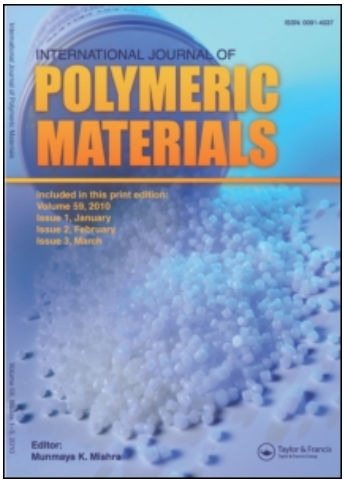

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Synthesis, Characterization and Biological Activity of some Poly(Coumarin Methylene)s

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Poly (3-substituted coumarin methylene)s (PCM_{1-7}) were prepared by reacting salicylaldehyde-formaldehyde polymer (SAL-F) under Wittig, Knoevenagel and Perkin reaction conditions. All the polymers were characterized by elemental analysis, IR spectral studies and thermogravimetric analysis (TGA). The polymers were also screened for their antifungal and antibacterial activity.

Keywords: Poly (3-substituted coumarin methylene)s; salicylaldehyde-formaldehyde polymer; Wittig reaction; Knoevenagel condensation; Perkin reaction

INTRODUCTION

Coumarins (2H-1-benzopyran-2-ones) are well known oxygen containing heterocycles and are widely used in drugs and dyes. Literature studies reveal that a considerable amount of work has been carried out on monomeric coumarin derivatives. However, compared to this, little attention has been given to coumarin polymers. Reports found in the literature for coumarin polymers are of very much interest. Coumarin-acrylonitrile copolymers are used in synthetic fibres [1]. Coumarin-N-vinyl indole copolymer is reported to have photo-conducting properties [2]. Copolymer derived from coumarin and N-vinyl pyrrolidine has been reported to decrease the blood pressure in cats [3]. 4-Methyl-7-hydroxy coumarin-formaldehyde polymers possess good thermal stability [4].

Certain coumarin polymers derived by reacting the preformed phenol-formaldehyde polymers have been reported to have interesting physiological properties. Yen *et al.* [5] have reacted resorcinol-formaldehyde polymer with ethyl acetoacetate under Pechmann reaction condition. The resultant poly(coumarin methylene)s were reported to have anticlotting and antihemorrhagic properties. Patel and Patel [6] have reported some 3-phenoxy substituted poly(coumarin methylene)s having antifungal properties. In this report authors have prepared some 3-phenoxy substituted poly(coumarin methylene)s by modifing salicylaldehyde formaldehyde polymer with some phenoxy acetic acid under Perkin reaction condition.

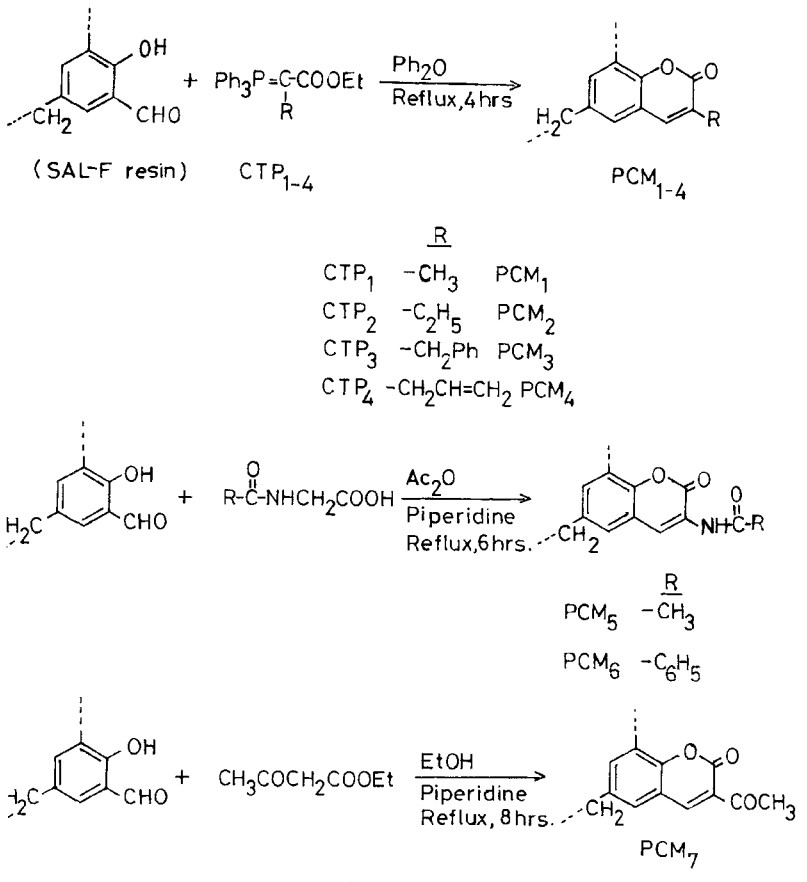
These interesting properties of coumarin copolymers [1–3] and poly(coumarin methylene)s [5, 6], prompted us to explore further the field of coumarin polymers and hence in the present paper we report the synthesis of various poly(3-substituted coumarin methylene)s (PCMs). The PCMs have been prepared by reacting salicylaldehyde-formaldehyde polymer (SAL-F) with various carbethoxytriphenyl alkylidine phosphoranes (CTP_{1-4}) under Wittig reaction condition, with ethyl acetoacetate under Knoevenagel reaction condition and with N-acetyl glycine or hippuric acid under Perkin reaction condition (Scheme-1).

All the polymers prepared were characterized by elemental analysis and IR spectral characteristics. Thermal properties of the polymers were studied by thermogravimetric analysis (TGA). The antifungal and antibacterial screenings were carried out using various fungi and bacteria.

RESULTS AND DISCUSSION

All the poly(coumarin methylene)s (PCM_{1-7}) were obtained in high yields ranging from 65 to 95%. All the PCMs were solid powders having yellow, brown or reddish brown colours and were insoluble in common organic solvents. Except PCM_2 and PCM_6, all the other polymers were only partially soluble in DMF.

The elemental analysis (Tab. I) of the PCMs very nearly agree with those predicted on the basis of structures of the respective repeat units. This indicates that the salicylaldehyde units of almost all the repeat units of SAL-F polymer have been converted into coumarin nucleus during the reactions.



Scheme 1.

TABLE I Characterization data for PCM_{1-7}

Polymer (Scheme 1)	*Colour*	*Yield (%)*	*Elemental Analysis (%)*					
			C		*H*		*N*	
			Calc.	*Found*	*Calc.*	*Found*	*Calc.*	*Found*
PCM_1	Brown	65	76.74	76.95	4.65	4.88	–	–
PCM_2	Brown	75	77.42	77.64	5.38	5.56		–
PCM_3	Brown	85	82.26	82.51	4.84	4.98	–	–
PCM_4	Brown	84	78.79	78.92	5.05	5.29	–	–
PCM_5	Reddish brown	95	66.98	67.12	4.19	4.32	6.50	6.38
PCM_6	Yellow	90	73.65	73.84	3.97	4.18	5.05	5.25
PCM_7	Yellow	92	72.00	72.28	4.00	4.22	–	–

The IR spectra of some typical polymers are shown in Figure 1. Examination of the IR spectra of all the PCMs reveals that all the spectra contain prominent characteristic band at 1720 cm^{-1} because of the δ-lactone of the coumarin moiety. They also show bands characteristic of aromatic nucleus and of $-CH_2-$ bridge at the expected positions. An additional band at 1690 cm^{-1} in the IR of PCM_7 is due to the $c=0$ of the ketone group at 3 position. Similarly bands corresponding to acetamido and benzamido functions have also been observed at 1765 and 1760 cm^{-1} in the IR of PCM_5 and PCM_6 respectively. The comparision of the IR spectra of PCMs with that of the parent polymer reveals that the carbonyl band due to aldehyde function at 1670 cm^{-1} has disappeared in all the PCMs. The broad band characteristic due to chelated OH function has also been almost disappeared in the spectra of PCMs. Thus the IR spectral studies indicate that the parent SAL-F polymer has been reacted smoothly under Wittig, Knoevenagel and Perkin reaction conditions and has been transformed into poly(coumarin methylene)s.

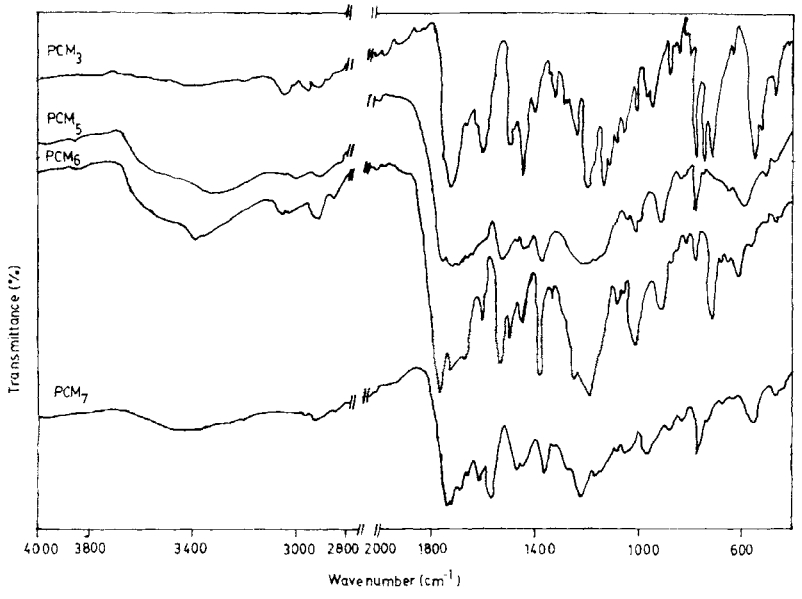


FIGURE 1 IR spectra of polymer samples PCMs.

TG thermograms of some typical polymers are shown in Figure 2 and the percentage weight loss at various temperatures are tabulated in Table-II. From these data it can be seen that poly (coumarin methylene)s (PCM_4, PCM_5, PCM_6 and PCM_7) degrade in one step whereas PCM_1, PCM_2 and PCM_3 degrade in two steps. The coumarin polymers

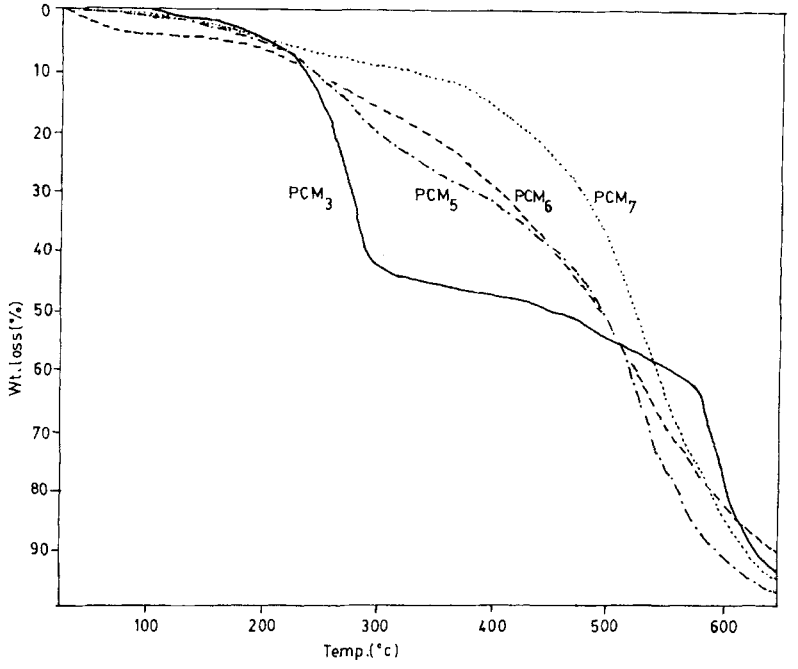


FIGURE 2 TG thermogram of PCMs

TABLE II Thermogravimetric Analysis of PCM_{1-7}

Polymer (Scheme I)	*Percentage weight loss at various temperature (°C)*						
	100	*200*	*300*	*400*	*500*	*600*	*Energy of activation Ea Kcal/mol*
PCM_1	0.5	6.0	28.5	36.0	45.0	99.8	$Ea_1 = 10.22$, $Ea_2 = 17.9$
PCM_2	0.6	6.7	40.0	46.1	53.3	83.3	$Ea_1 = 12.75$, $Ea_2 = 11.9$
PCM_3	0.6	6.1	47.8	54.5	62.8	87.2	$Ea_1 = 13.34$, $Ea_2 = 9.05$
PCM_4	0.6	5.0	24.4	42.5	68.1	90.6	$Ea_1 = 6.8$
PCM_5	2.4	7.7	26.5	40.6	67.1	99.0	$Ea_1 = 5.96$
PCM_6	3.5	6.6	16.9	30.1	53.9	85.8	$Ea_1 = 6.96$
PCM_7	1.6	4.7	10.0	16.8	40.5	87.9	$Ea_1 = 4.43$

exhibited only less than 3.5% weight loss at 100°C. The degradation of PCM_{1-7} commences around 200°C depending upon the nature of the polymer. Slow degradation is observed till 400°C and about 40% weight loss is found upto this temperature. The rate of loss of weight becomes larger over temperature range 450°–600°C, the major weight loss occurs in this temperature range. A 50% weight loss is observed around 450°C. PCM_1 and PCM_5 suffer almost complete degradation by 600°C. other show about 80–90% weight loss at 600°C. The activation energies of degradation reaction were calculated using Broido [7] and Metzger [8] method and were found to vary from 4.43 to 17.9 kcal mol.

The results of antifungal and antibacterial screening are presented in Table-III. Patel and Patel [6] have reported 80–100 percentage inhibition of growth at 100 ppm concentration of various fungi by poly(3-phenoxy substituted coumarin methylene)s using zone inhibition method. The polymers prepared by us (PCM_{1-7}) showed less than 40% inhibition of growth of fungi - *Aspergillus niger* and *Antrodiella species* at higher concentration of 10 mg ml. Since considerable inhibition is not shown even at higher concentration of the test compounds, it can be concluded that there is no significant toxic effect on the growth of the fungi.

PCM_5 and PCM_6 showed 70–90% inhibition of growth of bacteria *Escherichia coli* and *Alkaligenes faecalis*. All other PCM_5 show less than 30% inhibition except PCM_3 which exhibits 55% inhibition of growth of *A. faecalies* but is ineffective against *E. coli*.

TABLE III Antifungal and antibacterial screening data of PCMs. Percentage inhibition of growth by PCM_{1-7}

Polymer (Scheme 1)	*Aspergillus niger*	*Antrodiella species*	*Escherecia coli*	*Alkaligenes faecalies*
PCM_1	17.4	0.0	0.0	0.0
PCM_2	0.0	20.0	13.6	8.2
PCM_3	0.7	15.0	0.0	54.8
PCM_4	30.4	40.4	6.4	28.5
PCM_5	4.4	0.0	79.8	79.1
PCM_6	0.0	10.0	72.4	90.7
PCM_7	0.0	5.0	8.0	8.7

EXPERIMENTAL

Materials

Salicylaldehyde, ethyl bromoacetate and triphenylphosphine were obtained from Chiti-Chem, Baroda, India. Methyl iodide and ethyl iodide were procured from Sisco Chem Industries, Bombay, India. Benzyl bromide of Merck's and allyl bromide of Robert-Johnson's was used. All the other chemicals used were of Analar or laboratory grade.

SAL-F resin was prepared by acid catalyzed method reported in literature [9]. The acid catalysed method was selected as it gives thermally more stable SAL-F resin having decomposition temperature above 250°C. Thermally more stable resin was required as its conversion to PCM_{1-4} needed high temperature.

General Preparation of Carbethoxy Alkylidine Triphenyl Phosphoranes (Wittig Reagents) CTP_{1-4}

To a solution of carbethoxy methylene triphenylphosphorane [10] (CTP) (Wittig reagent) (0.034 mole) in dry chloroform (30 ml), halide Rx(CH_3I, C_2H_5I, $C_6H_5CH_2Br$, $CH_2{=}CH{-}CH_2Br$) (0.068 mole) was added slowly with stirring. The reaction mixture was then refluxed for 4 hours. The solvent was removed under reduced pressure and solvent ether (20 ml) was added to the oily residue. It was then cooled to 0°C and scratched to get a white solid salt which was filtered and washed with dry benzene.

The salt obtained was dissolved in water (130 ml), benzene (35 ml) and a drop of phenolpthalein was added to the above solution. 10% solution of sodium hydroxide was added with stirring till the pink colour of the solution persisted. The benzene layer was separated out. The aqueous layer was extracted with benzene (3 × 30 ml). The combined benzene extract was dried over anhydrous sodium sulphate. Removal of benzene under reduced pressure gave solid product, which was recrystallized from benzene-pet. ether. It furnished phosphoranes (CTP_{1-4}) in good yield.

CTP_1: 80% yield, m.p. 137–138°C (lit. [11] m.p. 140°C); CTP_2: 82% yield, m.p. 126–128°C (lit. [12] m.p. 126–130°C); CTP_3: 65% yield, m.p. 137–139°C (lit. [12] m.p. 139°C) and CTP_4: 78% yield, m.p. 122°C (lit. [11] m.p. 122°C).

Synthesis of Poly (Coumarin Methylene)s PCM_{1-7} Synthesis of PCM_{1-4} (Wittig Method) General Procedure

The reaction mixture of SAL-F resin (0.01 mole), substituted Wittig reagent (CTP_{1-4}) (0.03 mol) and diphenyl ether (15 ml) was refluxed gently on a sand bath for 4 hr. After cooling pet. ether (40 ml) was added to the reaction mixture. The polymer was separated out as a solid mass. It was filtered and washed with benzene, diethylether and finally with per. ether to remove the unreacted Wittig reagent and triphenyl phosphine oxide formed as a side product. The resultant polymer was then dried at 50°C. Thus PCM_{1-4} were obtained in 65 to 85% yield (Tab. I).

Synthesis of PCM_5 and PCM_6 (Perkin Method)

A mixture of SAL-F resin (0.02 mole) and N-acetylglycine/hippuric acid (0.03 mole) in 15 ml acetic anhydride with trace amount of piperidine was refluxed for 6 hr. After cooling it, 20 ml of water was added and the reaction was further refluxed for half an hour. The polymer was separated out as a solid mass, which was filtered out and tituirated with R. spirit/solvent ether to give PCM_5 and PCM_6 in good yield.

Synthesis of PCM_7 (Knoevenagel Method)

SAL-F resin (0.02 mole) and ethyl acetoacetate (0.025 mole) was taken in 50 ml ethanol and a catalytic amount of piperidine (2 drops) was added to it. The reaction mixture was refluxed for 8 hr. The yellow solid obtained was filtered out and was washed with ethanol and dried at 50°C.

The yield, colour and elemental analysis of poly (coumarin methylene)s PCM_{1-7} are shown in Table-I.

Biological Activity of Poly(Coumarin Methylene)s

Photometric assay method was used to determine the toxicity effect of PCM_{1-7} on the bacteria *E. coli* and *Alkaligenes faecalies* (in terms of turbidity [13]) and on fungi *Aspergillus niger* and *Antrodiella species* (in terms of dry weight [14]).

Antifungal Activity

Freshly prepared Sabroud's agar slant of *Aspergillus niger* and *Antrodiella species* were incubated at room temparature for 24–28 hrs. Medium of following composition in distilled water was employed for the experiment.

Dextrose	–	0.5%
NH_4Cl	–	0.3%
$MgSO_4 \cdot 7H_2O$	–	0.05%
K_2HPO_4	–	0.05%
Yeast extract	–	0.02%
$MnSO_4$	–	0.002%
$ZnSO_4$	–	0.002%
$FeSO_4$	–	0.002%
pH	–	7.6

Fungal spores in sterile distilled water (with Tween-80) were used to innoculate the sterile test medium of 10 ml each containing 100 mg of PCM_{1-7}. The experiment was terminated after 7 days when the control showed complete utilization of sugar. The fungal cell mass was filtered out, dried and weighed. The percentage inhibition for fungi was calculated after 7 days using the formula given below.

$$\text{Percentage of inhibition} = \frac{100(X - Y)}{X}$$

where X = Weight of dry fungal cell mass in control set.

Y= Weight of dry fungal cell mass in test set.

Antibacterial Activity

Medium of the above composition was used. The bacterial culture of *E. coli* and *Alkaligenes faecalis* were incubated at 37°C in Nutrient broth and 28 hours old actively growing bacterial cultures were used for inhibition studies. The sets were prepared having 20 ml of sterile medium and 200 mg of PCM_{1-7}. The growth of the bacteria was determined by measuring the turbidity after 48 hrs. For this purpose 5 ml of the test

medium was taken out under sterile condition. It was centrifuged at 6000 rpm for 15 min. The supernent liquid was decanted and the pellet was suspended in 5 ml normal saline solution. The process was repeated again. The pellet was finally suspended in 5 ml normal saline solution. The turbidity of the bacterial suspension was measured at 660 nm. The percentage inhibition for bacteria was calculated by the following formula.

$$\text{Percentage of inhibition} = \frac{100(X - Y)}{X}$$

where X = Optical density of bacterial suspension in control set.

Y = Optical density of bacterial suspension in test set.

MEASUREMENTS

Elemental analysis were carried out on Haraeus C, H, N Elemental Analyser. The infrared spectra were scanned in KBr on a Perkin-Elmer 983 spectrophotometer. Thermogravimetric analysis (TGA) of all the polymer samples were carried out on a Du Pont 951 thermal analyser at a heating rate of 10°C/min. The optical density measurements in the biological activity testing was measured on Systronic Spectrophotometer 106 model.

CONCLUSIONS

1. SAL-F resin reacted smoothly to give poly(coumarin methylene)s (PCM_{1-7}) in high yield under Wittig, Perkin and Knoevenagel reaction conditions.
2. The poly(coumarin methylene)s (PCM_{1-7}) were stable upto 200°C and showed almost complete degradation by 650°C.
3. Though most of the poly(coumarin methylene)s did not show any significant toxicity on the growth of fungi *A-niger* and *Antrodiella species*, PCM_5 and PCM_6 exhibited 70–90% inhibition of growth of bacteria *E. coli* and *A. faecalis* at higher concentration of 10 mg/ml.

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