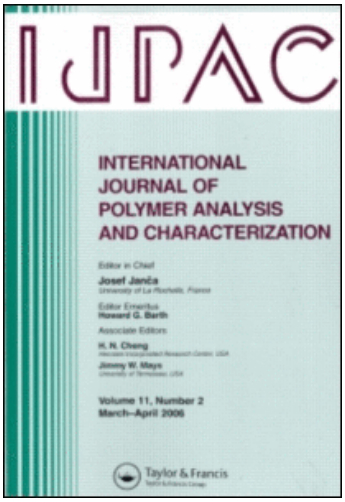

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Synthesis of Poly(Vinyl Alcohol) and Telechelic Poly(Vinyl Alcohol): Characterization, Complexation, and Biological Activity

Othman A. Al-Fulaij[a]; Abdel-Zaher A. Elassar[a]; Naeem M. El-Sawy[b]
[a] Chemistry Department, Faculty of Science, Kuwait University, Safat, Kuwait [b] National Center for Radiation Research and Technology, Nasr City, Cairo, Egypt

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Synthesis of Poly(Vinyl Alcohol) and Telechelic Poly(Vinyl Alcohol): Characterization, Complexation, and Biological Activity

Othman A. Al-Fulaij and Abdel-Zaher A. Elassar
Chemistry Department, Faculty of Science, Kuwait University, Safat, Kuwait

Naeem M. El-Sawy
National Center for Radiation Research and Technology, Nasr City, Cairo, Egypt

Abstract: Telechelic poly(vinyl alcohol) was condensed with phenyl hydrazine and malononitrile in a basic medium to give hydrazone and pyran derivatives, respectively. In further studies, poly(vinyl alcohol) (PVA) was reacted with chloroacetonitrile, biuret, thiophene carbonyl chloride, acrylonitrile, and phenyl isothiocyanate to give modified polymeric materials. An addition product of acrylonitrile was treated with hydroxylamine hydrochloride to give the amidoxime derivative. The prepared amidoxime and carbamate ester of polymeric material were complexed with $CuCl_2$ solution. The complexation was confirmed by UV and EDS measurements. The morphology of PVA and copper (II) complex of amidoximated-PVA was studied by SEM. Biological activity of some of the prepared compounds was investigated against bacterial and fungal microorganisms.

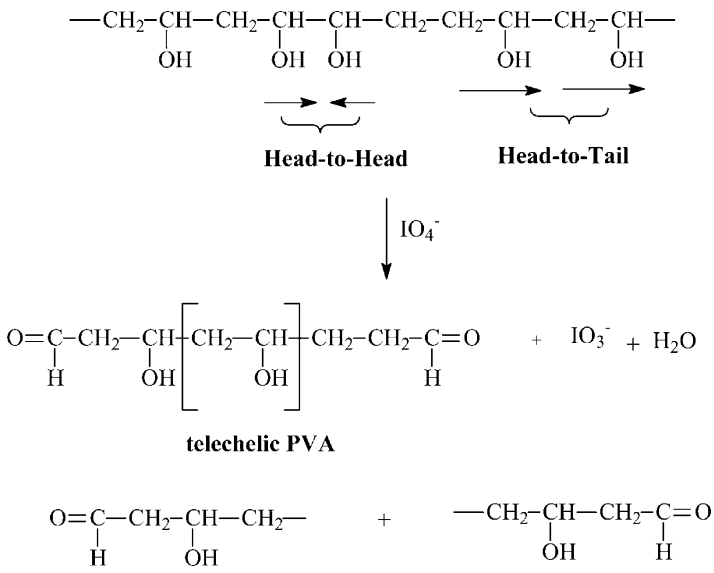
Keywords: PVA; Telechelic poly(vinyl alcohol); Pyran; Hydrazone

Address correspondence to Abdel-Zaher A. Elassar, Chemistry Department, Faculty of Science, Kuwait University, P.O. Box 5969-Safat-13060, Kuwait. E-mail: aelassar@yahoo.com

INTRODUCTION

Poly(vinyl alcohol) (PVA) comprises a very interesting class of polymeric materials because of its significant industrial use and biological activities.[1–3] A modern biomaterial should have the ability to accomplish multiple functions; for example, vitreoretinal surgery demands new vitreous tamponade agents able accomplish positional support and drug release therapy at the same time. PVA versatility is a good asset for complying with such demanding requirements.[4,5] Hydrogels based on PVA were obtained by reacting telechelic PVA bearing aldehydic groups at both ends.[5,6] As with any vinyl polymer, PVA has some defects in the backbone sequence. These defects are called head-to-head units and made of a few 1,2-glycil units (vicinal diol) in addition to the usual 1,3-glycolic sequences (Scheme 1). Our approach in the synthesis exploits the presence in the PVA chain of sporadic head-to-head sequences consisting of glycolic unit subjected to specific and quantitative splitting by periodate.[5,6]In this way macromers of PVA, hereafter called telechelic PVA (TPVA), having an aldehydic group at each end of the chain are obtained. Such a modification may find a very promising application in the preparation of biomaterials.

The observed anti-HIV activity of some pyran derivatives recently stimulated extensive interest in the synthesis and chemistry of pyran derivatives.[7] In this work our goal was to synthesize pyran and other biologically active PVA derivatives using TPVA or PVA as a building block.



Scheme 1.

Investigations of the modified polymer towards complexation as well as the investigation of some of the prepared compounds towards bacterial and fungal microorganisms were carried out.

EXPERIMENTAL

Materials

Powder PVA from BDH (USA) of purity 99% was used as received. Other chemicals were reagent grade and used without further purification.

Characteristic Methods

IR Spectra

IR spectra were carried out for the polymer and modified polymer using a Shimadzu (Japan) 5000 FTIR spectrophotometer.

^{1}H and ^{13}C NMR Spectra

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-400 spectrometer with DMSO-d_6 or DMF as solvent using tetramethylsilane (TMS) as an internal standard; chemical shifts are expressed as δ (ppm) values.

Scanning Electron Microscopy (SEM)

The scanning electron microscope (SEM) images were recorded on a model JSM-6300 JEOL at 20 kV.

Energy Dispersive Spectroscopy (EDS)

EDS chemical area mapping with various metal-treated films was performed with link eXL-II energy dispersive spectrometer (Oxford Instruments, U.K.) attached to the scanning electron microscope to measure the absorbed ions from solution. Analytical data were obtained from the Analab, Chemistry Department, Kuwait University.

Synthetic Procedures

Synthesis of Pyran and Hyrazone

To a solution of TPVA (prepared as described in literature [5,6]) in pyridine (10 mL), malononitrile or phenylhydrazine (0.01 mol) was added.

The reaction mixture was heated under reflux for 2 h. Cold ethanol was added and the solid product was collected by filtration, washed with cold ethanol, and dried in an oven at 50°C for 24 h.

Reaction of PVA with Different Organic Reagents

- **Method A:** A solution of PVA (0.1 g) in DMF (30 mL), organic reagents (chloroacetonitrile, biuret, 2-thiophenecarbonyl chloride, phenyl isothiocyanate, and acrylonitrile), and 5 mL of piperidine was heated under reflux for 3 h. The solvent was evaporated under vacuum, and the residue was treated with cold ethanol. The solid product was collected by filtration, washed with ice-cold ethanol, and dried in an oven at 50°C for 24 h.
- **Method B:** A mixture of PVA (0.1 g), organic reagents (chloroacetonitrile, biuret, 2-thiophenecarbonyl chloride, phenyl isothiocyanate, and acrylonitrile), and few drops of piperidine was heated in the absence of solvent at 160–180°C for 3 h and then treated with cold ethanol. The solid product so formed was collected by filtration, washed with ice-cold ethanol, and dried in an oven at 50°C for 24 h.

Amidoxime Formation

In the following, bold numbers refer to compounds in the schemes.

To a solution of the nitrile derivative **16** in DMF, hydroxylamine hydrochloride (3 g) and sodium hydroxide (1 g) in water (10 mL) were heated under reflux 3 h. The solvent was evaporated and the residue was treated with ethanol (20 mL). The solid product was collected by filtration, washed with ice-cold ethanol, and dried in an oven at 50°C for 24 h.

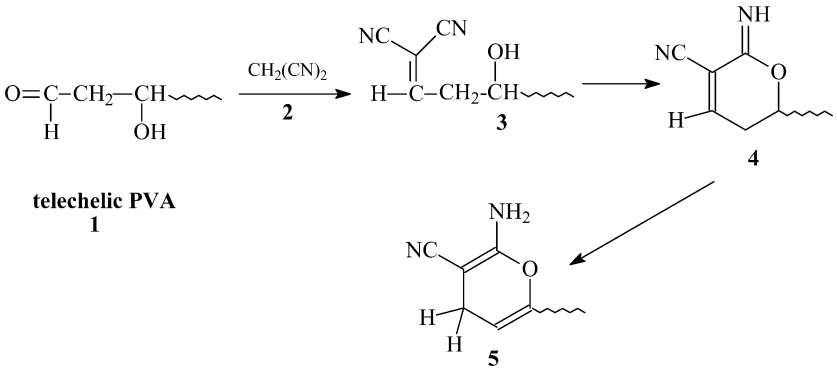
Complex Formation

A solution of $CuCl_2$ in H_2O (50 mL) was added to a hot DMF solution of amidoxime or modified polymeric material **11.** The solid product formed was collected by filtration, washed, and dried in an oven at 50°C for 24 h.

RESULTS AND DISCUSSION

Synthesis

TPVA **1** was reacted with malononitrile **2** to give pyran derivative **5**. The reaction mechanism was believed to be formed via condensation of malononitrile **2** with the terminal aldehydic group giving the ylidene



Scheme 2.

derivative **3**. This ylidene is cyclized under reaction condition to give the pyran derivative **4**, which was rearranged to give the final isolated 4-H-pyran derivative **5** (Scheme 2). The reaction product **5** was confirmed based on its elemental analysis and spectral data (see Tables I and II). The data in Table I show that the nitrogen content is 20.22%. The IR spectra reveal the presence of amino and cyano groups at 3200–3400 and 2191 cm^{-1}, respectively. ^1H NMR spectrum shows the amino band at δ 7.94 ppm. The 4-H and 5-H-pyran appeared at δ 2.50 and 5.30 ppm, respectively. The signals at δ 4.46, 3.82, and 2.89–1.33 ppm are due to CH-protons, hydroxyl, and CH_2-protons, respectively. Furthermore, ^{13}C NMR shows chemical shifts at δ 163.20–158.96 and 119.04, 115.88 ppm, due to (C−O) of pyran and cyano groups, respectively. Other skeletal carbons appeared at δ 80.03, 68.58, 45.49, 66.66, 66.83, and 23.68–36.66 ppm for C-1, C-2, C-3, C-4, C-5, and CH_2 of the unreacted part of TPVA, respectively.

TPVA was reacted with phenyl hydrazine in refluxing dimethyl formamide (DMF) to give the hydrazone derivative **7** (Scheme 3). The formation of hydrazone **7** was established based on elemental analysis and spectral data. Thus, elemental analysis reveals the presence of nitrogen, 1.21%, and IR shows NH, CH− aromatic, and CH− aliphatic at 3321, 3023, and 2980 cm^{-1}, respectively. The bands for C=C and C=N appeared at 1607 and 1580 cm^{-1}, respectively. ^1H NMR shows aromatic protons and NH at δ 7.73–7.13 and 6.76 ppm, respectively, while the aliphatic protons appeared at δ 2.67–1.23 ppm. The ^{13}C NMR agree with the proposed structure **7** (see Table I). The formation of hydrazone **7** was assumed to proceed via initial attack of nucleophilic nitrogen in phenyl hydrazine to the electrophilic carbonyl carbon of the aldehydic end group in TPVA, giving first the intermediate **6**. The intermediate **6** loses water molecule under the reaction condition to give the final product **7**.

Table I. Spectral data of the newly modified polymer

Compound no.	IR (cm^{-1})	^1H NMR (δ ppm)	^{13}C NMR (δ ppm)
5	3400–3200 (NH_2 and OH), 2942 (CH-al), 2191 (CN)	7.94 (br, NH_2), 5.80, 5.30 (d, 3H- and 4H-pyran), 4.46 (m, CH), 3.82 (br, OH), 2.89–1.33 (m, CH_2)	163.20, 162.38, 161.49, 161.38, 160.34, 159.70, 159.03, 158.96 (C−O), 119.04, 115.88 (CN), 80.03 (C-1), 68.58 (C-2), 45.49 (C-3), 66.66 (C-4), 66.83 (C-5), 23.68–36.66 (CH_2)
7	3400–3321 (NH_2 and OH), 3023 (CH-Ar), 2980 (CH-al), 1607 (C=C), 1580 (C=N)	7.73, 7.22, 7.17, 7.15, 7.13 (m, Ar-H), 6.76 (br, NH), 3.83 (br, D_2O-exchange, OH), 4.50 (m, CH), 2.67–1.23 (m, CH_2)	150.59 (C=N), 149.51, 129.85, 129.58, 129.19, 119.73, 119.49, 113.49, 113.36 (Ar-carbons), 40.53, 40.33, 40.14 (al-carbons)
9	3452 (OH), 2934 (CH-al), 2256, 2129 (CN)	4.50 (m, CH), 3.83 (br, D_2O-exchange, OH), 2.50–1.04 (m, CH_2)	—
11	3400–3200 (NH and NH_2), 2981 (CH-al) 1690, 1650 (2CO)	—	—
13	2980 (CH-al), 1735 (CO)	7.86–7.17 (m, thienyl-H), 3.84 (br, unreacted-OH), 2.51–1.04 (CH and CH_2)	163.75 (CO), 135.46, 134.12, 130.32, 129.07 (thienyl carbons), 80.04 (CH), 40.98–39.72 (CH_2)
15	3024 (CH-Ar), 2980 (CH-al), 3400–3220 (NH)	7.86–7.10 (m, Ar-H), 3.84 (br, unreacted-OH), 2.50–1.04 (CH and CH_2)	—
16	2943 (CH-al), 2191 (CN)	3.93–1.19 (m, CH and CH_2)	—

al: aliphatic, Ar: aromatic.

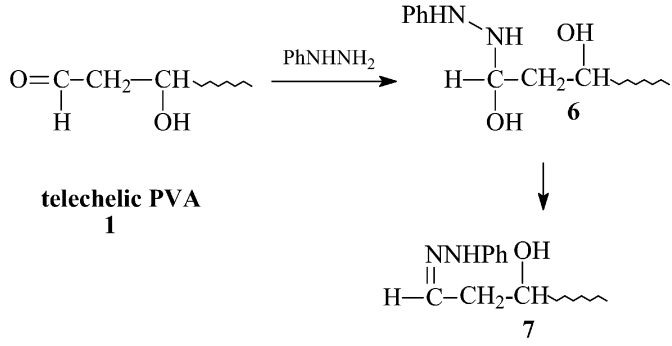
Table II. Elemental analysis of the newly modified polymer

Compound no.	C%	H%	N%	S%
5	54.78	6.35	20.22	—
7	51.48	8.90	1.22	—
9	51.11	8.14	10.3	—
11	48.10	7.30	6.03	—
13	48.94	7.07	—	6.61
15	67.83	6.32	7.92	9.29
16	52.60	8.49	2.54	—

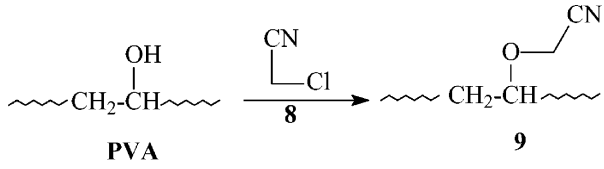
Chloroacetonitrile **8** was reacted readily with PVA without solvent to give cyano methyl ether derivative **9** (Scheme 4). The reaction product was established based on elemental analysis and spectral data. Elemental analysis showed the presence of 1.03% nitrogen. IR spectrum reveals the presence of cyano groups at 2129 and 2256 cm^{-1}. In addition, there are two bands at 3452 and 2934 cm^{-1} for the unreacted hydroxyl group and aliphatic –CH, respectively. ^1H NMR showed bands at δ 4.50, 3.83, and 2.50–1.04 ppm due to –CH–, –OH (D_2O-exchange), and –CH_2–, respectively. This can be explained on the basis of HCl removal during the reaction.

It is well known that urea can react with PVA to give polymeric carbamate ester.[8] Similarly, biuret compound **10** can react with PVA to yield the carbamate ester derivative **11** via loss of ammonia molecule (Scheme 5). The reaction product was characterized by its elemental analysis and spectral data.

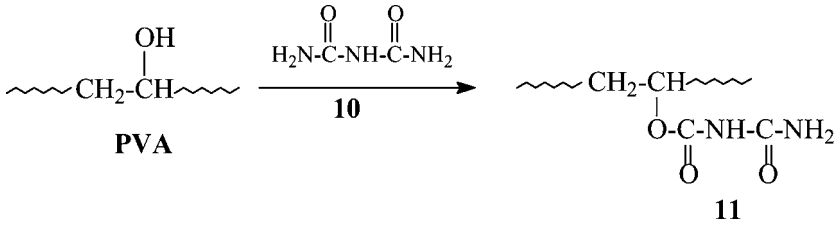
Sulfur-containing compounds comprise interesting biological activity.[9,10] Thus, thiophenecarbonyl chloride **12** was heated with PVA under reflux to give the thienyl ester derivative **13** (Scheme 6).



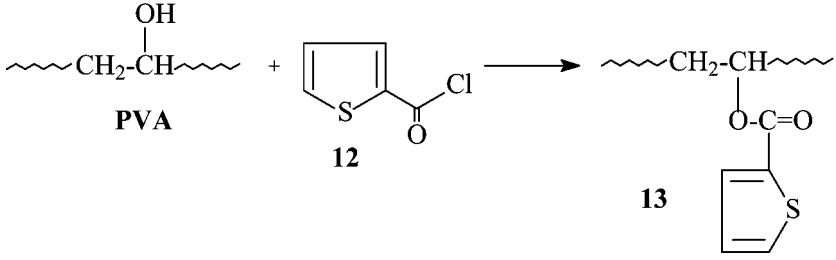
Scheme 3.



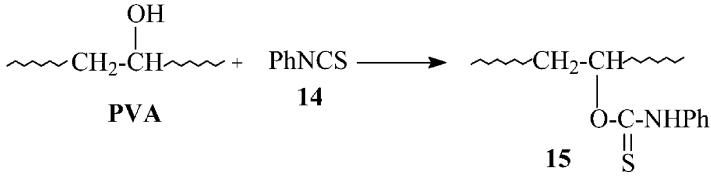
Scheme 4.



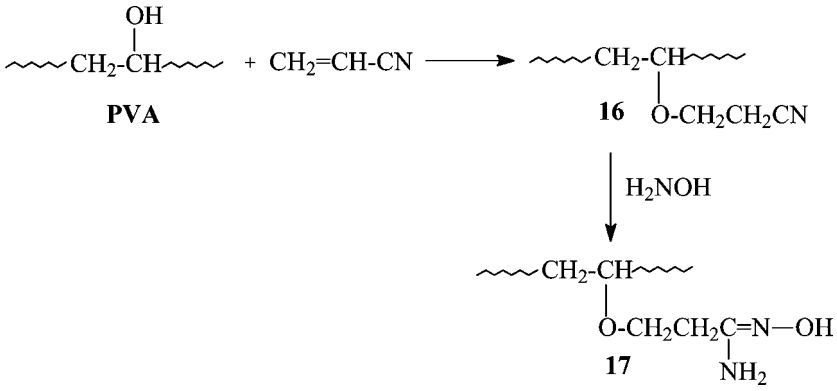
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

The reaction product was formulated based on its elemental analysis, which shows 5.83% sulfur. Furthermore, IR shows the ester carbonyl at 1735 cm^{-1}. ^{1}H NMR shows the thienyl protons at δ 7.86–7.17 ppm, in addition to other expected protons. ^{13}C NMR reveals the presence of ester carbonyl at δ 163.75 ppm and thienyl carbons at δ 135.48, 134.12, 130.32, and 129.07 ppm. Other carbons appeared at expected positions (Table I).

Alternatively, PVA reacts with phenyl isothiocyanate **14** to give the polymeric thiocarbamate ester **15** via addition of acidic hydroxyl proton to the isothiocyanate group (Scheme 7), similar to that reported for isocyanate.[11] The formulation of the product was proved from its elemental analysis, which shows 7.98% and 9.23% for nitrogen and sulfur, respectively.

Furthermore, a Michael addition product of PVA to acrylonitrile was obtained in a good yield, where the hydroxyl group in PVA was added to the ethylenic double bond in acrylonitrile to give the final isolated product **16**. The structure of the product was confirmed from its IR spectrum, which exhibits a characteristic band at 2254 cm^{-1} for cyano group; in addition, its elemental analysis shows a 2.54% nitrogen content, confirming its formulation. The reaction product was amidoximated with hydroxylamine hydrochloride to afford **17** (Scheme 8).

Figure 1 shows the UV spectrum for the complexation of biuret compound with Cu^{2+} ions in polymeric material. The electronic transitional band of $CuCl_2$ solution appeared at about 820 nm. However, the band of copper complex of biuret derivative appears at 574.86 nm, which represents the stable structure of six-membered rings of the complex. The change in the band position could be referred to the change of the ligand field and/or the coordination number of the Cu^{2+} as a result of the complex formation. Both **18** and **19** are probable. Compound **19** was ruled

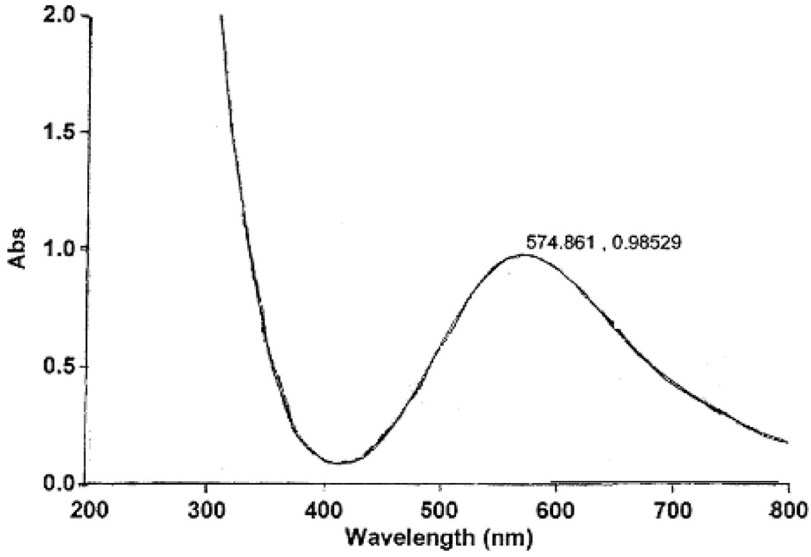
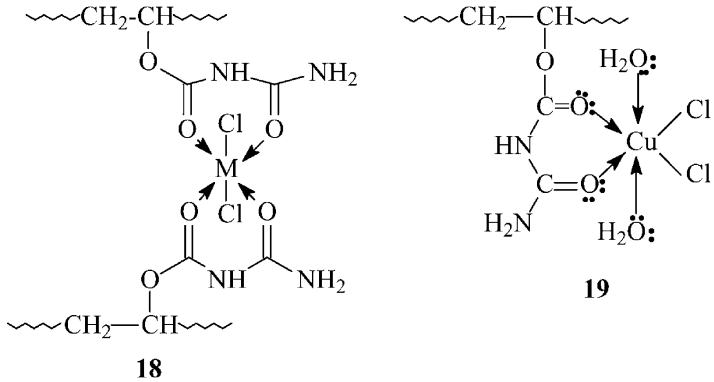


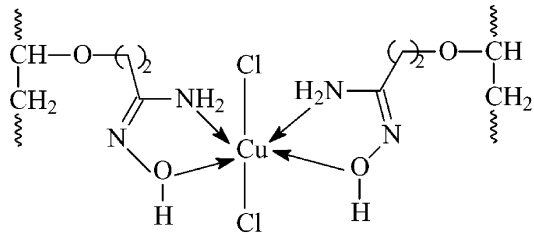
Figure 1. Change in relative absorbance with wavelength of PVA-biuret-Cu-complex.

out based on IR spectrum, which reveals the absence of water coordinate characteristic bands at 910 and 385 cm^{-1} (Scheme 9).

The amidoxime derivative **17** (PVA-Ao) was reacted with $CuCl_2$ to form compound **20** at pH > 9 as a dark green insoluble complex, (PVA-Ao-Cu) (Scheme 10). The quantitative analysis of the complex using energy dispersive spectroscopy (EDS), which reveals K_{α} Cu, and K_{ser} Cl, is shown in Figure 2.



Scheme 9.



20

Scheme 10.

Morphology

The morphologies of the trunk PVA and PVA-Ao-Cu are shown in Figures 3(a) and 3(b), respectively. The scanning electron micrographs of complexed PVA-Ao with Cu^{2+} ions (Figure 3(b)) shows that Cu^{2+} ions were embedded in polymer matrix, with the flower shape.

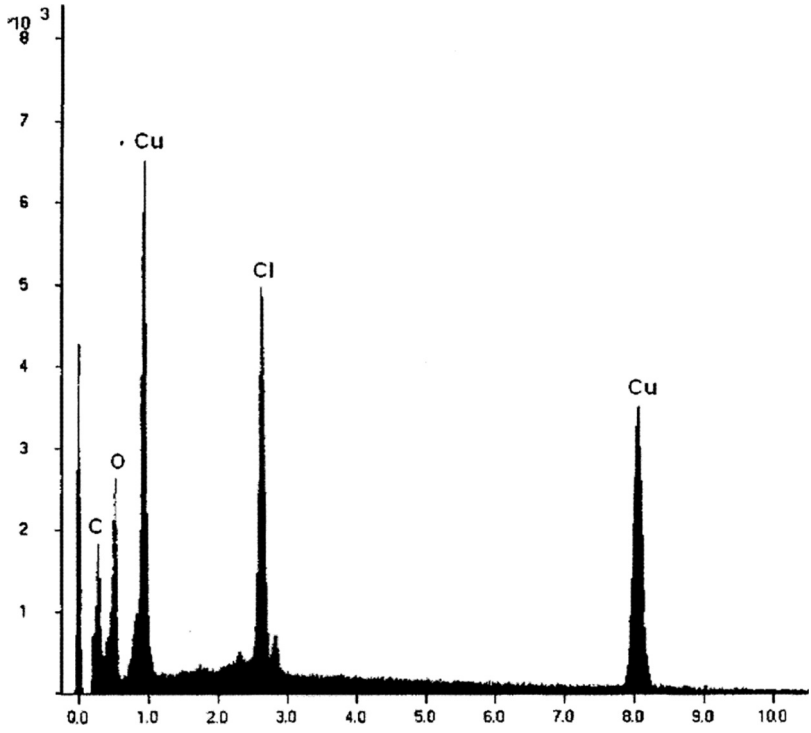
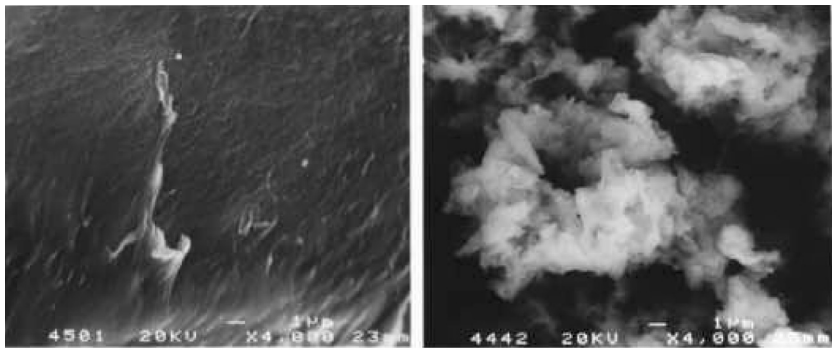


Figure 2. EDS of amidoximated-PVA-Cu-complex.



(a) (b)

Figure 3. Scanning electron micrographs of (a) PVA and (b) amidoximated-PVA-Cu complex.

This different morphology indicates the formation of polymer complexes and that the complex has higher crystallinity than the polymer itself.

Biological Activity

Both the heterocyclic compounds containing sulfur and the polymeric chain containing heterocyclic moiety showed a reasonable biological activity.[9,10] Table III shows the biological activity of the modified PVA polymer (compounds **5**, **7**, **13**, **15**, **16**, and **18**) against *E. coli, B. subtilis, S. aureus*, and *A. niger*. The activity of the PVA (blank), hydrazone derivative **7**, and Michael addition product **16** showed slightly antimicrobial potentialities against the bacterial tested organism as shown in Table III.

Table III. In vitro bactericidal and fungicidal activity of modified polymeric materials

Compound no.	*E. coli*	*B. subtilis*	*S. aurous*	*A. niger*
1	++	++	++	—
5	++	+++	+++	—
7	+	+	+	—
13	++++	+++	++++	—
15	+++	++++	++++	—
16	+	+	+	—
18	++++	+++	+++	+++

+, ++ slight effect; +++ moderate effect; ++++ severe effect.

However, the complex **18**, thiocarbomate derivative **15**, thienyl derivative **13**, and pyran derivative **5** showed a moderate to severe effect toward bacteria, while only complex **18** shows a moderate effect with the fungus (*A. niger*).

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