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Research Article

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A study on the synthesis and bactericidal efficacy of certain poly(ester-amides) containing 2,5-bis(benzylidene)cyclopentanone moiety in the main chain

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ABSTRACT

A series of four poly(ester-amides) were synthesized by direct polycondensation of an aromatic diacid namely 4,4´-oxybis(benzoicacid) and 4,4´-biphenyldicarboxylic acid with a diamine namely ethylene diamine and a diol namely 2,5-bis(4-hydroxybenzylidene)cyclopentanone (BHCP) and 2,5-bis(4-hydroxy-3-methoxybenzylidene) cyclopentanone (BVCP) in pyridine using diphenyl chlorophosphate as the condensation agent. These poly(ester-amides) were characterized by qualitative solubility data and viscosity values. The microstructure of the repeating units existing in the poly(ester-amide) backbone was established by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopic techniques. The inhibitory activity of the bisbenzylidenecyclopentanone diols and their poly(ester-amides) against pathogenic bacteria is well documented.

Key words: Bisbenzylidenecyclopentanone, Poly(ester-amides), Polycondensation, Bactericidal

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INTRODUCTION

For almost two decades arylidene-ketones have attracted the attention of macromolecular chemists [1-3]. They were found to be a potential mesogen [4-7] and their incorporation in the polymeric backbone has imparted thermotrophic liquid crystalline property to the polymeric materials. They also display photocrosslinking property [8-11] in solution and in film form. Mohamed A. Abd-Alla [12] generated a series of new polyesters of diarylidenecycloalkanones containing an azo group in the main chain to determine its electrical properties, and he also synthesized some new arylidene polyesters using diarylidenecyclopentanone in the polyester backbone to report its crystallinity [13]. Balaji, *et al* [14] synthesized and characterized certain photosensitive thermotrophic liquid crystalline poly(benzylidene-ether)s with alkanones and methylene spacers in the main chain. D. Jayalatha and coworkers [15] reported on the preparation and characterization of benzylidene and azobenzene liquid-crystalline polymers and studied their photocrosslinkability. Malathi *et al* [16] reported on the synthesis and antibacterial activity of certain random copolyesters containing arylidene-ketones in the main chain. Yum Eryanti and coworkers [17] reported on the study of the synthesis and toxic, antioxidant, and anti-inflammatory activities of 2,5-bis-(4-hydroxybenzylidene)cyclopentanone.

However, there is no literature information on the synthesis and bactericidal efficacy of poly(ester-amides) containing arylidenecyclopentanone moiety in the polymer backbone. The purpose of the current work is to synthesize four poly(ester-amides) containing arylidenecyclopentanone moiety in the polymer backbone and to evaluate its bactericidal efficacy. Poly(ester-amides) [18,19] are a category of polymeric materials which contains both ester and amide linkages and are synthesized by the copolymerization of a diacid with that of a diamine and a diol in the mole ratio of 2:1:1.

EXPERIMENTAL SECTION

2.1 Chemicals

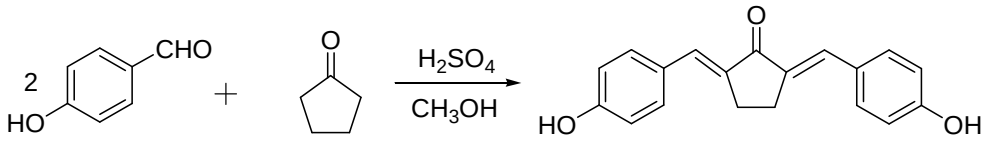
Aldrich samples of diphenyl chlorophosphate, 4,4´-oxybis(benzoicacid), 4,4´-biphenyldicarboxylic acid, 4-hydroxyacetophenone and 4-hydroxybenzaldehyde were used as received. Vanillin (CDH), ethylene diamine (BDH), lithium chloride (SD Fine) and cyclopentanone (Fluka) were used as received. Merck sample of pyridine was used as polymerization medium was refluxed over potassium hydroxide pellets, distilled (b.p. 115°C) and stored over potassium hydroxide pellets. Methanol was used as solvent for the preparation of the monomers and as a non-solvent for the poly(ester-amides). Merck, LR sample of methanol and SD fine AR sample of N,N-dimethylacetamide (DMAc) were purified as reported by Furniss *et al*. [20] and used. Spectral grade DMSO-d6 (Aldrich) containing TMS as internal standard was used as received for recording NMR spectra.

Synthesis of Diols

The arylidene-keto diols namely BHCP and BVCP were synthesized by the method reported in literature [21, 22].

Preparation of 2,5-bis(4-hydroxybenzylidene)cyclopentanone (BHCP)

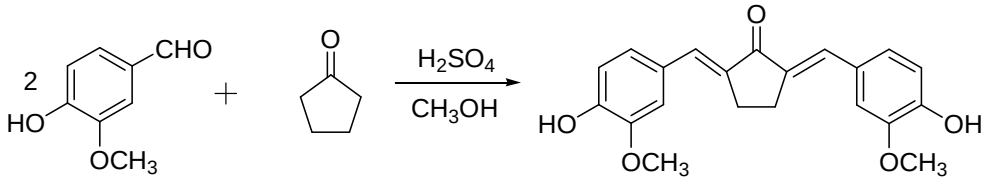
About 1 mL of sulphuric acid was added in drops to a well-cooled solution of 4-hydroxybenzaldehyde (100 mmol) and cyclopentanone (50 mmol) in 100 mL of dry methanol with occasional shaking taken in a 250-mL round-bottomed flask. A green-coloured solid of BHCP was precipitated. It was washed with aqueous methanol and re-crystallized from hot methanol. Yield: 90%; m.p. > 300^{o}C; FT-IR (KBr) 3438 cm^{-1} (b, O-H) and 1648 cm^{-1} (s, C=O); ^{1}H NMR (400 MHz, CDCl3) δ 2.92 (s, 4H), δ 6.79-7.49 (m, 10H) and δ 9.97 (s, 2H); MS (EI) m/z 292 [M]+.



2,5-bis(4-hydroxybenzylidene)cyclopentanone

Preparation of 2,5-bis(4-hydroxy-3-methoxybenzylidene)cyclopentanone (BVCP)

About 1 mL of sulphuric acid was added in drops to a well-cooled solution of vanillin (100 mmol) and cyclopentanone (50 mmol) in 100 mL of dry methanol with occasional shaking taken in a 250-mL round-bottomed flask. A yellow-coloured solid of BVCP was precipitated. It was washed with aqueous methanol and re-crystallized from hot methanol. Yield: 88%; m.p. 212^{o}C; FT-IR (KBr) 3448 cm^{-1} (b, OH) and 1654 cm^{-1} (s, C=O); ^{1}H NMR (400 MHz, CDCl3) □2.92 (s, 4H), 3.42 (s, 6H), 6.72-7.50 (m, 10H) and 9.94 (s, 2H); MS (EI) m/z 352 [M]+.



2,5-bis(4-hydroxy-3-methoxybenzylidene)cyclopentanone

Synthesis of Poly(ester-amides)

This method was reported by Arulmoli and coworkers [23]. The procedure for the synthesis of a typical poly(ester-amide) is represented here.

Diphenyl chlorophosphate (12 mmol) in pyridine (10 mL) was added to a solution containing LiCl (10 mmol) and 4,4′-oxybis(benzoic acid) (5 mmol) in pyridine (10 mL) taken in a 100 mL round-bottomed flask. The reaction mixture was continuously stirred at room temperature for a span of 30 minutes. Then the temperature was raised to 115°C and stirring was carried out at this temperature for about 10 minutes. The solution containing the diamine ethylene diamine (2.5 mmol) and the diol BHCP (2.5 mmol) was added over a period of 10 minutes with constant stirring. The reaction mixture was maintained at this temperature for a time frame of 3 hours. Then reaction mixture was cooled to room temperature and poured into 300 mL of methanol when the poly(ester-amide) was precipitated.

It was filtered, washed with dry methanol and dried in vacuum.

The diamine, the diacid and the diol together with the copolyester code of the four copolyesters are represented in table 1.

Table 1: Monomers used, polymer code of the four poly(ester-amides) and their respective percentage yield and inherent viscosities

Common diamine: Ethylene diamine		Polymer Code	Yield (%)	η_{inh}, (dL/g)
Diol	Diacid			
BHCP	4,4´-oxybis(benzoic acid)	PBEO	70	0.43
BHCP	4,4´-biphenyldicarboxylic acid	PBEB	77	1.05
BVCP	4,4´-oxybis(benzoic acid)	PVEO	75	0.50
BVCP	4,4´-biphenyldicarboxylic acid	PVEB	81	1.20

Bactericidal Study

The antibacterial activity [24-27] of two typical parent diols namely BHCP and BVCP and the four poly(ester-amides) namely PBEO, PBEB, PVEO and PVEB was assayed against *Enterococcus faecalis*, *Klebsiella pneumoniae* and *Escherichia coli* by disc diffusion method adopted by Rajkumar *et al* [28, 29].

Disc Diffusion Method: The test bacteria were sub-cultured in Muller–Hinton broth from which 1 mL of cell suspension was taken and the optical density was adjusted to 0.5, after which this was spread as a thin film over the Muller–Hinton agar plates. The synthetic compounds under investigation were loaded onto the discs at 50, 100 and 150 µg concentrations and air-dried. These were placed on the inoculated Muller–Hinton agar plates and incubated at 37°C for 48 hours. After incubation, the zone of inhibition was measured. A streptomycin disc (10 µg/disc) was used as the standard. A disc of 150 µl of DMSO served as the control.

CHARACTERIZATION

Solubility of all the poly(ester-amides) was determined in various solvents qualitatively. The inherent viscosity (η_{inh}) of all the poly(ester-amides) was determined in DMAc solution at a concentration 0.1 gdL^{-1} using Ubbelohde viscometer in which the pure solvent had a flow rate of 446 seconds at a temperature of 30°C. FT-IR spectra of the entire poly(ester-amides) were recorded using Nicolet 510 FT-IR instrument. The ^{1}H and ^{13}C NMR spectra were recorded with JEOL GSX-400MHz instrument in DMSO-d6 solvent.

RESULTS AND DISCUSSION

The poly(ester-amides) synthesized in the present work were characterized by solubility studies, viscosity measurements and spectral data. Disc diffusion method was employed to evaluate the anti-bacterial activity of the poly(ester-amides).

Solubility

The poly(ester-amides) reported here are found to be soluble in highly polar solvents such as dimethyl sulphoxide, DMAc and dimethyl formamide, partially soluble in moderately polar solvents like tetrahydrofuran (THF) and acetone and thoroughly insoluble in benzene and hexane. The results of the solubility of the copolyesters are presented in table 2.

Table 2: Solubility of poly(ester-amides) in common organic solvents

Polymer	Hexane	Benzene	$CHCl_3$	EtOAc	THF	Acetone	MeOH	DMAc	DMF	CH_3CN	TFA	DMSO
PBEO	– –	– –	– –	– –	+ –	+ +	+ –	+ +	+ +	+ +	+ +	+ +
PBEB	– –	– –	– –	– –	– –	+ –	– –	+ –	+ –	+ –	+ –	+ +
PVEO	– –	– –	– –	– –	+ –	+ +	+ +	+ +	+ +	+ +	+ +	+ +
PVEB	– –	– –	– –	– –	+ –	+ –	+ –	+ –	+ –	+ +	+ +	+ +

+ + = Soluble; – – = Sparingly soluble; + – = Partially soluble

Poly(ester-amides) with methoxy substituent in the benzene ring of the arylidenecyclopentanone moiety was found to be highly soluble because of their capacity to disrupt the macromolecular chain. Presence of ether linkage in the polymer backbone aids the solubility in these poly(ester-amides). Similar observations were made by Samuel and coworkers [30] in a series of copolyesters.

Viscosity Measurements

The η_{inh} values of all the four poly(ester-amides) were found to be in the range of 0.43–1.20 dL/g and are presented in table 1. It may be pointed out that the poly(ester-amides) synthesized from BVCP have higher η_{inh} values than those prepared from BHCP. This may be due to the presence of methoxy substituent in the aromatic ring which gets involved in increasing the dipolar interaction and hence have higher viscosity values.

Spectral Studies

The ester and amide functional groups present in the poly(ester-amide) chain were identified by FT-IR spectra. The IR spectra of all the four poly(ester-amides) showed characteristic absorption at $\overline{\upsilon}$ = 1730–1745 cm^{-1} due to ester C=O stretching frequency and an absorption at $\overline{\upsilon}$ = 3400–3430 cm^{1} due to the amide N-H stretching frequency. Similar observations were made by Khairou *et al* [31] in a new series of poly(ester-amide)s containing diarylidenecyclohexanone in the main chain.

The structural units present in the poly(ester-amide) chain were identified by ^{1}H and ^{13}C NMR spectra. The secondary amide proton appeared as a singlet in the range of 9.63–10.15 ppm. Related observation was made by Oswal *et al* [32]. The aromatic protons are observed in the range of 7.25–8.09 ppm. The methoxy protons in the vanillin moiety are indicated by a signal at 3.45 ppm. A signal at 2.65 ppm is attributed to the methylene protons attached to nitrogen atom. The signal in the range of δ 185–200 ppm in the ^{13}C NMR spectra of the poly(ester-amides) is due to the carbonyl carbon of the α,β-unsaturated ketone, and similar report was made by Sidharthan *et al* [33]. The signals in the range of δ 175–180 ppm and δ 168–172 ppm are due to the carbonyl carbon of the amide and ester groups [31] which indicates the formation of poly(ester-amide).

BACTERICIDAL STUDY

The antibacterial activity of the parent diols, HMPP and BHPP, and the poly(ester-amides) PHEO, PHEB, PMEO and PMEB, was assayed against *S. aureus, S. faecalis, K. pneumoniae, S. typhi, V. cholerae* and *P. mirabilis* by disc diffusion method. The zone of inhibition for each concentration against all the test bacteria is depicted in table 3.

The standard antibiotic disc (streptomycin disc 10 μg/disc) inhibited the growth of *Enterococcus faecalis* by 14 mm, *Klebsiella pneumoniae* by 15 mm and *Escherichia coli* by 12 mm. Analysis of the data in table 3 suggests that the two parent diols BHCP and BVCP exhibited antimicrobial activity towards *K. pneumoniae*, *E. faecalis* and *E. coli*. Both these diols are about 50% as active as streptomycin towards *E. coli*. Furthermore, the arylidene diol BVCP is more active towards the three microbial than BHCP, suggesting that the presence of ether group enhances the antibacterial activity in the three concentrations used in the present investigation, and similar observations were made by Christurajan and coworkers [34].

Table 3: Inhibition effects of arylidene diols and the poly(ester-amides) on the growth of *Enterococcus faecalis, Klebsiella pneumonia* and *Escherichia coli*

Test material	*Enterococcus faecalis*			*Klebsiella pneumoniae*			*Escherichia coli*		
	Zone of inhibition in diameter (mm)			Zone of inhibition in diameter (mm)			Zone of inhibition in diameter (mm)		
	50 μg/mL	100 μg/mL	150 μg/mL	50 μg/mL	100 μg/mL	150 μg/mL	50 μg/mL	100 μg/mL	150 μg/mL
BHCP	2.8	5.9	7.2	3.8	5.8	6.9	3.3	5.7	6.5
PBEO	3.7	7.3	9.4	4.2	7.1	8.8	4.1	7.8	8.2
PBEB	3.2	6.8	8.6	4.0	6.7	8.1	3.7	6.2	7.6
BVCP	4.0	6.3	8.1	4.0	6.1	7.6	3.5	5.9	7.5
PVEO	4.7	8.1	10.8	4.2	8.0	10.3	5.1	8.3	9.3
PVEB	4.2	7.9	9.6	4.1	7.2	8.9	5.0	7.4	8.8

It is interesting to note that the poly(ester-amides) PBEO, PBEB, PVEO and PVEB exhibited higher antibacterial activity than the arylidene diols from which the poly(ester-amides) were deduced. Thus, the incorporation of bisbenzylidenecyclopentanone moiety in the poly(ester-amides) main chain by polycondensation process significantly enhanced the antimicrobial activity. The activities of the poly(ester-amides) PBEO and PVEO are higher than those of PBEB and PVEB, which may be due to the presence of ether linkage in the oxybis(phenylene) moiety, and parallel observation was reported by Malathi *et al* [16] in a series of copolyesters derived from arylidene diols. For the same reason, higher activity was observed in vanillin-based poly(ester-amides) than the poly(ester-amides) obtained from 4-hydroxybenzaldehyde-based arylidene diols [35].

CONCLUSION

Four poly(ester-amides) are synthesized using a common diamine, ethylene diamine. The dicarboxylic acids and diols are varied. The dicarboxylic acids used are 4,4´-oxybis(benzoicacid) and 4,4´-biphenyldicarboxylic acid. The diols used are BHCP and BVCP. These poly(ester-amides) are highly soluble in polar organic solvents. The poly(ester-amides) are characterized by solubility studies, viscosity measurements and spectral data. These poly(ester-amides) exhibited significant bactericidal activity against pathogenic bacteria.

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