide) gels, regardless of the persulphate initiator used, were weaker than poly(4-vinyl pyridine *N*-oxide) gels. C, H, N analysis and infra-red spectroscopy indicated that the initiator becomes an integral part of the gels. A mechanism for the formation of the gels is proposed.

(Keywords: poly(vinylpyridine *N*-oxide); hydrogels; degradable gels; crosslinking)

INTRODUCTION

Products of synthetic polymeric origin are almost always designed to have service lives of at least several years. In the biomedical field, however, some requirements can best be solved if the products have predetermined and relatively short service lives. Biodegradable sustained-release drug systems constitute an appropriate example for such cases. The temporary presence of drug depot can be achieved if it is constructed from a biodegradable material. If the residence time in the body can be controlled, then it is possible to use the same well characterized system for various applications. In order to achieve these, one has to find a biocompatible polymer, characterize it and understand the underlying mechanism of degradation.

Poly(2-vinylpyridine *N*-oxide) (P2VNO) satisfies the requirement of biocompatibility. It has been put to use in clinical trials as a chemotherapeutic agent against silicosis[1]. It has been shown to be non-toxic, and is non-carcinogenic as long as its monomer or dimer do not remain in the polymer[2]. It has also been shown that it is not degradable unless it is subjected to rigorous conditions, which are not encountered in the body[3]. In its preparation poly(2-vinylpyridine) (P2VN), a hydrophobic polymer, is converted to its oxide P2VNO, which is hydrophilic. A crosslinked hydrophilic polymer always has a very good potential for use as a biomaterial due to its high water retention. Thus P2VNO becomes an excellent candidate as a starting material for construction of a degradable product if a degradable form can be obtained.

It was previously reported that a series of polymer networks can be synthesized from P2VNO with varying rates of degradation[4]. The nature of the degradation was, however, not known. Understanding and control of the process of degradation was thought to be important both for the sake of fundamental chemical research as well as to tailor-make materials with predetermined service life.

In that work degradable gels were synthesized from (a) P2VNO and (b) P2VNO and poly(1-vinylpyrrolidone) (PVP), through the action of ammonium persulphate. It was observed that, in both gel types, an increase in PVNO content led to an increase in instability. Generally, a covalent bond will not result in a degradable network unless it contains bonds in the polymer backbone that are easily hydrolysable. Since P2VNO is known to be quite stable, that possibility for gel degradation had to be excluded. The biodegradation had to result from an interaction that takes place only in the presence of ammonium persulphate during the process of gel formation.

One possibility was the retention of ammonium persulphate in the formed network through bond formation that in strength lies somewhere between covalent and hydrogen bonds. If this hypothesis was correct, then ammonium persulphate or its ions could be detected in the network and possibly in the initial degradation products.

The following sections contain the results of the experimental work, including analyses aimed at resolving the mode of crosslinking of hydrogels of the 2- and 4-isomers of PVNO (*Figures 1a* and *1b*) formed under the action of two different persulphates.

EXPERIMENTAL METHODS

P2VNO and P4VNO were prepared according to the procedure published previously[3], dried in vacuum oven at 45°C overnight and stored in vacuum.

Three different types of gels were prepared in order to investigate the effects of ingredients on the properties of the gels. The gels contained the following: P2VNO and

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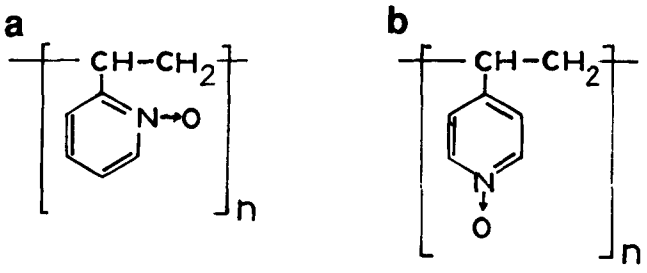

Figure 1 (a) Poly(2-vinylpyridine *N*-oxide) (P2VNO); (b) poly(4-vinylpyridine *N*-oxide) (P4VNO)

ammonium persulphate (G-040 series); P2VNO and potassium persulphate (G-140 series); and P4VNO and ammonium persulphate (G-240 series).

In the preparation of the gels, to a 5 ml distilled water solution of PVNO (0.165 M), varying amounts of persulphate were added to yield the molar ratios of PVNO: persulphate of 1:1.1, 1:2.2 and 1:4.4 for 040, 041 and 042, respectively. The stoppered tubes were then kept in a thermostated water bath (80°C) for 2 h. At the end of this period all three samples were completely gelled. The gels were washed three times with distilled water and once with acetone, dried in a vacuum oven at room temperature and stored in a desiccator. C, H, N analysis was carried out on the gels.

Small samples (2.5–10.0 mg) were used in the d.s.c. analysis (DuPont 1090 DSC).

In order to test their degradability, the gels (15 mg) were stored in distilled water. After 2 h, all the gels appeared swollen. After 72 h all G-040 series gels had completely dissolved while the others remained swollen.

The swollen G-140 and G-240 series gels in 3 ml distilled water were heated at 80°C for 2.5 h. At the end of this period, a large portion of G-140 series gels had dissolved. The G-240 series, however, were not affected by this digestion procedure. P2VNO, P4VNO and the gels were subjected to heating at 250°C for 2 h. The samples were all charred.

Infra-red spectra of the gels, P2VNO and P4VNO, before and after degradation, were obtained from their KBr pellets and the results are presented.

EXPERIMENTAL RESULTS AND DISCUSSION

Differential scanning calorimetry

The d.s.c of P2VNO contains a slight change in heat flow at around 130°C and a substantial change at around 270°C, which can be interpreted as peaks for glass transition and charring (decomposition), respectively (*Figure 2*).

The gel 041 (P2VNO–ammonium persulphate) shows the initial slight change at a lower temperature (110°C) than P2VNO and two major changes (in opposite directions) at 240°C and 270°C.

The gel 141 (P2VNO–potassium persulphate) is quite similar to gel 041 in general appearance. The second peak appears at 210°C, has a shoulder at around 240°C and the third peak is at 290°C with a shoulder at 270°C.

The d.s.c. of P4VNO is identical to its isomer P2VNO with initial change at 100°C and the second at 280°C (*Figure 3*).

The d.s.c. of the gel 241 (P4VNO–ammonium persulphate) is very similar to that of gel 041. There are three peaks, the first at 120°C, the second at 250°C and the third at 290°C. It again shows that the second peak of P4VNO has shifted 30°C lower and a third peak appears later.

If the directions of the peaks are taken into account, with the first becoming T_g, the middle peak might indicate that there is a distinct change in the orientation of the gel (possibly crystallization) followed by complete disruption of the structure by decomposition at the third.

C, H, N analysis

C, H, N analysis results indicate that the gels synthesized with ammonium persulphate from the 2- and 4-isomers of PVNO have quite close values of C (about 41% and 45%, respectively), but both are low with respect to that of the original polymers (about 62% and 59%, respectively). The 140 gels, however, have extremely low carbon values (between 11 and 24%), indicating the presence of substantial amounts of other elements in the structure.

Our calculations based on the C, H, N values show that, instead of peroxy bonds, the structures in *Figure 4* are more compatible with the data obtained: *Figure 4a* is for P2VNO–ammonium persulphate gels, G-040 series

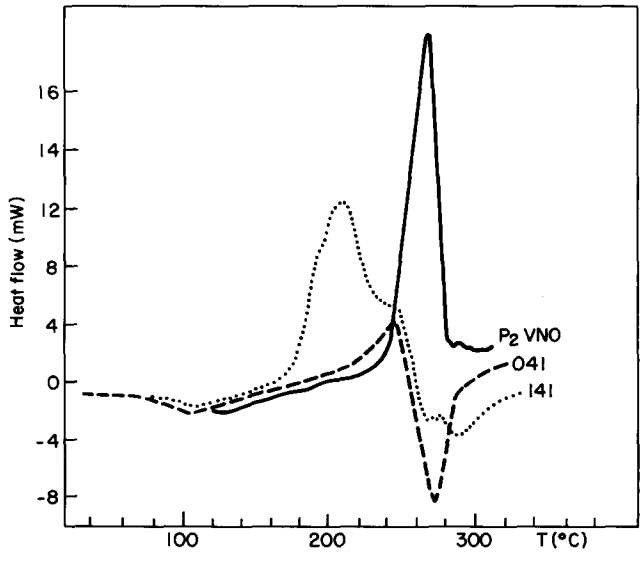

Figure 2 D.s.c. of P2VNO and gels 041 and 141

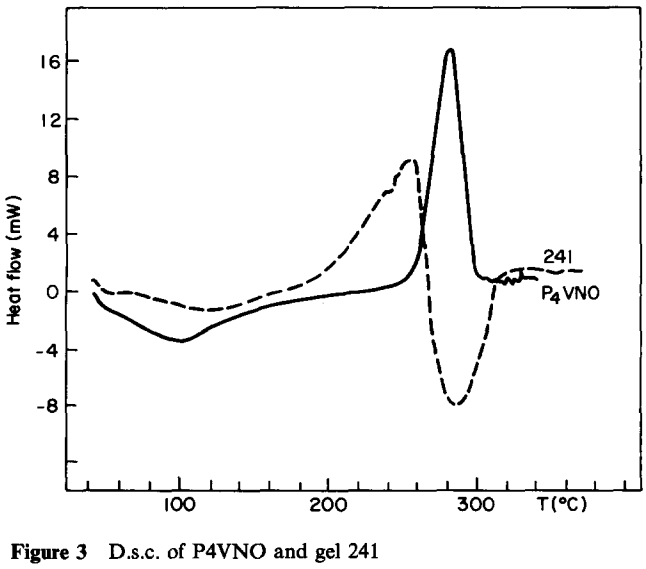

Figure 3 D.s.c. of P4VNO and gel 241

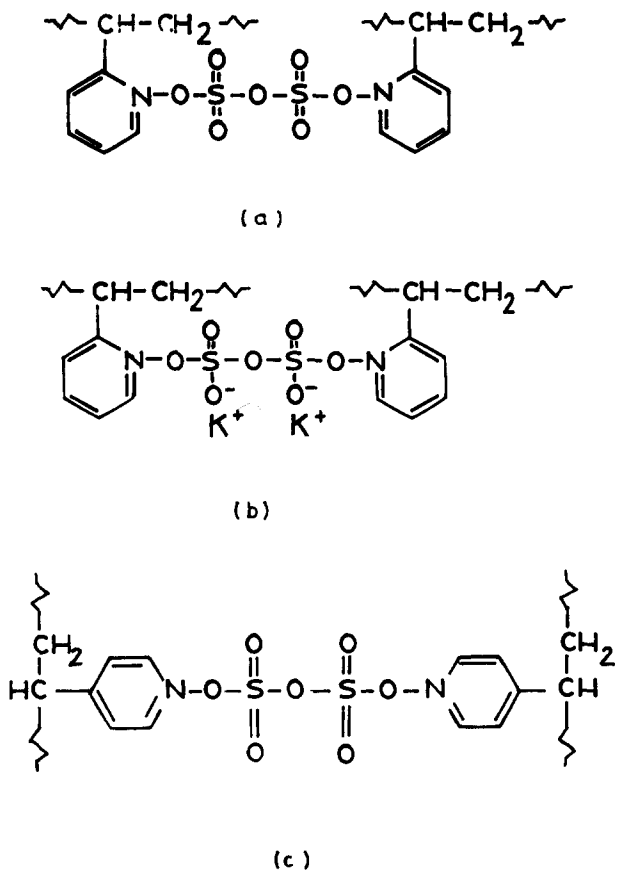

Figure 4 Proposed structure of PVNO gels: (a) 040 series; (b) 140 series; (c) 240 series

(one S_2O_5 chain connecting two pyridine oxide groups); *Figure 4b* is for P2VNO–potassium persulphate gels, G-140 series (one $K_2S_2O_5$ chain connecting two pyridine oxide groups); and *Figure 4c* is for P4VNO–ammonium persulphate gels, G-240 series (one S_2O_5 chain connecting two pyridine oxide groups). Obviously such a gel structure should yield peaks for $-SO_2-$ groups in the i.r. (and they were found).

Infra-red spectroscopy

Crosslinking of P2VNO or P4VNO could be achieved by any one of the following mechanisms:

(1) attachment through the backbone,

(2) ring opening, or

(3) attachment through the ring (especially through the ring nitrogen).

With ammonium persulphate initiated gels of P2VNO (040 series), aromatic CH wagging at 770 cm^{-1} is at the expected position, and ring vibration of 1490 cm^{-1} is also present (*Figure 5a*). Besides, nitrile formation that should lead to an absorption at 2200 cm^{-1} is not found. These mean that no ring-opening product is detectable and this is substantiated by the retention of ring aromaticity, ruling out the possibility of ring opening. In the spectrum of PVN, C=C and C=N ring stretchings are observed at 1590 and 1570 cm^{-1}, respectively. These peaks shift to 1700 and 1650 cm^{-1} in P2VNO. In the gels, they appear at 1700 and 1620 cm^{-1}, indicating that an interaction has influenced the nitrogen atom (like oxygen does when PVN is converted to P2VNO). The 1220 cm^{-1} peak is the most predominant peak of P2VNO and indicates the oxidation of the nitrogen of the ring. Its counterpart in PVN is at 1160 cm^{-1}. In the gels neither of these peaks is observed. Instead, two new strong and broad peaks are detected at 1260 and 1100 cm^{-1}.

With 140 series gels (P2VNO gels initiated with potassium persulphate), these new peaks are observed around 1300 and 1100 cm^{-1}, with the former being the most prominent.

With 240 series gels (P4VNO gels initiated with ammonium persulphate), a similar observation is made, with the 1100 cm^{-1} peak being dominant (*Figure 5b*).

When i.r. tables are examined[5], it is observed that SO_2N absorbs strongly at 1330 cm^{-1} and SO_2O at 1150–1200 cm^{-1}. These spectra indicate that ammonium persulphate initiator leads to gels (040 and 240 series) with strong absorbance at 1100 cm^{-1} and the potassium persulphate to gels with absorbance at 1300 cm^{-1}. This is quite remarkable because, although P2VNO and P4VNO are isomers, which yield slightly but distinctly different spectra, upon crosslinking in the presence of the same initiator they have the same new major peak, while P2VNO gels initiated with two different initiators have different new major peaks. Even with this evidence only, it could be proposed that the initiator takes part in the formed gel. Upon charring at 250°C, it is observed that the polymer peaks are reduced in strength in comparison to those of the new (initiator) peaks, and the observations made above are confirmed again (*Figures 6a* and *6b*).

Degradability tests

The gels when brought into contact with water all swell within the first 24 h, and within 72 h all 040 series dissolve while 140 and 240 series remain swollen. Upon application of heat (80–85°C) for 2.5 h, the 140 series completely dissolve but 240 series remain swollen.

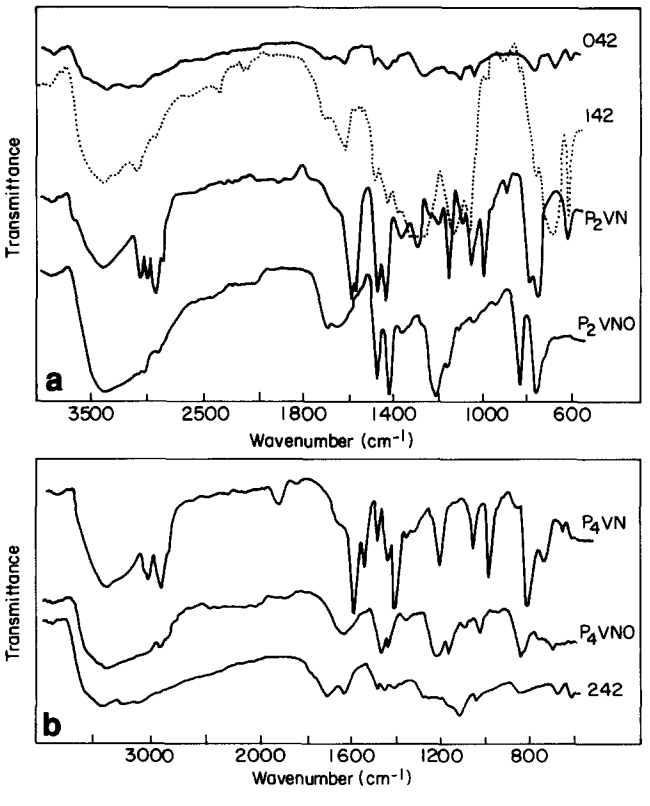

Figure 5 I.r. spectra of 2- and 4-isomers of PVN, PVNO and their gels: (a) 2-isomer; (b) 4-isomer

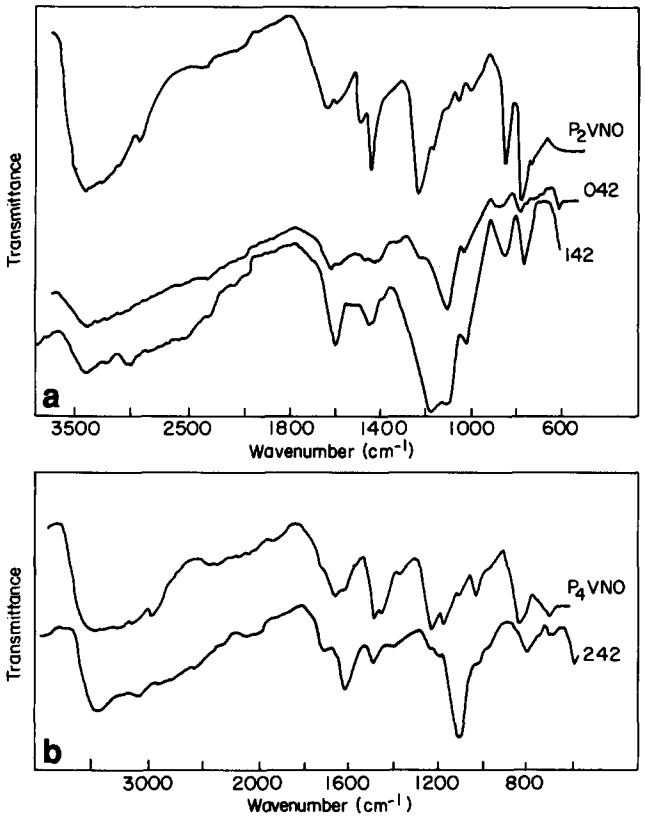

Figure 6 I.r. spectra of charred PVNOs and their gels: (a) 2-isomer; (b) 4-isomer

CONCLUSIONS

As shown by the degradation test, the gels of P2VNO, regardless of their initiator, are much weaker than that of P4VNO type. Since the only difference between them is the position of the nitrogen on the ring, the reason for this difference in strength (or stability) could be the strain imposed upon any linkage that occurs quite close to the polymer backbone (as it is in P2VNO). It seems that the presence of potassium ions somehow increases the strength of the P2VNO gel. The 240 series, due to their formation through the nitrogen, which is quite distal to the backbone, seem to be very stable under the circumstances. One might suggest that the 240 gels are forming through a linkage of pyridine groups of different polymer chains, reducing the strain imposed on the linkage. In conclusion, it can be stated that, by varying the monomer and the initiator, it is possible to form gels from PVNO with different stabilities. The data imply that the binding nature is quite similar but the counter-ion of the initiator and the position of the attachment with respect to the polymer backbone are highly influential on the stability of the resultant gel.

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