

A Computational Study on the Antioxidant Activity of Certain Random Copolyesters Containing Bis(arylidene) Cycloalkanone Moiety in the Main Chain

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Abstract

A series of five random copolyesters was synthesized by polycondensation of different arylidene diols with curcumin as a common diol and a common diacid chloride in the ratio of 1:1:2, respectively. The five arylidene diols were synthesized by an acid-catalyzed Claisen condensation reaction. The repeating units present in these five random copolyesters and also the backbone was identified by FT-IR, ¹H-NMR, and ¹³C-NMR spectroscopic techniques. The curcumin based copolyester exhibited good antioxidant activity, confirmed by various antioxidant activity determinations. Structural analysis such as HOMO and LUMO energies and the HOMO-LUMO energies gap of the molecule has been calculated using the B3LYP/6-311+G (d, p) level of theory. The antioxidant property of the molecule can be explained by the hydrogen atom transfer by theoretical study.

Keywords: Arylidene-ketones; Copolyesters; Polycondensation; Antioxidant activity; Computational study.

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1. Introduction

In recent years much attention has been paid to natural antioxidants [1], which are polyphenols containing phenolic moiety. One such natural antioxidant is curcumin, a major constituent of rhizome turmeric. It is a nutraceutical compound and exists in a stable enol form [2]. Generally, curcumin increases the shelf life of our food products [3, 4]. Curcumin and its analogs have demonstrated hepatoprotective [5], anti-diabetic [6], nephroprotective [7], anti-ulcer [8], cardioprotective [9], anti-obesity [10], neuroprotective [11], antirheumatic behavior [12], antimicrobial [13] and antitumor [14] activity among which its neuroprotective action against various neurodegenerative disorders which pulled researchers' attention in this area and recently it is found to be potent against COVID 19 [15,16]. Literature studies reveal the antioxidant activity of curcumin-based copolyesters containing different moieties in the main chain or side chain. Kalpana and coworkers reported on the antioxidant activity of random copolyesters using 1,4-dithiane-2,5-diol

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with sebacic acid and 1,4-cyclohexane diol [17], 1,12 dodecane diol and 1,12 dodecane dioic acid [18], succinic acid and 1,2 ethane diol [19] by DPPH assay. Sokmen reported on the antioxidant activity of some curcuminoids and chalcones by DPPH assay [20]. Yamini and coworkers reported on antioxidant activity by the DPPH method for copolyesters synthesized from 1,4 – cyclohexane diol, PEG 400, and dodecanedioic acid in the presence of Titanium (IV) isopropoxide as catalyst [21]. Even though a small fraction of the $-\text{CH}_2$ group in the curcumin structure is responsible for antioxidant activity, the number and position of hydrogen-donating phenolic hydroxyl groups are mainly responsible for the radical-scavenging activity via the HAT mechanism, i.e., (Hydrogen atom transfer) mechanism [22,23], i.e., donation of the hydrogen atoms from the phenolic group especially the ortho-methoxy phenolic OH group is required for antioxidant activity rather than SET mechanism, i.e., single electron transfer which is essential in the prevention of oxidative stress-related diseases [24]. Curcumin analogs are shown to have better scavenging ability than curcumin itself [25].

Furthermore, being more concerned in the field of medicine [26,27], researchers keep exploring [28,29] the relationship between the chemical structure and the activity of antioxidants. The theoretical method based on quantum chemical calculation [30] has been adopted to study the relationship between the structure and activity of antioxidants because of its efficiency and convenience.

In addition, computational methods have unlocked new ways to understand the chemical properties of molecules using calculations as a substitute for experimental investigation of the reactions. The computational approach is not laborious and can be effortlessly achieved. The recent effects of Density Functional Theory (DFT) methods, along with quantum chemical calculations, are significant [31]. As DFT is great at predicting molecules' chemical and physical properties with great accuracy, it is one of the best useful computational tools [32]. In order to structurally apprehend a molecule, some factors, such as molecular orbital energies should be understood. In the present work, geometric parameters and molecular orbitals have been studied at the B3LYP/6-311+G (d,p) level of theory. The frontier molecular orbitals have been analyzed. A hydrogen atom transfer mechanism (HAT) has been employed to describe the molecule's antioxidant capacity. The input structures have been drawn using Gaussview-5.0. [33]. All the computational works have been performed using Gaussian 09 package [34].

Experimental methods for antioxidant activity were well reported in many papers, and computational methods for antioxidant activity have been less reported [35] so far. Therefore, in our present work, we have synthesized five random copolyesters by incorporating the aryldiene-keto in the copolyester backbone by solution polycondensation method. The synthesized copolyesters were characterized by using appropriate methods. Antioxidant activity for the copolyesters was determined by using 2,2-diphenyl-1-picrylhydrazyl (DPPH), nitric oxide, ferric reducing antioxidant power (FRAP), superoxide dismutase (SOD) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) methods. The experimental data are compared with a computational

method based on density functional theory, and the coincidence of both the experimental and theoretical methods is discussed in this paper

2. Experimental

2.1. Materials and methods

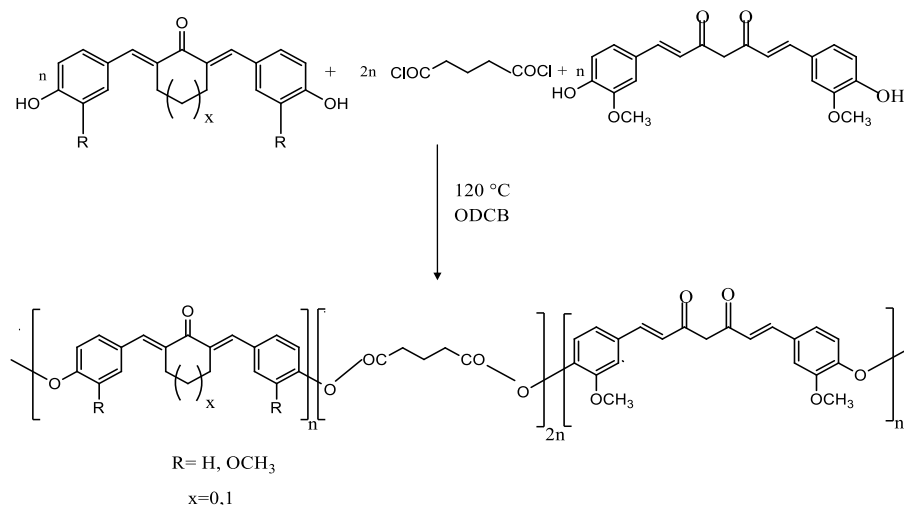
4-hydroxybenzaldehyde (Spectrochem, India), vanillin (Loba Chemie Pvt. Ltd, India), 3-ethoxy-4-hydroxy benzaldehyde (Sigma Aldrich, USA), cyclohexanone (Finar Chemicals, India) and cyclopentanone (Spectrochem, India) are the chemicals used for the synthesis of monomers i.e., arylidene diols which are used as a common diol for polymerization in which sulphuric acid (Rankem, India) is used as a catalyst. Ethanol (Merck, India) is used as both non-solvent and a solvent for the precipitation of copolyesters and for the preparation of the monomer diols, respectively. Aldrich samples of curcumin, glutaryl chloride (USA) and 1,2-orthodichlorobenzene (ODCB) (SD fine AR chemicals, India) were purchased for the copolymerization process. The synthesized copolyesters were characterized by a Fourier transform infrared (FT-IR) instrument (Shimadzu, Japan, IR Affinity 1) for recording FT-IR spectra of copolyesters. The DMSO-d₆ solvent was used for recording ¹H-NMR (BRUKER AV III 500 MHz, Japan, JEOL ECA) spectra. In this work, the structural analysis of the molecule has been done using B3LYP/6-311+G (d,p) level. The structure optimization was performed at B3LYP/6-311+G (d,p) level. The analysis and its results have been discussed in the subsequent sections. The optimized geometry and the frontier molecular orbitals images are taken using the ChemCraft software [36].

2.2. Synthesis of monomer-arylidene-keto diols

Arylidene-keto diol 2,6-bis-(4-hydroxy-3-methoxy benzylidene) cyclohexanone (BVCH) was synthesized by dissolving 4-hydroxy-3-methoxybenzaldehyde (0.04 mol) in 100 mL of ethanol followed by the addition of cyclohexanone (0.02 mol). To this ethanolic solution, 1 mL of conc. sulphuric acid was added dropwise with constant shaking, and the mixture was maintained at room temperature for 12 h. The precipitate (BVCH) was thus obtained as a pale green colored crude product when ice-cold water was added to it. It was then filtered, washed a few times with water, and then recrystallized using chloroform.

The rest of the monomers used for the synthesis of polymers, i.e., 2,6-bis-(4-hydroxybenzylidene)cyclohexanone (BHCH), 2,5-bis-(4-hydroxybenzylidene) cyclopentanone (BHCP), 2,5-bis-(4-hydroxy-3-methoxybenzylidene) cyclopentanone (BVCP) and 2,5-bis-(4-hydroxy-3-ethoxybenzylidene) cyclopentanone (BCEP) were synthesized by the same procedure reported elsewhere [37,38].

2.3. Synthesis of copolyesters



Scheme 1. Synthesis of random copolyester.

Arylidene diol was dissolved in 10 mL of ODCB solution in a 100 mL round-bottomed flask. To this solution, curcumin (1.6 mmol, 0.6 g) and 0.42 mL of glutaryl chloride were added, and then the mixture was heated by stirring up to 120 °C for 12 h. The copolyester was precipitated by pouring the reaction mixture into 100 mL n-hexane. It was then filtered, recrystallized with ethanol, and dried in a vacuum.

Table 1. Monomers used and copolyester code of the five copolyesters.

Varying Arylidene Diols	Common Diol	Common Diacid Chloride	Copolyester Code
BHCH	Curcumin	Glutaryl Chloride	PGCA
BVCH	Curcumin	Glutaryl Chloride	PGCB
BHCP	Curcumin	Glutaryl Chloride	PGCC
BVCP	Curcumin	Glutaryl Chloride	PGCD
BECP	Curcumin	Glutaryl Chloride	PGCE

The copolyesters PGCB, PGCC, PGCD, and PGCE were synthesized by following the same method using the aryldiene diols BVCH, BHCP, BVCP, and BECP respectively.

2.4. Antioxidant activity

2.4.1. DPPH method

The radical scavenging ability of the polymers was assessed through the reaction of materials with stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. Because of its unpaired electron, the picrylhydrazyl radical shows a strong absorption band at 517 nm, assuming a purple coloration. When these radical species are captured by an antioxidant,

the absorption decreases, and the resultant discoloration is directly proportional to the number of radicals captured. For this test, a stock solution of DPPH at a known concentration was used as a control. The percentage of each substance's antioxidant activity (AA %) was assessed by DPPH free radical scavenging assay. Different concentrations of the sample were added to all the tubes except the blank. Then 3 mL of ethanol and 0.3 mL of 0.5 mM DPPH radical solution in ethanol were added. The control solution was prepared by mixing ethanol (3.5 mL) and DPPH radical solution (0.3 mL). Absorbance was read at 517 nm after 30 min of reaction. The scavenging activity percentage (AA %) was calculated using the formula given below:

$$\% \text{ Antioxidant activity} = \left\{ \text{Absorbance at blank} - \left(\frac{\text{Absorbance at test}}{\text{Absorbance at blank}} \right) \right\} \times 100$$

2.4.2. Nitric oxide scavenging activity

Griess reagent was used to estimate Nitric oxide (NO). NO forms a pink color complex at 540 nm [39].

Procedure: To 0.5 mL of polymer solution in ethanol, 2 mL of sodium nitroprusside was added. After 4 h of incubation, 0.5 mL of Griess reagent was added. The test was also done with Vitamin C. The % scavenging and % scavenging activity compared to Vitamin C was calculated as same as the DPPH method.

2.4.3. Ferric ion reducing /antioxidant power assay

Antioxidants reduce Fe^{3+} to Fe^{2+} . This ion, on conjugation with ferricyanide ion, forms a Prussian blue-colored product measured spectrophotometrically at 700 nm. SDS present in the solution prevents the formation of turbidity.

Procedure: To 0.1 mL of the polymer solution, 0.9 mL of 96 % ethanol, 5 mL of distilled water, 1.5 mL of 1 M HCl, 1.5 mL of 1% potassium ferricyanide, 0.5 mL of 1% SDS (sodium dodecyl sulfate) and 0.2 % ferric chloride were added. Here, the reference used was Ascorbic acid. The mixture was boiled in a water bath at 50 °C for 20 min. It was then rapidly cooled and mixed well. All these solutions were taken in the control "tube." At 750 nm, the absorbance was measured [40,41]. The difference in OD between the test and control was noted.

2.4.4. ABTS scavenging activity

A Standard solution was prepared by mixing equal amounts of 7 mM ABTS solution and 2.4 mM potassium persulphate solution. It was then allowed to react for 12 h at RT in the dark. 1 mL of this standard solution was then allowed to react with 1 mL of the polymer solution with different concentrations ranging from 100 to 500 mg/mL and mixed thoroughly. A strong absorption peak was measured at 734 nm after 6 min. The % inhibition capacity of ABTS [42] for the synthesized polymer was calculated from the following equation:

$$\text{ABTS Scavenging activity (\%)} = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100$$

Where A_{control} is the absorbance of ABTS and methanol. A_{sample} is the absorbance of ABTS radical and sample (i.e., standard or polymer).

2.4.5. Superoxide radical scavenging activity

Superoxide radicals were generated in 3 mL of sodium phosphate buffer solution (100 mM, pH 7.4), which contains 1 mL NBT (nitro blue tetrazolium, 150 mM) solution, 1 mL NADH (reduced form of nicotinamide adenine dinucleotide, 468 mM) solution and various concentrations of CRE (25-250 mg/mL) in water. To this, 1 mL of PMS solution (Phenazine methosulfate, 60 mM) was added for the initiation of the reaction. The absorbance values were measured [43] against the blank solution by incubating the reaction mixture at 25 °C for about 5 min. Here, L-ascorbic acid was used as a positive control. The percentage of superoxide radical scavenging was calculated using the following formula:

$$\text{Superoxide radical scavenging activity (\%)} = [(A_0 - A_1) / A_0 \times 100]$$

where A_0 is the absorbance of the control and A_1 is the absorbance of the standard sample.

3. Results and Discussion

3.1. Solubility and viscosity measurements

In connection with solubility, all five random copolyesters were highly soluble in polar solvents such as DMAc and DMF, partially soluble in moderately polar solvents like THF and acetone, and insoluble in the least polar solvents like benzene and hexane [38].

The polyester's inherent viscosity (η_{inh}) was measured using Ubbelohde viscometer by dissolving 25 mg of pure dry copolyester sample in 25 mL DMF solution. From the flow time measurements, the η_{inh} values were found to be in the range of 0.24–1.36 dL/g, which accounts for the reasonably high molecular weight of the copolyesters [38].

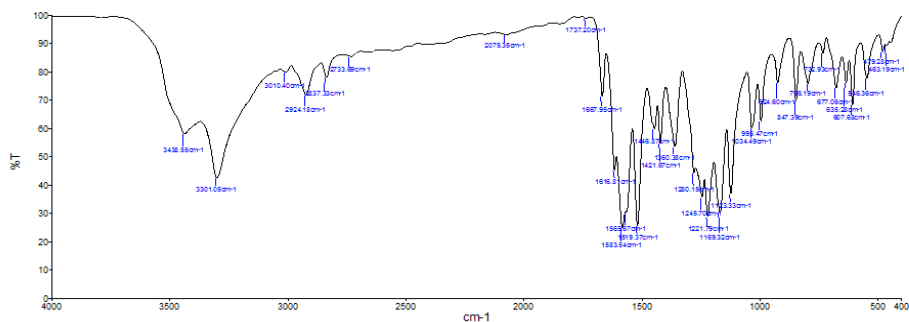


Fig.1. FT-IR Spectrum of the monomer BVCP.

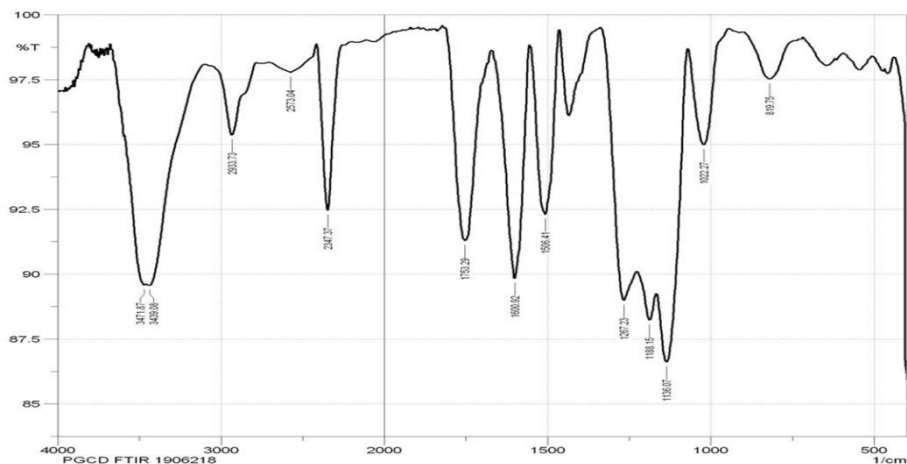


Fig. 2. Representative FT-IR spectrum of PGCD copolyester prepared from BVCP as variable diol and curcumin as a common diol.

Figs. 1 and 2 show the FT-IR spectrum of the monomer BVCP and the copolyester PGCD, respectively. The absorption peak at 819 cm^{-1} in Fig. 2. corresponds to the bending frequency of C-H bonds from the aromatic ring, 1022 cm^{-1} and 1136 cm^{-1} is due to $-\text{OCH}_3$ stretching, 1267 cm^{-1} is responsible for C-O stretching, 1506 cm^{-1} is due to aromatic C=C stretching, 1600 cm^{-1} corresponds to olefinic C=C stretching, 2933 cm^{-1} corresponds to $-\text{OCH}_3$ C-H stretching and peak at 3438 cm^{-1} corresponds to end $-\text{OH}$ stretching, 3438 cm^{-1} corresponds to end $-\text{OH}$ stretching. The FT-IR spectrum of all five copolyesters showed characteristic absorption at 1753 cm^{-1} due to ester C=O stretching frequency. Absorption at 3471 cm^{-1} is due to the terminal O-H group. Arulmoli [44], Vasanthi [45], and Devi [46] have reported similar observations for copolyesters containing arylidene moiety in the main chain.

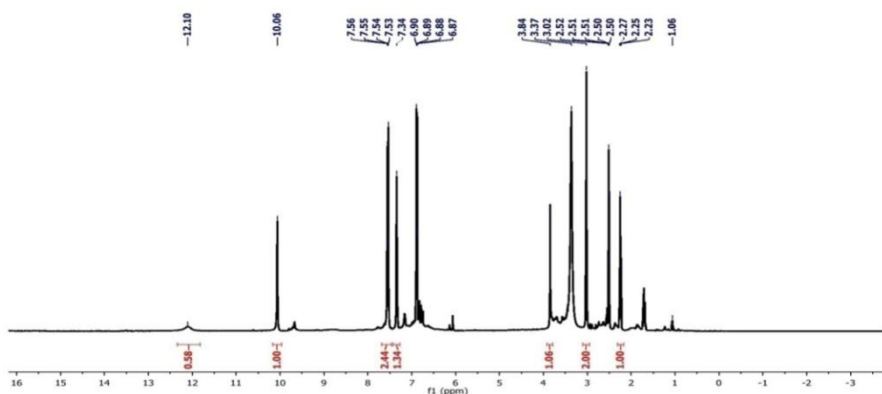


Fig. 3. Representative ^1H NMR of random copolyester.

Fig. 3 shows NMR spectra for the representative polymer PGCC. The aromatic protons were observed in the range of 7.2–7.6 ppm. The vinylic protons which are attached to the carbonyl carbon are observed in the range of 6.7–6.9 ppm. The methoxy protons in the arylidene moiety are represented in the 3.3–3.6 ppm range. The methylene protons of the cycloalkanone group are observed in the range of 2.5–2.6 ppm. The olefinic -H of the arylidene group is observed around 7.3 ppm. Similar observations were made by Sathish [47], Mayavathi [48], and Rajam [49] for copolyesters containing arylidene moiety.

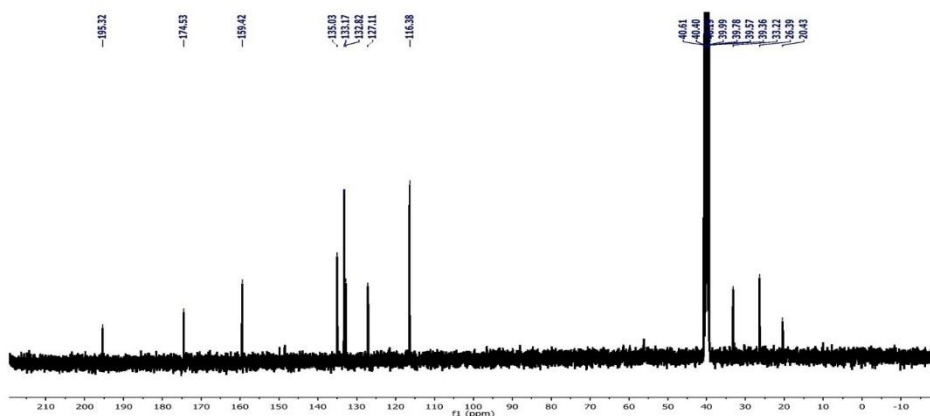


Fig. 4. Representative ^{13}C NMR of random copolyester.

Fig. 4 shows the ^{13}C NMR spectra of the copolyester. The peaks appeared around 174 ppm - 176 ppm confirm the presence of copolyester formed. Also, the peak around 195 ppm is due to the keto carbon in cyclopentanone. The ^{13}C peaks commonly obtained in the up-field region, 24 ppm - 26 ppm reveal the presence of carbon atoms of glutaryl chloride. Rajam [50], Muthusamy [51], and Malathi [52] reported similar observations for various copolyesters.

3.2. Antioxidant activity (DPPH method)

Fig. 5 shows the plot between the concentration of the polymer and % inhibition. The plot revealed that PGCA has IC_{50} value at a concentration of 385 μg , PGCD at 450 μg , and PGCE at 400 μg . For the polymer PGCB, % inhibition was found to be 62.5 at a concentration of 100 μg , and so antioxidant activity was studied at lower concentrations than 100 μg . From Table 2 and Fig. 6, the IC_{50} value was obtained at a lower concentration of around 48 μg which shows very good antioxidant activity. The % inhibition for the polymer PGCC was found to be 30.0 at a concentration of 500 μg . So to obtain the IC_{50} value, concentrations were increased to 1000 μg , but the IC_{50} value was not obtained even at such a very high concentration, as shown in Table. 3. This suggests that polymer PGCC may have less antioxidant activity. Similar types of observations were

made by Sudhakar *et al.* for random aliphatic copolythioesters [53,54], Yamini *et al.* for aliphatic copolyesters [55], Narendran *et al.* for biscoumarin-based random copolyesters [56] and Kothai *et al.* for aliphatic-aromatic copolyesters [57].

Table 2. Inhibition effects of the copolyester PGCB for antioxidant activity.

Concentration	600 µg	700 µg	800 µg	900 µg	1000 µg
PGCC % Inhibition	38.8	40.2	41.6	43.0	43.0

Table 3. Inhibition effects of the copolyester PGCB for antioxidant activity.

Concentration	10 µg	20 µg	40 µg	60 µg	80 µg
PGCB % Inhibition	40.2	44.4	48.6	52.7	56.9

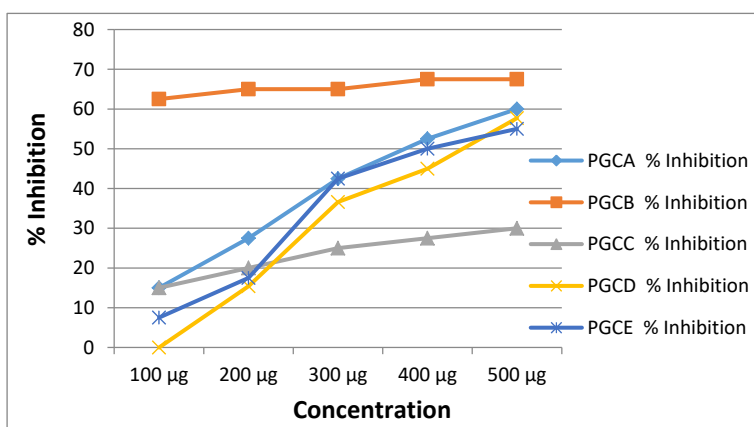


Fig. 5. Inhibition % and scavenging activity of polymers by DPPH method.

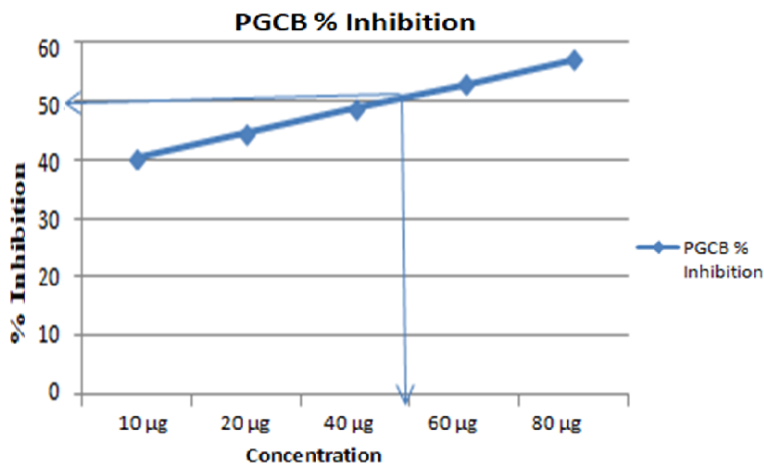


Fig. 6. Inhibition % and scavenging activity of the polymer PGCB.

3.3. Nitric oxide scavenging activity

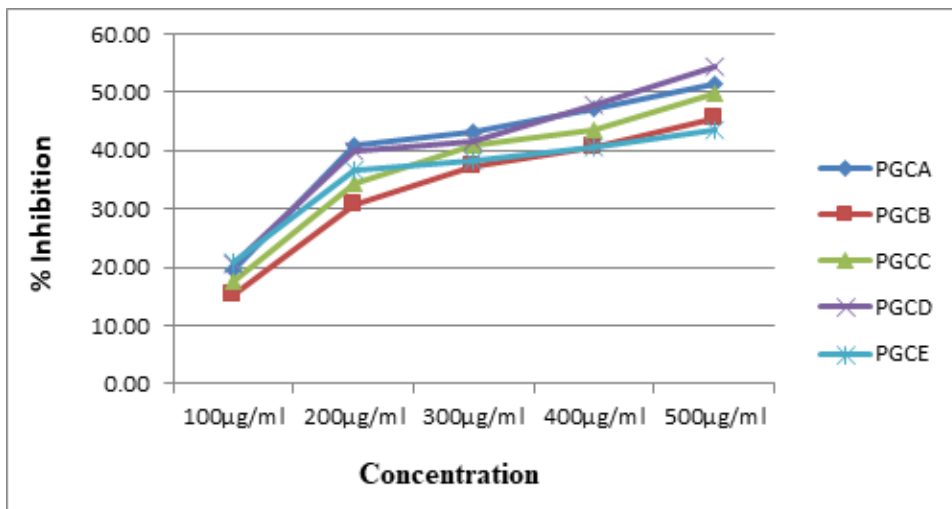


Fig. 7. Inhibition % and scavenging activity of polymers by nitric oxide scavenging assay.

3.4. Ferric ion reducing/antioxidant power assay

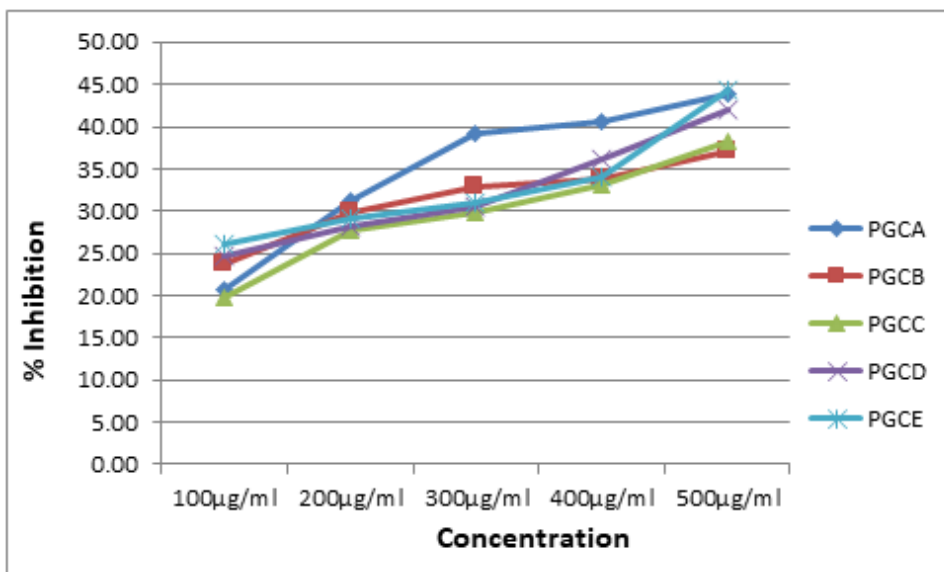


Fig. 8. Inhibition % and scavenging activity of polymers by ferric ion reducing antioxidant power scavenging assay.

3.5. ABTS scavenging activity

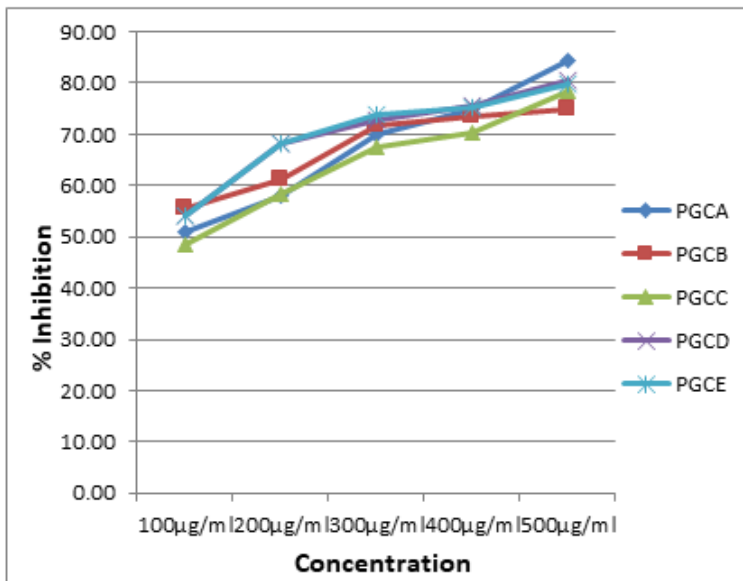


Fig. 9. Inhibition % and scavenging activity of polymers by ABTS method.

3.6. Superoxide radical scavenging activity

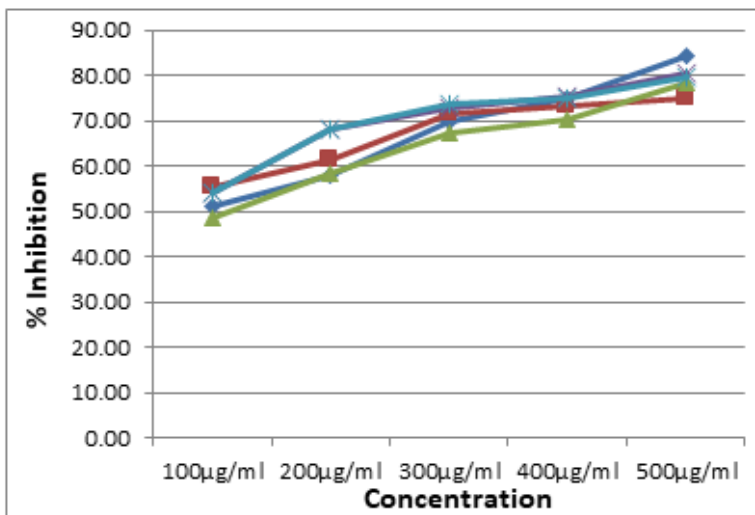


Fig. 10. Inhibition % and scavenging activity of polymers by superoxide dismutase method.

Figs. 7-10 represent the plot of inhibition % and scavenging activity of polymers by FRAP, ABTS, and superoxide dismutase method, respectively. Nitric oxide Scavenging method. Almost all methods show IC_{50} values within the concentration range of 100

$\mu\text{g/mL}$ and $500 \mu\text{g/mL}$ except the FRAP method. In the SOD method, all polymers have IC_{50} values within 100 and $500 \mu\text{g/mL}$ concentration range. So it may be considered as the best method for antioxidant assay of copolyester.

3.7. Chemical structure optimization

The optimized geometry of the molecule is given in Fig. 11. From the Fig, it was clear that the entire molecule is planar. The entire molecule was delocalized. The bond parameters of the molecule are given in Table 4. It was understood from the Table that the C-C bond lengths are in the range of 1.46-1.35 Å. This means that all the C-C bonds have a partial double bond character. Also, the bond distance of O28-H29...O31 is 1.60 Å, which suggests a hydrogen bond interaction. The dihedral angle of C-C-C-C is $\sim 179^\circ$ which reiterates that the structure of the molecule was planar.

3.7.1. FMO analysis

HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) of the molecule are given in Fig. 12. It can be seen that the HOMO and LUMO of the molecule were delocalized on the complete molecule. The HOMO-LUMO energy gap is depicted in Fig. 13. The HOMO-LUMO gap in the molecule was 3.34 eV.

3.7.2. Antioxidant capacity

3.7.2.1. Hydrogen atom transfer mechanism

This mechanism involves the reaction of natural radical species with phenolic antioxidants and thus yields the radical form of antioxidant. The bond dissociation enthalpy (BDE) was considered in this mechanism. The low amount of bond dissociation energy illustrated better antioxidant activity. It can be represented using the following reaction:

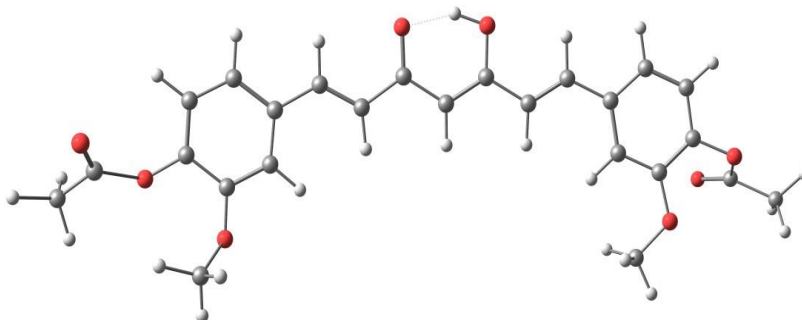


Fig. 11. Optimized geometry of the molecule.

BDE, as a parameter for the hydrogen atom transfer mechanism, defines the stability of the hydroxyl group. Low values of the BDE show the low stability of the O–H bond and high antioxidant capacity. The calculated BDE value of the molecule was 102.72 kcal/mol. This value showed that the molecule possesses antioxidant properties.

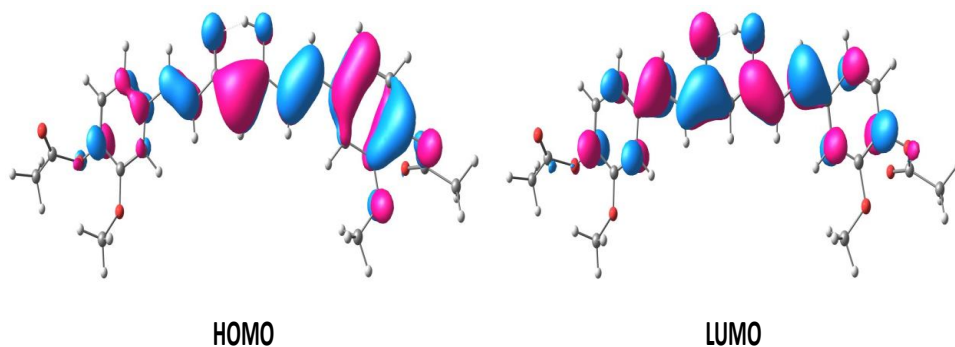


Fig. 12. Frontier molecular orbitals of the molecule.

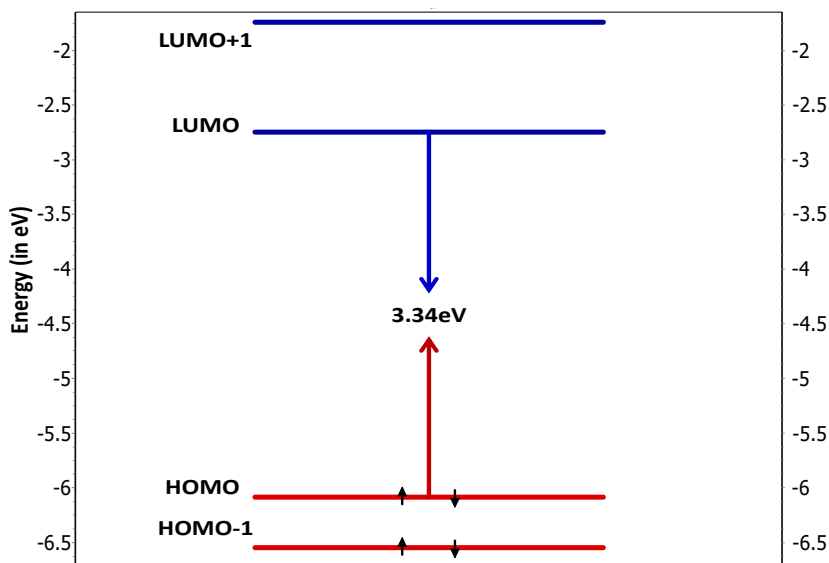


Fig. 13. HOMO-LUMO energy gap of the molecule.

Table 4. Bond parameters of the molecule.

Bond Angle (in °)	Bond length (in Å)	Dihedral Angle (in °)	Bond length (in Å)
C35-C34	1.46	C36-C34-C32-C30	179.72
C34-C32	1.35	C34-C32-C30-C26	179.69
C32-C30	1.47	C32-C30-C26-C25	179.85
C30-C26	1.44	C30-C26-C25-C23	179.89
C26-C25	1.38	C26-C25-C23-C21	179.44
C25-C23	1.45	C25-C23-C21-C57	179.76
C23-C21	1.35		
C21-C57	1.46		
O31-H29	1.60		
O28-H29	1.01		

4. Conclusion

Five copolyesters are synthesized with good yields using a common diol-I (Curcumin), a diol-II (synthesized arylidene diols), and a diacid chloride (Glutaryl chloride). These five random copolyesters are found to be highly soluble in polar solvents like DMSO and insoluble in non-polar solvents like hexane and benzene, and their viscosity measurements ranged between 0.24 and 1.36 dL/g. These copolyesters are characterized by FT-IR and NMR spectral data. In the theoretical method, the antioxidant property of the molecule can be described using a hydrogen atom transfer mechanism. The radical is formed at the O28 atom since the bond is the weakest, and the H29 atom can undergo simple dissociation in comparison with other O-H bonds. So, the hydrogen atom in the enolic form of curcumin contributes to the antioxidant activity shown by computational studies. The antioxidant activity of curcumin shown by computational studies was found to have a good coincidence with the experimental methods. The curcumin-based copolyesters have shown excellent antioxidant activity by DPPH, nitric oxide scavenging, ferric ion reducing / antioxidant power assay, ABTS, and superoxide dismutase methods, out of which the SOD method shows greater antioxidant activity even at lower concentrations when compared to other remaining methods. Hence, the synthesized copolyesters in the present work can be used in pharmaceutical applications.

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