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Original Article

Synthesis of polymers containing 3-hydroxypyridin-4-one bidentate ligands for treatment of iron overload

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Abstract

Iron overload is a clinical problem which can be prevented by using iron chelating agents. An alternative method of relieving iron overload is to reduce iron absorption from the intestine by administering specific iron chelating agents, which can bind iron to form nonabsorbable complexes. Based on this strategy, a series of polymeric ligands containing the chelating moiety 3-hydroxypyridin-4-ones (HPOs) were synthesized. The synthetic route involves the benzylation of hydroxyl group of (2-methyl-3-hydroxypyran-4-one (maltol) and conversion of benzylated maltol to 3-benzyloxypyridin-4-one derivatives by using three suitable primary amines (2,6-diaminohexanoic acid (lysine) and 1,6-diaminohexane and 5-aminopentanol). The resulted compounds incorporated into polymer by copolymerization with acryloyl chloride using 2, 2'-azobisisobutyronitrile (AIBN) as the initiator. Finally, the benzyl groups of polymers were removed by catalytic hydrogenation (Pd/C). In this work, three final polymers of HPO derivatives namely poly-2-propylamido-6-(3- hydroxy -1,4-dihydro-2-methy-4-oxopyrid-1-yl) hexanoic acid, 6-(3-hydroxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexyl-1-polypropylamide and 5-(3-hydroxy-1-,4-dihydro-2-methyl-4-oxopyrid-1-yl)-1-polyacrylate pentane were synthesized. Identification and structural elucidation of compounds were achieved by proton nuclear magnetic resonance (^{1}H NMR), carbon nuclear magnetic resonance (^{13}C NMR) and infrared (IR) spectroscopy.

Keywords: 3-Hydroxypyridin-4-ones; Iron overload; Iron chelating agents

INTRODUCTION

There are a number of disease states which are associated with the gradual accumulation of iron in the body (1-2). Excessive iron overload, like iron deficiency, can be equally detrimental, as evidenced by the genetic disorder haemochromatosis, which leads to tissue damage and pathological siderosis (3-4).

Iron overload falls into three major categories: 1) an inappropriate increase in the absorption of iron by iron specific transport proteins in the gut mucosa. This occurs in idiopathic haemochromatosis and thalassaemia intermedia (5,6); 2) from repeated blood transfusions associated with thalassemia and aplastic anemia (7-9) and 3) acute iron poisoning. The accidental ingestion of iron-containing preparations is relatively common in children.

With regard to this latter category the lethal oral dose of elemental iron is estimated to be 200-300 mg/Kg body weight and because supplementary tablets contain up to 105 mg of elemental iron, the ingestion of several tablets can result in severe poisoning in small children (10-15). The ingestion of iron and ascorbate, the combination found in many iron preparations accessible over-the-counter, may generate hydroxyl radicals *in vivo* which may lead to a cascade of adverse reactions (16). Prompt removal of the drug by gastrointestinal decontamination using either syrup of ipecac or gastric lavage using sodium bicarbonate solution are primary actions taken in cases of acute iron poisoning. Loss of consciousness followed by death can occur within 24 h subsequent to acute iron poisoning if the patient is left untreated (15,17). Primary events such as severe hypotension and metabolic

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acidosis caused primarily by the conversion of ferrous iron to ferric iron and consequential release of hydrogen ions, may lead to changes in the functioning of the lungs, heart and kidneys (17,18).

Iron overload can be minimized by the use of iron-specific chelating agents which have a systemic distribution (6). An alternative method of relieving iron overload is to reduce the efficiency of iron absorption from the intestine by administering iron chelators, which can bind iron irreversibly to form nontoxic, kinetically inert complexes that are not absorbed and are therefore excreted in the feces.

The flux of iron across the intestinal mucosa is a function of the soluble iron concentration within the lumen. Then one of the most commonly used treatment modalities is the use of orally administered sodium bicarbonate or sodium hydrogen phosphate. These salts render iron less soluble and thereby reduce its bioavailability by converting it to ferric hydroxide-based polymers. However previous studies using rats as an animal model demonstrated that neither sodium bicarbonate nor phosphate are efficient complexing agents for iron (19,20). Present therapy in severe cases includes oral and intravenous administration of a high dose of an iron chelating agent such as desferrioxamine (DFO) (Fig. 1). However, Geffiner and Opas demonstrated that the use of DFO at the necessary required dose frequently causes hypotension (21). Given that the administration of DFO causes hypotension, Mahoney and coworkers investigated the use of DFO covalently attached to high molecular weight carbohydrates such as dexran and hydroxyethyl starch in animal models (22). They reported that these macromolecular forms of DFO do not cause detectable decrease in blood pressure of experiment animals, have a longer half-life than the free drug and the chelating property is unaffected. The effectiveness of DFO as an iron(III) chelator is not questioned, however the use of DFO is not ideal for the treatment of iron poisoning due to the associated pathological changes in patients with acute iron poisoning, necessity of a high dose and higher cost of the drug (23,24).

Efficient chelation of ingested iron in the gastrointestinal tract would be an efficient means of dealing with acute iron poisoning. Thus the use of a macromolecule bearing an effective iron(III) chelator, could be useful in the treatment of acute iron poisoning. A series of polymeric chelators have been designed, using the bidentate ligands 3-hydroxypyridin-4-one (Fig. 1) to act as nonabsorbable iron-selective additives. 3-Hydroxypyridin-4-ones are currently one of the main candidates for the development of orally active iron chelators alternatives to DFO (4,25-27). This class of ligand is highly selective for iron(III) under biological conditions (Table 1) (4). Specifically, three 3-hydroxypyridin-4-one bidentate ligands, 1-(5′-amino-5′-carboxy-pentyl)-2-methyl-3-hydroxypyridin -4-one, 1-(6′-aminohexyl)-2-methyl-3-hydroxy-pyridin-4-one and 1-(5′-hydroxypentyl)-2-methyl-3-hydroxypyridin-4-one have been incorporated into polymers by copolymerisation with 2-propenoyl chloride (acryloyl chloride) using AIBN as an initiator.

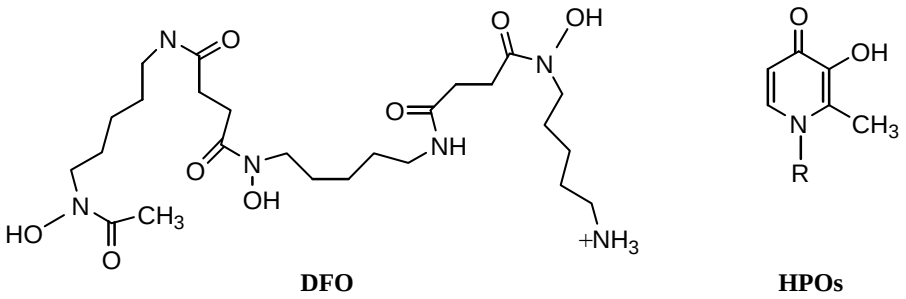


Fig. 1. Structure of iron-chelating agents desferrioxamine and 3-hydroxypyridin-4-ones.

Table 1. Logarithms of overall stability constants for desferrioxamine and 3-hydroxypyridin-4-ones HPOs with selected metal ions.

Metal ion	DFO	HPOs
Fe (III)	31	37
Cu (II)	14	17
Zn (II)	11	12.5
Mg (II)	4	7
Ca (II)	2.3	4.5

MATERIALS AND METHODS

All the chemicals used in this project were obtained from Aldrich (Gillingham, UK). Melting points were determined using an Electrothermal IA 9100 digital melting point (Germany). IR spectra were recorded on a perkin-Elmer 1420. The proton nuclear magnetic resonance (^{1}H NMR) spectra were determined with a Bruker 400 MHz spectrometer (Germany). Chemical shifts (δ) are reported in ppm downfield from the internal standard tetramethylsilane (TMS). Mass spectra were taken using a Vacuum Generaters16F (35eV). Elemental analysis (LecoCHNCl-932) was performed by micro analytical laboratories, University of Manchester, Manchester M13 9PL UK.

General procedure for preparation of 3-hydroxypyridin-4-one polymers

In this work 3 polymers namely, poly-2-propylamido-6-(3-hydroxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl)hexanoic acid (**17**), 6-(3-hydroxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexyl-1-polypropylamide (**18**) and 5-(3-hydroxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl)-1-polyacrylatep-entane (**19**) were successfully synthesized (Fig. 2). The syntheses of these polymers (**17-19**) were achieved in four steps: I)amination of benzyl maltol (**2**), II) acylation or esterification of the resulting pyridin-4-one compounds (**6**, **7** and **9**), III) polymerization of the monomers (**11-13**) and finally IV) hydrogenolysis of the protected pyridin-4-one polymers (**14-16**). The detailed description of the synthesis of each polymer is given in following sections.

Synthesis of pyridine-4-one polymers

Schematic syntheses of pyridine-4-one polymers are shown in Fig. 2.

Synthesis of poly-2-propylamido-6-(3-hydroxy-1,4-dihydro-2-methy-4-oxopyrid-1-yl) hexanoic acid (17)

I) Synthesis of 2-methyl-3-benzyloxypran-4-one (Benzyl maltol)(2)

To a solution of 2-methyl-3-hydroxypyran-4-one (**1**) (24 g, 0.2 mol) in methanol (200 ml) was added 20 ml of aqueous solution of sodium hydroxide (8.8 g, 0.22 mol) and benzyl chloride (27.8, 0.22 mol) and the mixture was refluxed for 6 h. After removal of solvent by rotary evaporation, the residue was mixed with water (100 ml) and extracted into dichloromethane (3 × 100 ml). The combined extracts were washed with 5% sodium hydroxide (3 × 300 ml) and with water (2 × 300 ml) respectively. The organic fraction was dried over anhydrous sodium sulphate, filtered and rotary evaporated to yield an orange oil which became solid on cooling. Recrystallization from diethyl ether gave the pure product as colorless needles (35.4 g, 82%); mp 53-54 ºC.

II) Synthesis of 2-Amino-6-(3-benzyloxy-1,4-dihydro-2-methyl-4-oxopyrid-1-yl) hexanoic acid dihydrochloride (trihydrate) (6)

To a solution of benzyl maltol (**2**) (10.80 g, 0.05 mol) in ethanol (50 ml)/water (50 ml) was added 2, 6-diaminohexanoic acid (**3**) (7.3 g, 0.05 mol) followed by 2 N sodium hydroxide solution until pH 12 was attained. The mixture was stirred for 5 days at room temperature. After adjustment to pH 1 with hydrochloric acid, 12 M, volume was reduced to 50 ml by rotary evaporation prior to addition of water (50 ml) and washing with diethyl ether (100 ml). Subsequent adjustment of the aqueous fraction to pH 12 with 10 N sodium hydroxide solution was followed by extraction into dichloromethane (3 × 100 ml), the organic layers then being dried over anhydrous sodium

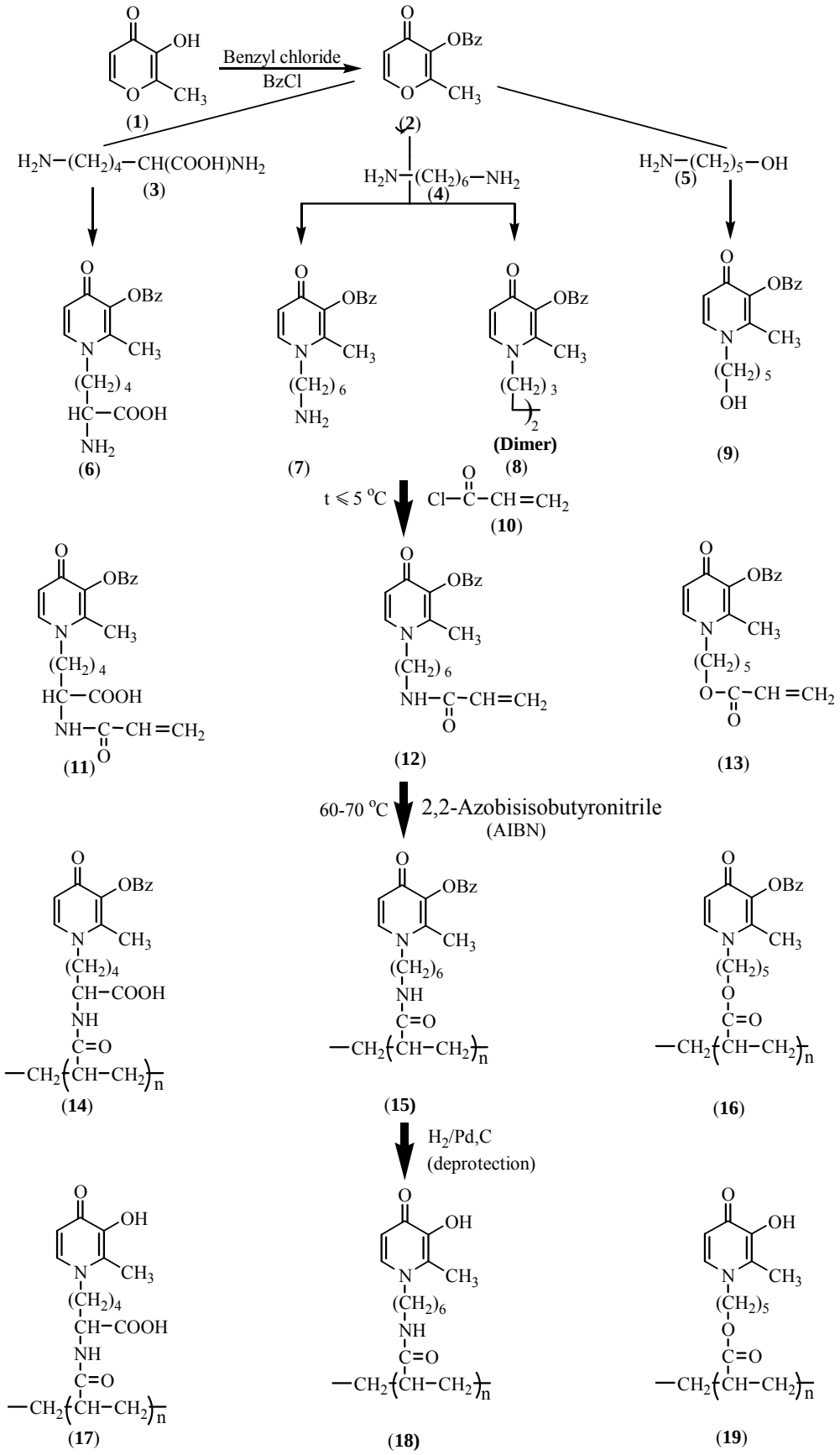


Fig. 2. Synthesis of 3-hydroxypyridin-4-one polymers**.**

sulphate, filtered and rotary evaporated to give a yellowish-brown "honeycomb" solid. The methanolic filtrate of the yellowish-brown solid was acidified using HCl 12 M and then recrystallized in ethanol/diethyl to give the desired solid as yellow flakes (9.5 g, 40%); mp 135-136 °C.

III) Synthesis of 2-acrylmido-6-(3-benzyloxy-1,4-dihydro-2-methyl-4-oxopyrid-1-yl)hexanoic acid (11)

A modified procedure described by Winston (28) was used. Acryloyl chloride (**10**) (20.3 ml, 0.25 mol) was added in aliquots with vigorous stirring to a solution of 2-amino-6-(3-benzyloxy-1,4-dihydro-2-methyl-4-oxopyrid-1-yl) hexanoic acid (**6**) (23.56 g, 0.05 mol) in aqueous solution of sodium hydroxide (5%). The solution was maintained at 3-5 ^{o}C during and after the addition. The mixture was stirred for 2 h and acidified to pH 5.0 using concentrated hydrochloric acid. 2-Acrylmido-6-(3-benzyloxy-1,4-dihydro-2-methyl-4-oxopyrid-1-yl) hexanoic acid monomer(**11**) was isolated in 40% yield (8.00 g) by repeated extraction with chloroform followed by concentrating *in vacuo* and lyophylization, mp 112-113 °C.

IV) Synthesis of poly-2-propylamido-6-(3-benzyloxy-1,4-dihydro-2-methy-4-oxopyrid-1-yl) hexanoic acid (14)

A solution of 2-acrylamido-6-(3-benzyloxy-1,4-dihydro-2-methyl–4-oxopyrid-1-yl)hexanoic acid (**11**) (11.0 g, 0.028 mol) in dimethylformamide (DMF) (100 ml), was purged with oxygen free dry nitrogen. The initiator, AIBN (1% w/w of sample) was added and the reaction mixture heated at 60-70 °C for 20 days. Aliquots of the initiator were added on days 2, 11 and 15. The solvent was removed by rotary evaporation and 10% aqueous methanol was added to the resulting beige 'honeycomb' solid. The resulting suspension was filtered. The filtrate and the residue (5.4 g) were processed and analyzed as described below.

Low molecular weight fraction: The filtrate was subjected to dialysis against 10% aqueous methanol using visking tubing 18/32 (MW. Cut off 12000-14,000 Dalton, Copeland and Sons, U.S.A). Dialysis was continued for 24 h with frequent changes of solvent (10% aqueous methanol). The dialysed solution was filtered and lyophilized to give beige polymeric flakes, 660 mg, mp 35-41 °C.

HPLC/size exclusion chromatography (Waters, U.S.A) (10^4 A + 500 A PL gel columns, polystyrene calibration, DMF) indicated a molecular weight of the order 1000 to 1800 Dalton (low molecular weight fraction).

High molecular weight fraction: The residue, 5.4 g, was dried under vacuum over phosphoruspentaoxide (5.2 g), mp 38-44 °C.

^{1}H NMR and ^{13}C NMR in dimethyl sulfoxide (DMSO)-d_6 showed the nature of the compound to be the same as that of the filtrate. HPLC/size exclusion chromatography (10^4 A + 500 A PL gel columns, polystyrene calibration, DMF) indicated a molecular weight of the order 24,000 to 36,000 Dalton (high molecular weight fraction).

V) Synthesis of poly-2-propylamido-6-(3-hydroxy-1,4-dihydro-2-methy-4-oxopyrid-1-yl) hexanoic acid (17) (Deprotected polymer)

Low molecular weight fraction: The freeze dried polymeric material (**14**), 500 mg, was hydrogenated over Pd/C (2% w/w) in aqueous 95% ethanol (50 ml). The filtrate was concentrated *in vacuo* and freeze dried to give the deprotected polymer, 155 mg. mp 47-53 °C.

High molecular weight fraction: The polymeric material, 500 mg was hydrogenated over Pd/C (2% w/w) in a mixture of DMF and aqueous 95% ethanol (50 ml; 1:9). The filtrate was concentrated *in vacuo* and freeze dried, 170 mg, mp 52-59 °C. Details of ^{1}H NMR (DMSO-d_6) were identical to those of the low molecular weight fraction.

Synthesis of 6-(3-hydroxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexyl-1-polyp-ropylamide (18)

I) Synthesis of 1-Amino-6-(3-benzyloxy-1,4-dihydro-2-methyl-4-oxopyrid-1-yl) hexylamine (7)

To a solution of benzyl maltol (**2**) (10.80 g, 0.05 mol) in 200 ml of (ethanol/water: 1/1) was added 1, 6-diaminohexane (**4**) (11.6 g, 0.1

mol) and after adjustment of the pH to 13 with 2 N sodium hydroxide solution, the mixture was stirred for 7 days at room temperature. The volume of the mixture was reduced *in vacuo* and the aqueous mixture was acidified to pH 5.0 using concentrated hydrochloric acid followed by repeated extraction with dichloromethane (3 × 100 ml).Rotary evaporation of the combined organic extract gave a beige solid. To the obtained solid was added methanol and the mixture was acidified to pH 1 using concentrated hydrochloric acid. After evaporation of the solvent, the resulted solid was recrystallized from ethanol to give the hydrochloride salt of the dimericpyridinone compound, 1, 6-di-(3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexylaminedihydrochloride (**8**) 7.4 g (25%). mp 182-183 °C.

The aqueous mixture was basified with sodium hydroxide (10 M) to pH 11.0 and extracted further with dichloromethane. The organic extract was concentrated *in vacuo* and then was washed with acidified distilled water (pH 5). For further purification a column chromatography was performed using chlroroform:methanol (8:2) as eluent. After removal of the solvents ligand **7** was obtained as yellowish-brown waxy product (4.8 g, yield=30%). mp 132-133 °C.

II) Synthesis of 1-Acrylmido-6-(3-benzyloxy-1,4-dihydro-2-methyl-4-oxopyrid-1-yl)hexyl-amine (12)

Acryloyl chloride (**10**) (20.3 ml, 0.25 mol) and 1-amino-6-(3-benzyloxy-1,4-dihydro-2-methyl-4-oxopyrid-1-yl) hexylamine (**8**) (15.7 g, 0.05 mol) were reacted as described for compound **11** to afford the monomer **12** in 71% yield (13.0 g), mp 108-109 °C.

III) Synthesis of 6-(3-Benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexyl-1-polypropyl-amide (15)

1-Acrylamido-6- (3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexylamine (**12**), (11g, 0.03 mol) in DMF, was purged with oxygen-free dry nitrogen. The initiator, AIBN (1% w/w) was added and the reaction mixture heated at 60-70 °C for 20 days. Aliquots of the initiator were added on days 3, 7 and 16. The solvent was removed *in vacuo* and the resulting oil mixed with 50% aqueous methanol and dialyzed against the same solvent for four days using visking tubing 18/32 (MW cut off 12,000-14,000 Daltons) with frequent changes of solvent. The contents of the visking tubing were filtered and freeze dried to give the dry polymer in the form of beige crystals (1.01 g), mp 39-44 °C.

HPLC/size exclusion chromatography (10^4 A + 500 A PL gel columns, polystyrene calibration, DMF) indicated molecular weight of the order of 43,000 to 45,000 Daltons.

IV) Synthesis of 6-(3-hydroxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexyl-1-polypropyl-amide (18)

6-(3-Benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexyl-1-polypropylamide (**15**), 600 mg, in methanol (47.5 ml)/ ethanol (2.5 ml) was hydrogenated over Pd/C catalyst (2% w/w). The volume of the filtrate was concentrated *in vacuo* and freeze dried to give the deprotected polymer, 380 mg, mp56-61 °C.

Synthesis of 5-(3-Hydroxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl)-1-polyacrylatepentane (19)

I) Synthesis of 1-Hydroxy-5-(3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) pentane hydrochloride (9)

To a solution of compound **2** (10.8 g, 0.05 mol) in ethanol (100 ml)/water (100 ml) was added 5-aminopentanol (6.2 g, 0.06 mol) (5) followed by 2 N sodium hydroxide solution until pH 13 was obtained.

The mixture was then stirred for 6 days at 40-45 °C. After adjustment to pH 1 with concentrated hydrochloride acid, the solvent was removed by rotary evaporation prior to addition of water (50 ml) and washing with diethyl ether (2 × 50 ml). Subsequent adjustment of the aqueous fraction to pH 7 with 10 N sodium hydroxide solution was followed by extraction into dichloromethane (4 × 50 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and rotary evaporated to give an orange oil.

This oil was dissolved in ethanol /concentrated hydrochloric acid and rotary evaporated, the resulting white solid

recrystallized from ethanol/diethyl ether to give the desired compound in 60% yield (10.2 g), mp 141-142 °C.

II) Synthesis of 1-Propenoate-5-(3-benzyloxy-1, 4-dihdro-2-methyl-4-oxopyrid-1-yl) pentane (13)

Acryloyl chloride (**10**) (20.3 ml, 0.25 mol) and 1-hydroxy-6-(3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) pentane (**9**) (15.1 g, 0.05 mol) were reacted as described for compound **11** to afford the monomer **13** in 60% yield (10.5 g), mp 104-105 °C.

III) Synthesis of 5-(3-Benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl)-1-polyacrylate pentane (16)

A solution of 1-propenoate-5-(3-benzyloxy-1, 4-dihydro-2-metyl-4-oxopyrid-1-yl) pentane (**13**), (11.0 g, 0.03 mol) in DMF, was purged with oxygen-free dry nitrogen. The initiator, 2, 2-azobisisobutyronitrile (1% w/w) was added and the reaction mixture heated at 60-70 °C for 20 days. Aliquots of the initiator were added on days 3, 10 and 15.

The solution was concentrated *in vacuo* and dialyzed against 50% aqueous methanol for 24 h using visking tubing 18/32 (MW cut off 12,000-14,000 Daltons) with frequent changes of the solvent. The aqueous suspension from the visking tube was filtered and freeze dried to give the polymer in the form of a flaky white powder (380 mg) mp 34-39 °C.

HPLC/size exclusion chromatography (10^4 A + 500 A PL gel columns, polystyrene calibration, DMF) indicated molecular weight of the order 17,000 to 21,000 Dalton.

IV) Synthesis of 5-(3-Hydroxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl)-1-polyacrylatepentane (19)

5-(3-Benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl)-1-polyacrylate pentane (**16**), (380 mg) was dissolved in DMF (5 ml)/aqueous ethanol (95%) (45 ml). The solution was hydrogenated over Pd/C catalyst (5% w/w). Removal of the solvent *in vacuo* gave the desired deprotected polymer, 105 mg, mp 51-56 °C.

RESULTS

Compound 2 (Fig. 2)

^{1}H NMR (DMSO-d_6): δ (ppm) 2.1 (s, 3H, 2-C**H**$_3$), 5.1 (s, 2H, O-C**H**$_2$-Ph), 6.4 (d, J=5.6 Hz, 1H, 5-H), 7.2-7.5 (m, 5H, Ph), 7.9 (d, j=5.6 Hz,1H, 6-H); MS (EI)): m/z=216 (M^+), IR (KBr) (cm^{-1}): 1640 (C=O), 1575 (C=C), 1185 (C-O).

Anal.CalCd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59%. Found: C, 72.30; H, 5.66%.

Compound 6 (Fig. 2)

^{1}H NMR (DMSO-d_6): δ 1.2-1.9 (m, 6H, N-CH_2-(**CH$_2$**)$_3$-CH-), 2.3 (s, 3H, 2-CH_3), 3.8 (t, j=7.2 Hz, 2H, N-**CH$_2$**-CH_2-), 4.2 (m, 1H, N-CH_2-$(CH_2)_3$-**CH**(NH_2)(COOH)), 5.1 (s, 2H, O-CH_2-Ph), 6.8 (d, j=7.1 Hz, 1H, 5-H), 7.2-7.5 (m, 5H,Ph), 8.4 (d, j=7.1 Hz, 1H, 6-H): MS (EI)): m/z=344 (M-2HCl), IR (KBr) cm^{-1}: 1640 (pyridinone ring C=O), 1070 (C-N), 1580 (acid C=O).

Anal.CalCd for $C_{19}H_{26}O_4N_2Cl_2$. $3H_2O$: C, 48.44; H, 6.79; N, 5.94; Cl, 15.05%. Found: C, 48.56; H, 6.81; N, 5.93; Cl, 15.10%.

Compound 7 (Fig. 2)

^{1}H NMR (Methanol-d_4, CD_3OD): δ 1.1-1.7 (m, 8H, N-CH_2-**(CH$_2$)$_4$**-CH_2-NH_2), 2.2 (s, 3H, 2-CH_3), 2,5-2.8 (m, 2H, N-$(CH_2)_5$-**CH$_2$**-NH_2), 3.6-3.9 (t, j=7.2 Hz, 2H, N-**CH$_2$**-$(CH_2)_5$-NH_2), 5.0 (s, 2H, O-CH_2-Ph), 6.5 (d, j=7.2 Hz, 1H, 5-H), 7.1-7.6 (m, 5H, Ph), 7.9 (d, j=7.1 Hz, 1H, 6-H): MS (EI)): m/z=314 (M), IR (KBr): 1645 (pyridinone ring C=O), 1045 (C-N), 1530 (C=C) cm^{-1}.

Anal.CalCd for $C_{19}H_{26}O_2N_2$: C, 72.83; H, 8.28; N, 8.91%. Found: C, 72.81; H, 8.30; N, 8.89%.

Compound 8 (Fig. 2)

^{1}H NMR (CD_3OD-d_3): δ 1.1-1.9 (m, 8H, N-CH_2-**(CH$_2$)$_4$**-CH_2-N), 2.3 (s, 2×3H, 2-CH_3), 4.1-4.5 (t, j=7.1 Hz, 4H, N-**CH$_2$**-$(CH_2)_4$-**CH$_2$**-N), 5.2 (s, 2×2H, O-CH_2-Ph), 7.0 (d, j=7.2 Hz, 2×1H, 5-H), 7.1-7.6 (m, 2×5H, Ph), 8.4 (d, j=7.2 Hz, 2×1H, 6-H): MS (EI)): m/z=512 (M-2HCl), IR (KBr): 1640 (pyridinone ring C=O), 1040 (C-N), 1525 (C=C) cm^{-1}.

Anal.CalCd for $C_{32}H_{38}O_4N_2Cl_2$: C, 65.67; H, 6.49; N, 4.79; Cl, 12.12%. Found: C, 65.86; H, 6.51; N, 4.78; Cl, 12.15%.

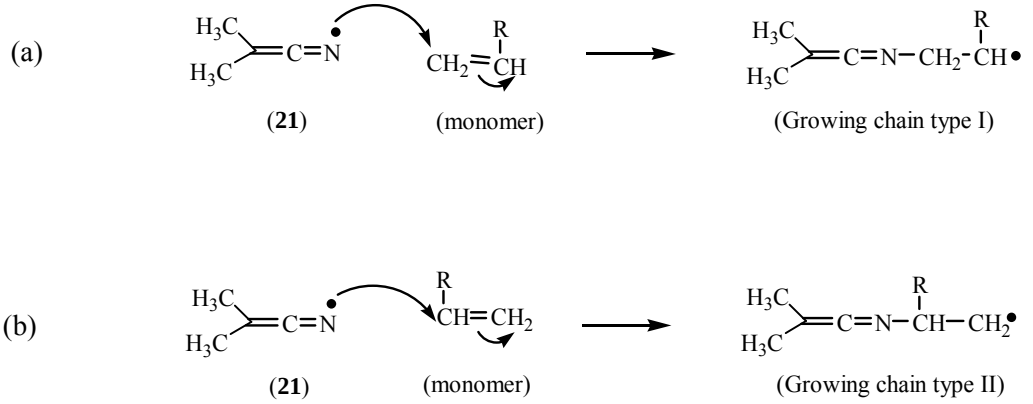


Fig. 3. Conferment of stabilization on the pyridine-4-one radical by the substituent R.

Compound 9 (Fig. 3)

^{1}H NMR (DMSO-d6): δ 1.2-1.8 (m,6H, N-CH2-**(CH2)$_3$**-CH2-O); 2.5 (s, 3H, 2-**CH$_3$**); 3.4 (m, 2H, N-(CH2)4-**CH$_2$**-OH); 4.1 (t, j=7.2 Hz, 2H, N- **CH$_2$**-(CH2)4-OH); 5.2 (s, 2H, O-CH$_2$-Ph); 6.9 (d, j=7.1 Hz, 1H, 5-H); 7.3-7.6 (m, 5H, Ph); 8.2 (d, j=7.1Hz1H, 6-H); MS (EI)): m/z=301 (M - HCl), IR (KBr): 1640 (pyridinone ring C=O), 2400-3400 (O-H) cm^{-1}

Anal.CalCd for $C_{18}H_{24}O_3NCl$: C, 64.03; H, 7.11; N, 4.15; Cl, 10.50%. Found: C, 64.21; H, 7.13; N, 4.16; Cl, 10.47%.

Compound 11 (Fig. 2)

^{1}H NMR (DMSO-d$_6$): δ 1.3-2.0 (m, 6H, N-CH$_2$-(**CH$_2$**)$_3$-CH-), 2.2 (s, 3H, 2-CH$_3$), 3.9 (t, j=7.1 Hz, 2H, N-**CH$_2$**-CH$_2$-), 4.2 (m, 1H, N-CH$_2$-(CH$_2$)$_3$-**CH**(NH$_2$)(COOH)), 5.1 (s, 2H, O-CH$_2$-Ph), 5.3 (d, j=11.7 Hz, 1H, NH-CO-CH=C**H**H), 5.9 (d, j=17.3Hz, 1H, NH-CO-CH=CH**H**), 6.1-6.4 (m, 1H, NH-CO-C**H**=CHH), 6.7 (d, j=7.3 Hz, 1H, 5-H), 7.3-7.6 (m, 5H**,** Ph), 8.1 (d, j=7.3 Hz, 1H, 6-H); MS (EI)): m/z=398 (M), IR (KBr) cm^{-1}: 1640 (pyridinone ring C=O), 1075 (C-N), 1650 (amide C=O)

Anal.CalCd for $C_{22}H_{26}O_5N_2$: C, 66.35; H, 6.53; N, 7.03%. Found: C, 66.50; H, 6.55; N, 7.05%.

^{13}C NMR ppm (DMSO-d$_6$): 12.1 (2-CH$_3$); 22.1, 29.3,29.9 (N-CH$_2$-**(CH$_2$)$_3$**-CH-); 52.0 (N-**CH$_2$**-CH$_2$-); 53.2 (N-CH$_2$-(CH$_2$)$_3$-**CH**(NH)(COOH)); 72.4 (O-**CH$_2$**-Ph); 115.0 (pyridinone ring); 127.9, 128.4, 128.5 (phenyl ring); 129.0 (-NH-CO-CH=**CH$_2$**); 133.1 (-NH-CO-**CH**=CH$_2$); 137.3 (pyridinone ring); 139.9 (pyridinone ring CQ); 142.9 (phenyl ring CQ); 144.6 (pyridinone ring CQ); 166.8 (pyridinone ring C=O); 170.7 (-COOH); 174.0 (-NH-**CO**-CH=CH$_2$).

Compound 12 (Fig. 2)

^{1}H NMR (DMSO-d$_6$): δ 1.2-1.8 (m, 8H, N-CH$_2$-**(CH$_2$)$_4$**-CH$_2$-NH$_2$), 2.3 (s, 3H, 2-CH$_3$), 2,6-2.9 (m, 2H, N-(CH$_2$)$_5$-**CH$_2$**-NH$_2$), 3.7-4.1 (t, j=7.1 Hz, 2H, N-CH$_2$-(CH$_2$)$_5$-NH$_2$), 5.1 (s, 2H, O-CH$_2$-Ph), 5.4 (d, j=11.6 Hz, 1H, -NH-CO-CH=**H**H), 5.9 (d, j=17.1 Hz, 1H, -NH-CO-CH=H**H**), 6.0-6.3 (m, 1H, -NH-CO-C**H**=CH$_2$), 6.7 (d, j=7.2 Hz, 1H, 5-H), 7.2-7.6 (m, 5H, Ph), 7.8 (d, j=7.2 Hz, 1H, 6-H): MS (EI)): m/z=368 (M), IR (KBr): 1640 (pyridinone ring C=O), 1650 (amide C=O) cm^{-1}.

Anal.CalCd for $C_{22}H_{28}O_3N_2$: C, 71.76; H, 7.60; N, 7.70%. Found: C, 71.79; H, 7.62; N, 7.59%.

^{13}C NMR ppm (DMSO-d$_6$): 11.8, (2-CH$_3$); 25.3, 26.1, 28.8, 30.0 N-CH$_2$-**(CH$_2$)$_4$**-CH$_2$-NH-); 40.0 (N-CH$_2$-(CH$_2$)$_4$-**CH$_2$**-NH-), 52.6 (N-**CH$_2$**-(CH$_2$)$_4$-CH$_2$-NH-); 71.7 (O-CH$_2$-Ph); 115.7 (pyridinone ring); 127.0 (-NH-CO-CH=**CH$_2$**); 127.7, 128.1, 128.4 (phenyl ring); 131.7 (-NH-CO-**CH**=CH$_2$); 137.7 (pyridinone ring CQ); 139.4 (pyridinone ring); 140.5 (phenyl ring CQ); 145.2 (pyridinone ring CQ); 164.4 (pyridinone ring C=O); 171.8 (-NH-**CO**-CH=CH$_2$).

Compound 13 (Fig. 2)

^{1}H NMR (DMSO-d6): δ 1.2-1.9 (m ,6H, N-CH$_2$-**(CH$_2$)$_3$**-CH$_2$-O-); 2.4, (s, 3H, 2-CH$_3$); 3.9, (m, 2H, N-(CH$_2$)$_4$-**CH$_2$**-O-CO-); 4.2 (t, j=7.1

Hz, 2H, N-**CH_2**-$(CH_2)_4$-O-); 5.1 (s, 2H, O-CH2-Ph); 5.5 (d, j=11.8 Hz, 1H, O-CO-CH=C**H**H)); 6.1 (d, j=17.8 Hz, 1H, O-CO-CH=CH**H**); 6.4 (m, 1H, O-CO-C**H**=CHH); 7.2 (d, j=7.2 Hz, 1H, 5-H); 7.3-7.6 (m, 5H, Ph); 8.5 (d, j=7.2 Hz, 1H, 6-H);MS (EI)): m/z=355 (M); IR (KBr): 1640 (pyridinone ring C=O), 1730 (esther C=O) cm^{-1}.

Anal.CalCd for $C_{21}H_{25}O_4N$: C, 71.00; H, 7.04; N, 3.94%. Found: C, 71.21; H, 7.06; N, 3.89%.

^{13}C NMR ppm (DMSO-d_6): 11.9 (2-CH_3); 25.1, 29.5, 30.4 N-CH_2-**$(CH_2)_3$**-CH_2-O-), 52.9 (N-**CH_2**-$(CH_2)_4$-CH_2-NH-), 63.7 (N-$(CH_2)_4$-**CH_2**-O-CO-), 71.9 (O-CH_2-Ph), 115.5 (pyridinone ring), 127.8, 128.1, 128.3 (phenyl ring), 128.4 (-NH-CO-CH=**CH_2**), 132.2 (-NH-CO-**C**H=CH_2), 137.5 (pyridinone ring CQ), 139.7 (pyridinone ring), 141.6 (phenyl ring CQ), 144.9 (pyridinone ring CQ), 165.4 (pyridinone ring C=O), 170.9 (-NH-**CO**-CH=CH_2).

Compound 14 (Fig. 2)

^{1}H NMR (DMSO-d_6): δ 1.2-1.9 (m, 6H, N-CH_2-(**CH_2**)**$_3$**-CH-), 2.1 (s, 3H, 2-CH_3), 2.2-2-4 (m, 2H, -CH(R)-**CH_2**-CH(R)-), 2.5 (m, 1H, -CH_2-C**H**(R)-CH_2-), 3.9 (t, j=7.2 Hz, 2H, N-**CH_2**-CH_2-), 4.3 (m, 1H, N-CH_2-$(CH_2)_3$-**CH**(NH_2)(COOH)), 5.2 (s, 2H, O-CH_2-Ph), 6.5 (d, j=7.2 Hz, 1H, 5-H), 7.4-7.9 (m, 5H, Ph), 7.9 (d, j=7.2 Hz, 1H, 6-H); IR (KBr) cm^{-1}: 1640 (pyridinone ring C=O), 1075 (C-N), 1650 (amide C=O)

^{13}C NMR ppm (CD_3OD-d_3): 12.5 (2-CH_3); 23. 5, 31.1,33.1 (N-CH_2-**$(CH_2)_3$**-CH-); 35.7 (-CH_2-CH(R)-**CH_2**-); 44.0 (-CH_2-**CH**(R)-CH_2-); 54.5 (N-CH_2-$(CH_2)_3$-**CH**(NH)(COOH)); 53.1 (N-**CH_2**-CH_2-); 74.5 (O-**CH_2**-Ph); 117.3 (pyridinone ring); 129.4, 130.2, 131.0 (phenyl ring); 138.4 (pyridinone ring); 141.9 (pyridinone ring CQ); 143.9(phenyl ring CQ); 146.8 (pyridinone ring CQ); 167.9 (pyridinone ring C=O); 171.1 (-COOH); 174.62 (-NH-**CO**-CH(R)-CH_2).

Compound 15 (Fig. 2)

^{1}H NMR (MeOD-d_3): δ 1.2-1.9 (m, 8H, N-CH_2-**$(CH_2)_4$**-CH_2-NH_2), 2.0 (s, 3H, 2-CH_3), 2.2-2-4 (m, 2H, -CH(R)-**CH_2**-CH(R)-), 3.0-3.3 (m, 2H, m, 2H, N-$(CH_2)_5$-**CH_2**-NH-) (2.7 (m, 1H, -CH_2-C**H**(R)-CH_2-), 3.9 (t, j=7.2 Hz, 2H, N-**CH_2**-$(CH_2)_5$- NH-), 5.1 (s, 2H, O-CH_2-Ph), 6.5 (d, j=7.1 Hz, 1H, 5-H), 7.2-7.6 (m, 5H, Ph), 7.5 (d, j=7.1, Hz, 1H, 6-H): IR (KBr): 1640 (pyridinone ring C=O) cm^{-1}, 1653 (amide C=O) cm^{-1}.

^{13}CNMR ppm (MeOD-d_3): 12.9, (2-CH_3); 26.9, 27.3, 30.5, 31.9 (N-NH_2-**$(CH_2)_4$** CH_2-NH-); 35.7 (-CH(R)-**CH_2**-CH(R)-); 40.0 (N-CH_2-(CH_2)4-**CH_2**-NH-), 44.6 (-CH_2-**CH(R)**-CH_2-); 55.2 (N-**CH_2**-(CH_2)4-CH_2-NH-); 71.4 (O-CH_2-Ph); 117.3 (pyridinone ring); 1287.2, 129.4, 130.3 (phenyl ring); 137.4 (pyridinone ring CQ); 141.2 (pyridinone ring); 142.1 (phenyl ring CQ); 147.0 (pyridinone ring CQ); 164.8 (pyridinone ring C=O); 173.6(-NH-**CO**-CH-CH_2-).

Compound 16 (Fig. 2)

^{1}H NMR (MeOD-d_3): δ 1.2-1.9 (m, 6H, N-CH_2-**$(CH_2)_3$**-CH_2-O-), 2.0-2.4 (m, 5H, 2-CH_3 and -CH(R)-**CH_2**-CH(R)-), 2.7 (m, 1H, -CH_2-C**H**(R)-CH_2-), 3.9 (m, 2H, m, 2H, N-$(CH_2)_4$-**CH_2**-O-CO-) 4.2 (t, j=7.2 Hz, 2H, N-**CH_2**-$(CH_2)_4$- O-), 5.1 (s, 2H, O-CH_2-Ph), 7.4 (d, j=7.0 Hz, 1H, 5-H), 7.1-7.6 (m, 5H, Ph), 8.4 (d, j=7.0, Hz, 1H, 6-H) : IR (KBr): 1640 (pyridinone ring C=O), 172o (esther C=O) cm^{-1}.

^{13}C NMR ppm (DMSO-d_6): 12.8 (2-CH_3); 26.5, 29.6, 30.5 N-CH_2-**$(CH_2)_3$**-CH_2-O-), 35.9 (-CH(R)-**CH_2**-CH(R)-), 45.6 (-CH_2-**CH**(R)-CH_2-) 52.5 (N-**CH_2**-$(CH_2)_4$-O-), 64.0 (N-$(CH_2)_4$-**CH_2**-O-CO-), 71.7 (O-CH_2-Ph); 116.2 (pyridinone ring); 127.7, 128.1, 128.3 (phenyl ring); 137.7 (pyridinone ring CQ); 139.3 (pyridinone ring); 140.5 (phenyl ring CQ); 145.2 (pyridinone ring CQ); 166.1 (pyridinone ring C=O); 171.7 (-NH-**CO**-CH=CH_2).

Compound 17 (Fig. 2)

^{1}H NMR (DMSO-d_6): δ 1.3-2.0 (m, 6H, N-CH_2-(**CH_2**)**$_2$**- CH_2-CH-), 2.1 (s, 3H, 2-CH_3), 2.2-2-5 (m, 2H, -CH(R)-**CH_2**-CH(R)-), 2.6 (m, 1H, -CH_2-C**H**(R)-CH_2-), 4.0 (t, j=7.1 Hz, 2H, N-**CH_2**-CH_2-), 4.2 (m, 1H, N-CH_2-$(CH_2)_3$-**CH**(NH_2)(COOH)), 6.4 (d, j=7.2 Hz, 1H, 5-H), 7.6 (d, j=7.2 Hz, 1H, 6-H); IR (KBr) 1640 (pyridinone ring C=O), 1070 (C-N), 1663 (amide C=O), 3152 (O-H) [1] cm^{-1}.

Compound 18 (Fig. 2)

^{1}H NMR (MeOD-d_3): δ 1.2-1.8 (m, 8H, N-CH_2-**$(CH_2)_4$**-CH_2-NH_2), 2.2 (s, 3H, 2-CH_3), 2.1-2-4 (m, 2H, -CH(R)-**CH_2**-CH(R-), 2.5 -2.7 (m, 1H, -CH_2-C**H**(R)-CH_2-), 3.1-3.4 (m, 2H, m, 2H, N-$(CH_2)_5$-**CH_2**-NH-),3.8 (t, j=7.1 Hz, 2H, N-**CH_2**-$(CH_2)_5$-NH-), 6.4 (d, j=7.2 Hz, 1H, 5-H), 7.6 (d, j=7.2, Hz, 1H, 6-H): IR (KBr): 1635 (pyridinone ring C=O) cm^{-1}, 1650 (amide C=O), 3167 (O-H) ^{1} cm^{-1}.

Compound 19 (Fig. 2)

^{1}H NMR (MeOD-d_3): δ 1.1-1.9 (m, 6H, N-CH_2-**$(CH_2)_3$**-CH_2-O-), 2.1-2.5 (m, 5H, 2-CH_3 and -CH(R)-**CH_2**-CH(R)-), 2.8 (m, 1H, -CH_2-C**H**(R)-CH_2-), 4.0 (m, 2H, m, 2H, N-$(CH_2)_4$-**CH_2**-O-CO-) 4.3 (t, j=7.1 Hz, 2H, N-**CH_2**-$(CH_2)_4$- O-), 5.2 (s, 2H, O-CH_2-Ph), 7.1 (d, j=6.9. Hz, 1H, 5-H), 8.3 (d, j=6.9, Hz, 1H, 6-H): IR (KBr): 1640 (pyridinone ring C=O), 174o (esther C=O), 3232 (O-H) cm^{-1}.

DISCUSSION

Amination of benzyl maltol

The observations noted during the amination of benzyl maltol using 2,6-diamino-hexanoic acid (**3**), (DL-lysine), 1,6-diaminohexane (**4**) and 5-aminopentanol (**5**) were in agreement with the findings of previous reports (4,26). The successful isolation of the desired bidentatepyridin-4-one compounds was achieved by using precise extraction procedures based on the pK_a values and the chemistry of the relevant group. For example, for the synthesis of 2-amino-6-(3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-l-yl) hexanoic acid (**6**) (Fig. 2), washing of the concentrated aqueous reaction mixture with diethyl ether at pH 1 separated the product (**6**) and unreacted 2, 6-diaminohexanoic acid (**3**) present in the mixture from unreacted benzyl maltol (**2**). This was as expected, given the pK_a of the functional groups and the readily soluble nature of diprotonated compounds **3** and **6** in water. Thin layer chromatography showed the absence of detectable quantities of unreacted benzyl maltol.

Subsequent adjustment of the aqueous fraction to pH 12 and then extraction it into dichloromethane separated the desired product (**6**) from unreacted 2, 6-diaminohexanoic acid (**3**) (due to water solubility of lysine) present in the mixture.

For the 1-amino-6- (3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexylamine (**7**, Fig. 2), because of the additional complication of the dimer 1,6-di-(3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexylaminedihydrochloride (**8**), a stepwise extraction procedure was necessary. The pK_a of the pyridin-4-one nitrogen is 3.6 (29). Thus at pH 5.0 the dimer was extracted from the aqueous mixture into dichloromethane. Further extraction of the aqueous mixture at pH 11.0 with dichloromethane separated the bulk of the unreacted amine from the desired monosubstituted compound. The isolated monosubstituted compound and the dimer were washed with acidified distilled water to remove any remaining traces of unreacted 1, 6-diaminohexane.

Acylation of the pyridin-4-one bidentates

The treatment of acyl halides such as acryloyl chloride with amines or ammonia is a general reaction for the preparation of amides. Primary amines such as 1-amino-6- (3-benzylxoy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexylamine (**7**) undergo nucleophilic substitution to give N-substituted amides. In synthesizing the pyridin-4-one compounds (**11** and **12**, Fig. 2), the acryloyl chloride was added in small aliquots to prevent local overheating due to the exothermic nature of the reaction, and the temperature was maintained below 5 °C, preventing the hydrolysis of the acid chloride. The use of the aqueous sodium hydroxide (5%) served to neutralize the hydrogen chloride that would have been liberated and which could lead to formation of salts and consequently to a low percentage yield of the desired monomer. The excess acryloyl chloride was used to ensure that an acceptable yield of the amide was obtained despite its susceptibility to hydrolysis by the water and sodium hydroxide present in the reaction mixture.

The difference in the percentage yields for the 2-acrylamido-6-(3-benzyloxy-1, 4-dihydro-

2-methyl-4-oxopyrid-1-yl) hexanoic acid (**11**) and the 1-acrylamido-6- (3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexylamine (**12**), 40 and 71% respectively, can be accounted for by the mechanism of the reaction. The nucleophilic substitution proceeds by two steps with intermediate formation of a tetrahedral compound. Generally the overall rate is affected by the rate of both steps, but the first step, the formation of the tetrahedral intermediate, is more critical due to greater stereochemical crowding. This intermediate is favored by the presence of electron withdrawing groups which stabilize the developing negative charge and its formation, and it is hindered by the presence of bulky groups which become crowded together in the transition state. It is thus expected that the less bulky amine, 1-amino-6-(3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexylamine (**7**) should be more easily acylated and hence produce a higher yield than the 2-amino-6-(3-benzyloxy-1, 4-dihydro-2-methyl4-oxopyrid-1-yl) hexanoic acid (**6**), (Fig. 2).

The basis of acylation of alcohols such as l-hydroxy-5-(3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) pentane (**9**) is not dissimilar to that of acylation of amines, already discussed. Acid chlorides added in small portions, followed by vigorous shaking to a mixture of the hydroxy compound and a base, in this instance aqueous sodium hydroxide, is the best general method for preparation of the ester (30). The base serves not only to neutralize the hydrogen chloride produced, but also catalyzes the reaction. Accumulation of hydrogen chloride in the reaction mixture may cause the hydrolysis of the ester or may react in other ways in addition to the desired reaction. For example, in the reaction of crotonyl chloride with ethanol, the accumulated hydrogen chloride adds to the double bond of the acid chloride in good yield to give the β-chlorobutyrate. The isolation of the 1-propenoate-5-(3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) pentane (**13**) in a 60% yield was as expected.

The structure of the parent alcohol, lacking any bulky groups at the reaction site, favors formation of the ester and also, given the relatively low concentration of aqueous sodium hydroxide present in the mixture, saponification was considered unlikely. Base catalyzed hydrolysis of the esters (saponification is an irreversible reaction because once the acid is formed it is immediately converted to the carboxylate anion which is not further attacked by base). As a result the reaction goes to completion in the direction of the hydrolysis. Water alone does not hydrolyze most esters (31).

Vinyl polymerization and deprotection of polymers

The same method and conditions were employed in the synthesis of the three polymer classes, namely: poly-2-propylamido-6-(3-hydroxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexanoic acid (**17**), 6-(3-hydroxy1-, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexyl-1-polypropylamide (**18**) and 5-(3-hydroxy -1,4-dihydro-2-methyl-4-oxopyrid-1-yl)-1-poly-acrylate-pentane (**19**), (Fig. 2).

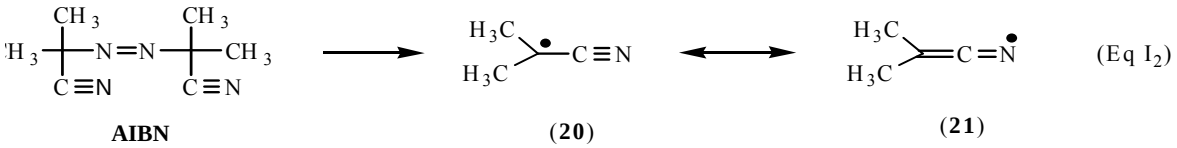
The process of vinyl polymerization involves 3 steps: I) Initiation step; II) Propagation step and III) Termination step.

I) Initiation step:

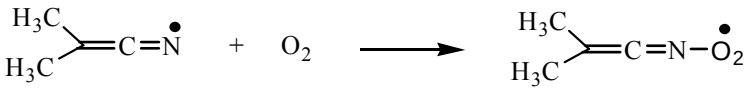
The initiation step involves the reaction of the free radical, R_0, derived from the initiator, in this instance AIBN, with the pyridin-4-one monomer, M (compounds 11, 12 and 13, Equation I_1)

$$R_0 + M \longrightarrow R_1 \qquad (Eq\ I_1)$$

Radicals may be produced either by thermal or photochemical reactions. AIBN in the solvent DMF gives an optimum rate of free radicals at 60-70 °C (Equation I_2).



AIBN (**20**) (**21**) (Eq I_2)



(Eq I_3)

(**21**) (**22**)

Talat-Erben and Bywater, (32) demonstrated that the reaction products observed in vinyl polymerization were mainly consistent with the 1-cyanoalkyl structures, **21**, (Equation I_2), being the attacking radical. The polymerization reaction was conducted under nitrogen because of the possible production of a peroxy radical (Equation I_3)

This is a complication associated with the use of AIBN. The free radical, **21**, (Equation I_3) may react with oxygen to give the peroxy radical, **22**. Unfortunately the reactivity of the peroxy radical is quite different from that of the original radical, **21**, and consequently could reduce the concentration of the required free radical for the reaction (33).

II) Propagation step:

The reactive species derived from the initiator (Equation I_2) are chain carriers which propagate the chain reactions bringing about addition polymerization (Fig. 3). The growing free radicals may not only add to the double bond of a monomer but also abstract hydrogen from a chain formed, which in turn generates a free radical center from which a branch could grow.

In chain propagation the entire synthesis of an individual polymer molecule from unreacted monomers occurs within a brief interval of time, often within a few seconds or less, but the overall conversion of monomer to a good yield may require hours. During the course of this project, 20 days found to be the optimum reaction time to give the largest polymer Thus at any instant during the polymerization process the reaction mixture consists almost entirely of unchanged monomer and of high molecular weight polymer, material at intervening stages of growth is virtually absent. In general the active center of the kinetic chain is retained by a single polymer molecule throughout its growth, however it is possible for this to be transferred to another molecule, for example a solvent or monomer. In the case of any such transfer the growth of the chain previously bearing the free radical would be terminated, the molecule acquiring the radical starting a new chain (33). This could explain the isolation of the two different molecular weight polymer populations during the synthesis of the poly-2-propylamido-6-(3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexanoic acid (**14**). Addition of a free radical to a vinyl monomer may occur in either of two ways. The alternative processes depend on the relative stabilities of the product, types I and II, (Figs. 3a and 3b). The substituent "R" occurring on the carbon atom bearing the unpaired electron can provide resonance structures in which the unpaired electron appears on the substituent and effectively stabilizes the radical. The extent of any such stabilization depends on the capacity of the substituent for resonance. For the synthesis of the polymer, poly-2-propylamido-6- (3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexanoic acid (**14**), (Fig. 2), 11.0 g of the monomer (**11**) yielded 5.4 g of polymer, order of molecular weight 24,000 to 36,000 and 660 mg of polymer, order of molecular weight 1,000 to 1,800, whereas in the synthesis of 5-(3-benzyloxy-1, 4-dihydro-2-methyl-4-oxopyrid-l-yl)-1-polyacrylatepentane (**16**), 11.0g of the monomer (**13**) yielded 380 mg of polymer, order of molecular weight 17,000 to 21,000. The difference in the yields could be partly due to the degree of stabilization conferred by the substituent groups. The nature of "R" (Fig. 3a), that is conferment of stabilization on the radical in addition to any steric hindrance caused by the substituent "R" on the growing chain to the incoming monomer, contributes to the overall percentage yield of the polymer.

Successive addition of monomer molecules one after another in accordance with growing chain type 1 (Fig. 3a) produces a polymer chain bearing the substituent on alternate carbon atoms (33). The substituted carbon atom of the unit in this head-to-tail arrangement, otherwise referred to as the 1, 3-structure, is asymmetric and both d and 1 forms can be expected to occur in more or less random sequence along the chains (Fig. 4).

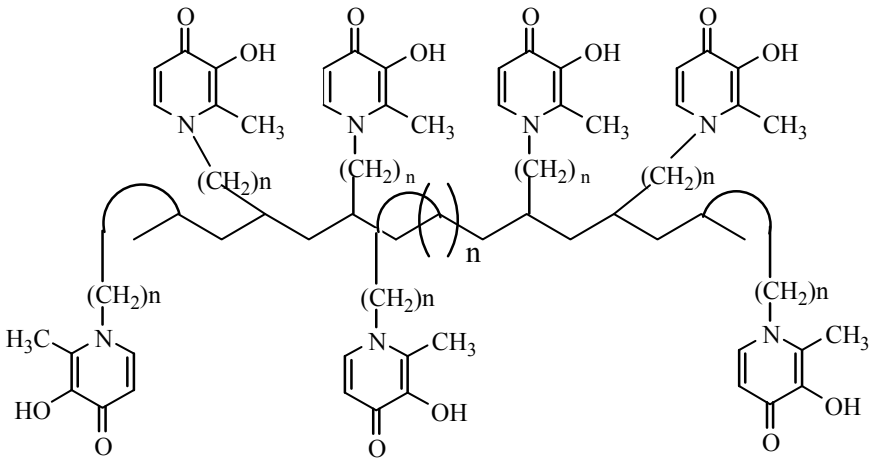


Fig. 4. Proposed structure of a 3-hydroxypyridine-4-one polymer.

In the fully extended polymer having the chain atoms in the planar zigzag arrangement, substituents of one type of unit will occur above the plane and those of the other below it. It is this structural irregularity which appears to be responsible for the infrequency of occurrence of crystallinity among vinyl polymers, a feature observed in all the three polymers synthesized demonstrated by the low melting points. The degree of crystallinity (formation of crystallites) depends on the size of "R" (Fig. 3).

III) Termination step:

Stable polymers are formed only when the chain-carriers undergo chain termination. This proceeds in competition with propagation reactions. Given that the initiator is consumed during the reaction, in order for the propagation to predominate it must be replenished. Termination may occur in several ways. The free radicals produced by the decomposition of AIBN are in pairs. In consequence, for a period of time following their formation in liquids, the two radicals produced lie closer to one another than to any other free radical in the system and are more likely to react with one another during this time. Consequently the concentration of the free radicals available to participate in the initiation reaction would be reduced.

Deprotection of polymers

The hydrogenolysis reaction was performed in an identical manner to that described for the bidentatepyridin-4-one compounds (26). Substituting the 95% ethanol used in the hydrogenolysis of the bidentates with suitable solvents for the polymers, for example a mixture of DMF and aqueous 95% ethanol in the case of the higher molecular weight poly-2-propylamido-6-(3-hydroxy-1, 4-dihydro-2-methyl-4-oxopyrid-1-yl) hexanoic acid (**14**) appears to have had no effect on the Pd/C catalyst used , and ^{1}H NMR confirmed that the polymers were deprotected. However, it was observed that the uptake of hydrogen was comparatively slower for the polymers and a longer time period was required to ensure that all the benzyl groups had been removed.

CONCLUSION

In this study, three 3-hydroxypyridinonebidentate ligands, were synthesized and incorporated into polymers by copolymerization with 2-propenoyl chloride using AIBN as an initiator. Identification and structural elucidation of polymers were confirmed by ^{1}H NMR, ^{13}C NMR and IR.

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