

1-1-2009

Synthesis and in vitro anti-*Helicobacter pylori* activity of 2-(substituted benzylthio)-5-(5-nitro-2-furyl)-1,3,4-thiadiazole derivatives

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ISFAHANI, HOSSEIN NASR; FAGHIHI, KHALIL; IZADKHAH, ATENA; and SHABANIAN, MEISAM (2009) "Synthesis and in vitro anti-*Helicobacter pylori* activity of 2-(substituted benzylthio)-5-(5-nitro-2-furyl)-1,3,4-thiadiazole derivatives," *Turkish Journal of Chemistry*. Vol. 33: No. 4, Article 3. <https://doi.org/10.3906/kim-0811-34>

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Synthesis and characterization of new optically active and heat resistant poly(amide-imide)s derived from N,N'-(bicyclo[2,2,2]oct-7-ene-2,3,5,6-tetracarboxylic)-bis-L-leucine and aromatic diamines

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Received 24.11.2008

A series of new optically active and thermally stable poly(amide-imide)s (**6a-e**) were synthesized by direct polycondensation reaction of N,N'-(bicyclo[2,2,2]oct-7-ene-2,3,5,6-tetracarboxylic)-bis-L-leucine (**4**) with various aromatic diamines using polar aprotic solvents such as N-methyl-2-pyrrolidone (NMP). In this technique triphenylphosphite (TPP) and pyridine were used as condensing agents to form poly(amide-imide) through the N-phosphonium salts of pyridine. The resulting new polymers (**6a-e**) were obtained in high yields, with inherent viscosities between 0.21 and 0.32 dL/g, and were characterized by ¹H-NMR, FTIR spectroscopy, elemental analysis, specific rotation, gel permeation chromatography (GPC), and thermogravimetric analysis (TGA and DTG). The solubility of these polymers was good in polar aprotic solvents such as N,N-dimethyl acetamide (DMAc), N,N-dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), NMP (N-methyl-2-pyrrolidone), and solvents such as sulfuric acid. The diimide-diacide **4** was prepared by condensing reaction of bicyclo[2,2,2]oct-7-ene-2,3,5,6-tetracarboxylic dianhydride **1** with L-leucine **2** in the acetic acid solution.

Key Words: Poly(amide-imide)s, Direct polycondensation, Optically active polymer, L-leucine, Thermally stable.

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Introduction

The development of heat-resistant, high-performance polymers in the past decades has been quite dramatic and has drawn the attention of many polymer scientists all over the world. Wholly aromatic polymers such as polyimides and polyamides have already been noted for their high temperature resistance and excellent physico-mechanical properties. However, they are difficult to process due to their insolubility in organic solvents and infusibility.^{1–8} Considerable efforts have been made to improve their processing properties by structural modifications. One of these methods is the preparation of copolymers such as poly(amide-imide)s, which are high performance materials with good compromise between thermal stability and processability when compared to polyamides or polyimides of analogous structure.^{9–19}

Moreover, the synthesis and application of optically active polymers are topics currently attracting much attention. This may arise mainly from their chiral structure, which is common to naturally occurring polymers. In the history of synthetic polymer chemistry, it seems that one of the most challenging tasks is to construct functional polymeric systems and optically active synthetic polymers that are as effective as those in living systems.^{20–28} One of the most practical and widely accepted applications of chiral polymers is their use as the chiral stationary phase (CSP) for the separation of racemic mixtures by high-performance liquid chromatography (HPLC).^{29,30}

In this article, we describe the synthesis and characterization of a series of novel poly(amide-imide)s (**6a-e**) containing rigid segments bicyclo[2,2,2]oct-7-ene-2,3,5,6-tetracarboxylic diimide in the main chain by direct polycondensation reaction of N,N'-(bicyclo[2,2,2]oct-7-ene-2,3,5,6-tetracarboxylic)-bis-L-leucine (**4**) with 5 aromatic diamines, namely 4,4'-diaminodiphenylether (**5a**), 4,4'-diaminodiphenyl sulfone (**5b**), 3,3'-diaminodiphenyl sulfone (**5c**), 1,4-phenylenediamine (**5d**), and 1,5-diamino naphthalene (**5e**), in a medium consisting of N-methyl-2-pyrrolidone, triphenyl phosphite, calcium chloride, and pyridine. The results showed that these new polymers with amide-imide groups and bicyclo segments in the main chain have better solubility in organic solvents compared to aromatic polyamides.

Experimental

Materials

Bicyclo[2,2,2]oct-7-ene-2,3,5,6-tetracarboxylic dianhydride (**1**), L-leucine (**2**), 4,4'-diamino diphenyl ether (**5a**), 4,4'-diamino diphenyl sulfone (**5b**), 3,3'-diamino diphenyl sulfone (**5c**), 1,4-phenylene diamine (**5d**), 1,5-naphthalene diamine (**5e**), triphenyl phosphite, N-methyl-2-pyrrolidone, and pyridine were purchased from Merck Chemical Company and used without previous purification. Commercially available calcium chloride was purchased from Merck Chemical Company and was dried under vacuum at 150 °C for 6 h.

Techniques

¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker 300 MHz instrument (Germany). Fourier transform infrared (FTIR) spectra were recorded on a Galaxy series FTIR 5000 spectrophotometer (England) as solid by using KBr pellets. Vibration transition frequencies were reported in wave number (cm⁻¹). Band intensities

were assigned as weak (w), medium (m), shoulder (sh), strong (s), and broad (br). Inherent viscosities were measured by a standard procedure using a Technico[®] Viscometer. Specific rotations were measured by an A-Kruss polarimeter. Weight-average (M_w) and number-average molecular weights (M_n) were determined by gel permeation chromatography (GPC). The eluents were monitored with a UV detector (JMST Systems, USA, VUV-24) at 254 nm. Polystyrene was used as the standard. Thermal gravimetric analysis (TGA and DTG) data of these polymers were obtained on a Mettler TA4000 System under N₂ atmosphere at rate of 10 °C/min. Elemental analyses were performed with Vario EL equipment in Arak University.

Monomer synthesis

N,N'-(bicyclo[2,2,2]oct-7-ene-2,3,5,6-tetracarboxylic)-bis-L-leucine (**4**) was prepared according to a typical procedure as shown in Scheme 1. Into a 250 mL round-bottomed flask were placed 2.48 g (10.0 mmol) of bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic dianhydride (**1**), 2.62 g (20.0 mmol) of L-leucine (**2**), and 100 mL of concentrated acetic acid. The mixture was stirred at room temperature for 8 h and then refluxed for 5 h. The solvent was removed under reduced pressure and 5 mL of cold concentrated HCl was added to the residue until a white precipitate formed. The precipitate was washed with cold water and dried under reduced pressure to give 4.13 g (87%) of compound **4**. Mp = 309-310 °C, $[\alpha]_D^{25} = 60^\circ$ (0.05 g in 10 mL of DMF).

FT-IR (KBr): 2500-3400 (m, br), 1776 (w), 1707 (s), 1388 (m), 1309 (w), 1195 (m), 1066 (w), 788 (w), 736(w), 671 (w) cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆, δ , ppm): 12.91 (s, br, 2H), 5.93-6.01 (m, 2H), 4.44-4.49 (m, 2H), 3.21-3.30 (m, 6H), 1.85-1.86(d, 2H), 1.65 (s, 2H), 1.25 (s, 2H), 0.75-0.81 (m, 12H). ¹³C-NMR (DMSO-d₆, δ ppm): 177.09, 170.47, 130.97, 50.72, 42.51, 36.60, 33.79, 24.59, 23.47, 21.17. Elemental analysis: calcd for C₂₄H₃₀N₂O₈: C, 60.75%; H, 6.37%; N, 5.90%; found: C, 60.72%; H, 6.30%; N, 5.80%.

Polymer synthesis

As a typical example, PAI **6b** was prepared as follows: into a 50 mL round-bottom flask with a stirring bar were placed 0.309 g (0.652 mmol) of diacid **4**, 0.130 g (0.652 mmol) of 4,4'-diamino diphenyl sulfone (**5b**), 0.10 g of calcium chloride, 1.0 mL of NMP, 0.8 mL of triphenyl phosphite, and 0.3 mL of pyridine. The mixture was stirred at room temperature for 2 h and then was heated while stirring at 120-130 °C for 8 h. At the end of the reaction for quenching growth of polymer chain the polymer solution was slowly trickled into stirred methanol, giving a stringy precipitate. The precipitate was washed thoroughly with hot methanol, collected by filtration, and dried at 80 °C for 12 h under vacuum to leave 0.395 g (95%) of solid polymer **6b**.

The elemental analysis of resulting PAIs **6a-e**:

6a calcd for C₃₆H₃₈N₄O₇: C, 67.6%; H, 5.9%; N, 8.7%; found: C, 67.0%; H, 6.2%; N, 8.0%.

6b calcd for C₃₆H₃₈N₄O₈S: C, 62.9%; H, 5.5%; N, 8.1%; found: C, 61.9%; H, 5.2%; N, 8.0%.

6c calcd for C₃₆H₃₈N₄O₈S: C, 62.9%; H, 5.5%; N, 8.1%; found: C, 62.0%; H, 5.2%; N, 7.9%.

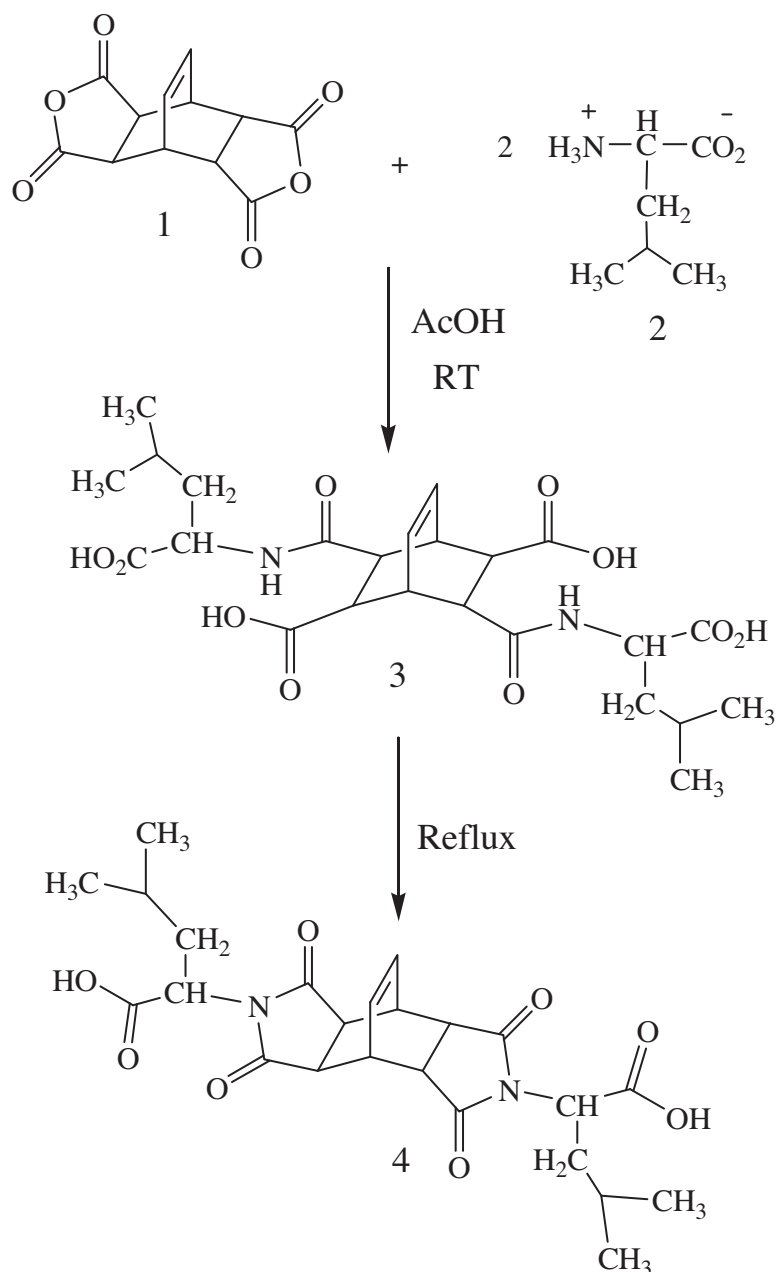
6d calcd for C₃₀H₃₄N₄O₆: C, 65.9%; H, 6.2%; N, 10.2%; found: C, 65.1%; H, 6.0%; N, 10.0%.

6e calcd for C₃₄H₃₆N₄O₆: C, 68.4%; H, 6.0%; N, 9.3%; found: C, 67.9%; H, 5.8%; N, 9.0%.

Results and Discussion

Monomer synthesis

The asymmetric diacid **4** was synthesized by the condensation reaction of 1 equimolar of bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic dianhydride **1** with 2 equimolars of L- leucine **2** in an acetic acid solution (Scheme 1).



Scheme 1

The chemical structure and purity of diimide-diacid **4** were proved by using elemental analysis, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, and FTIR spectroscopy. The measured results in elemental analyses closely corresponded to the calculated ones, demonstrating that the expected compound was obtained. Figure 1 displays the FTIR spectrum of diimide-diacid **4**. Peaks appearing at $2500\text{--}3400\text{ cm}^{-1}$ (acid O-H stretching), 1776 cm^{-1} (C=O asymmetric imide stretching), 1707 cm^{-1} (C=O acid and symmetric imide stretching), 1388 cm^{-1} , and 736 cm^{-1} (imide characteristic ring vibration) confirmed the presence of an imide ring and carboxylic groups in this compound.

The $^1\text{H-NMR}$ spectrum of diacid **4** is shown in Figure 2. The peak relevant to O-H carboxylic acid groups appeared at 12.91 ppm. The peak in 4.44–4.49 ppm as a quarter was assigned to the CH(c) protons as a chiral center, peaks between 0.75 and 0.91 ppm were assigned to aliphatic CH_3 (h), and olefin protons H(b) in the bicyclo ring appeared at 5.93–6.01 ppm.

The $^{13}\text{C-NMR}$ spectrum of diacid **4** showed 9 signals, including C(a) and C(b) in carboxylic acid and imide rings, with C(c) related to carbon atoms of olefin and C(d) relevant to chiral carbon atoms (Figure 3).

Polymer synthesis

PAIs **6a-e** were synthesized by direct polycondensation reaction of diacid **4** with 5 different derivatives of aromatic diamines **5a-e** as shown in Scheme 2.

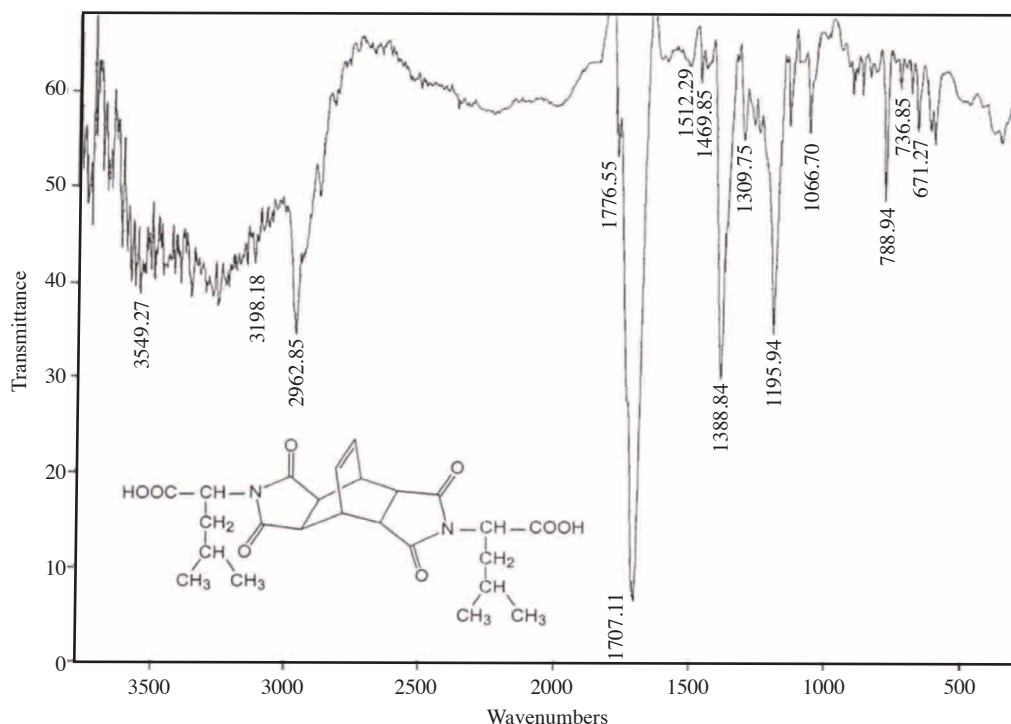


Figure 1. FTIR spectrum of diimide-diacid **4**.

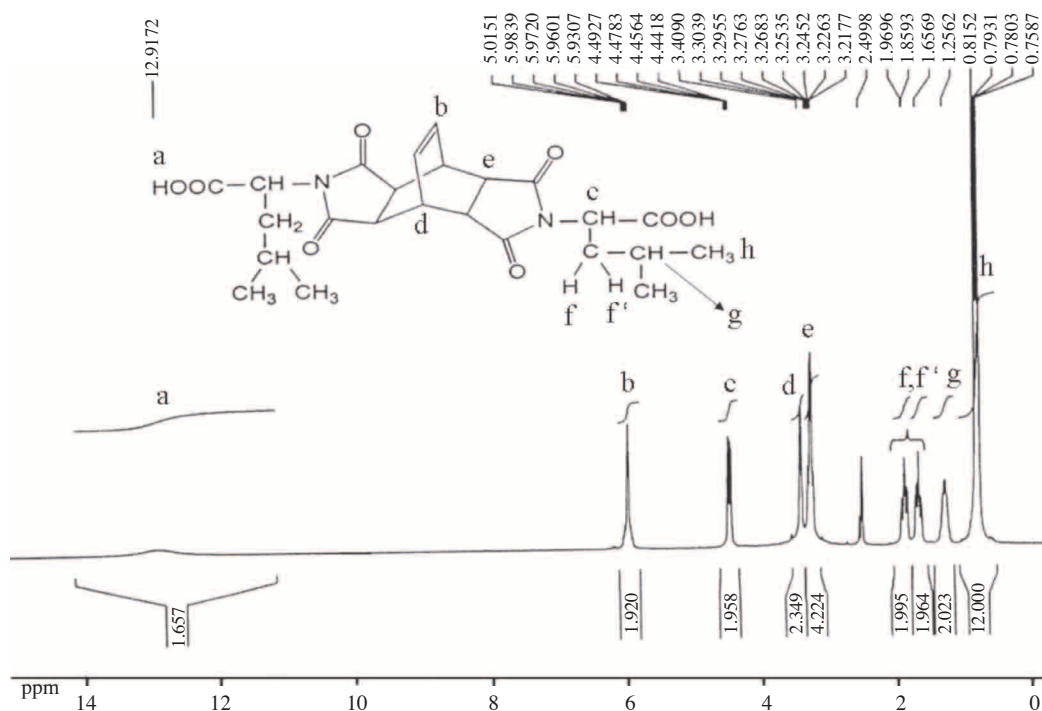


Figure 2. $^1\text{H-NMR}$ spectrum of diimide-diacid **4**.

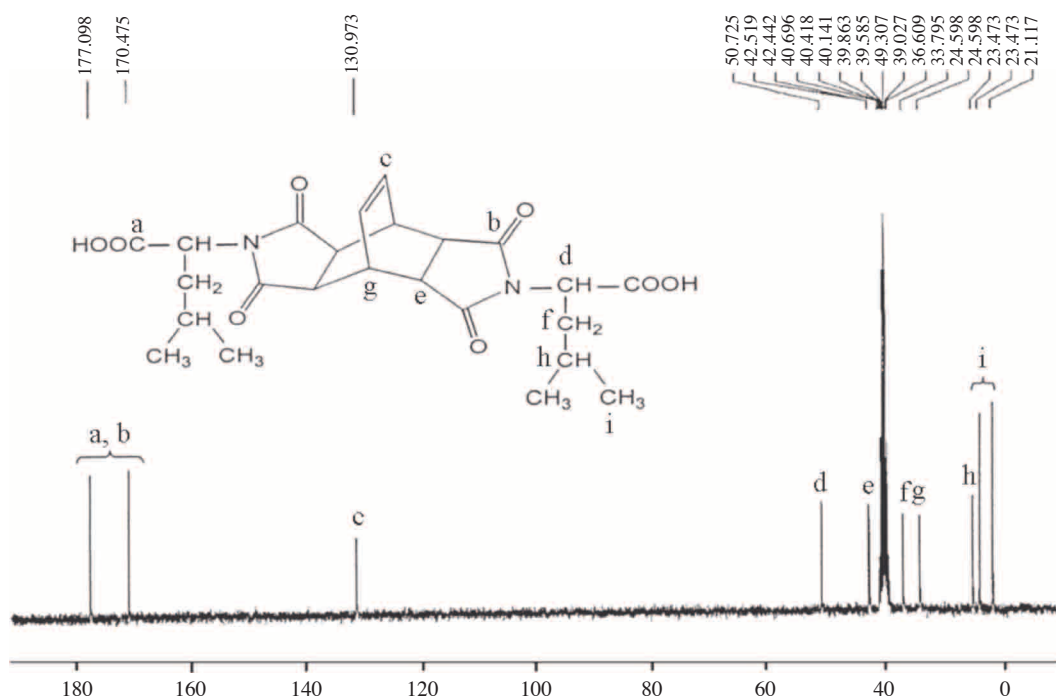
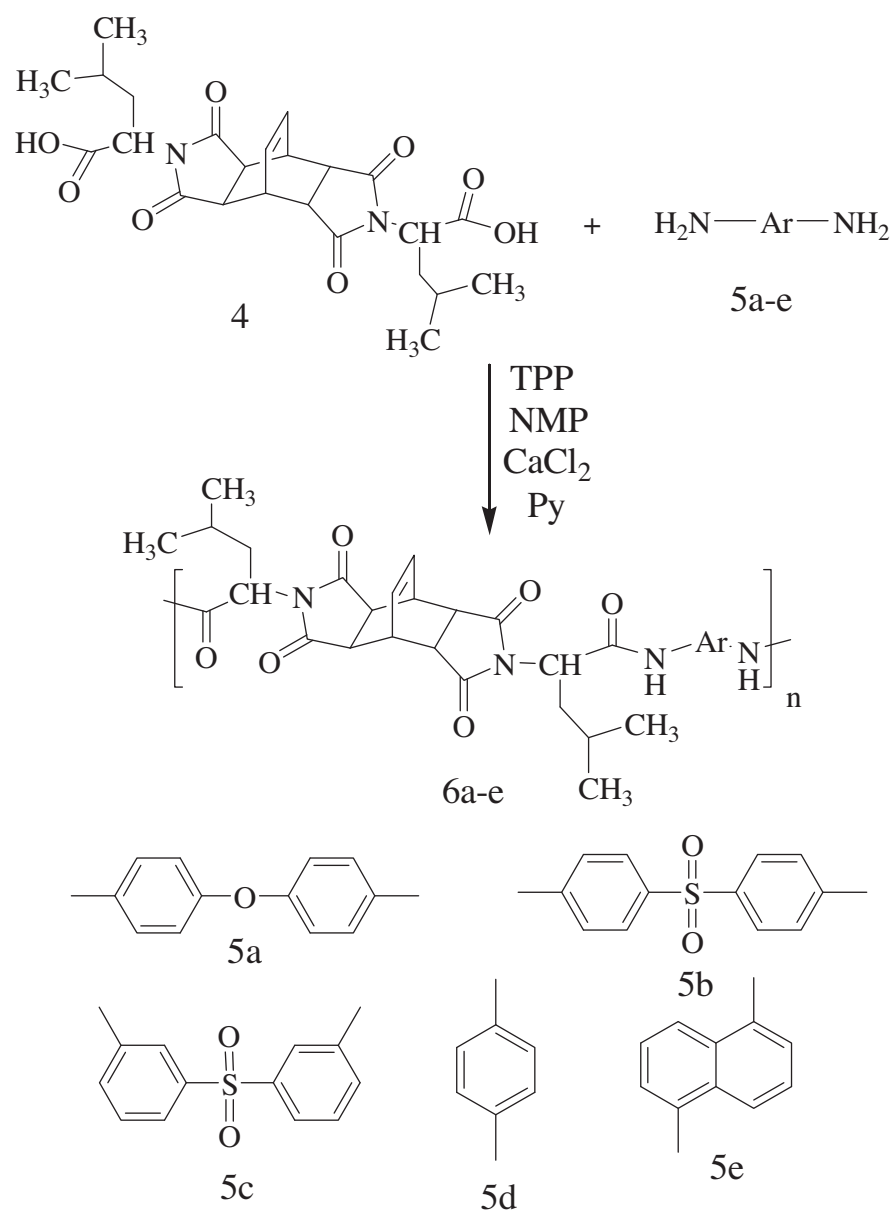


Figure 3. $^{13}\text{C-NMR}$ spectrum of diimide-diacid **4**.



Scheme 2

Synthesis and some physical properties of PAIs **6a-e** are summarized in Table 1. These polymers have inherent viscosities in the range of 0.21-0.32 dL/g and all of the resulting polymers show optical rotation and are optically active.

Polymer characterization

The structures of these polymers were confirmed as PAIs by means of FTIR spectroscopy and elemental analyses. FTIR spectroscopies of all PAIs are listed in Table 2.

Table 1. Synthesis and some physical properties of PAIs **6a-e**.

Diamine	Polymer	Yield (%)	η_{inh} (dL/g) ^a	$[\alpha]_D^{25}$ ^a	Color	$\overline{M}_n(10^4)^b$	$\overline{M}_w(10^4)^b$	PDI
5a	6a	96	0.24	+80.0	White	2.0	4.9	2.45
5b	6b	95	0.32	+100.0	Cream	1.8	5.4	3.00
5c	6c	96	0.28	+80.0	White	1.7	3.9	2.29
5d	6d	84	0.28	+100.0	White	2.1	5.8	2.76
5e	6e	98	0.21	+120.0	Cream	2.2	4.9	2.22

^a Measured at a concentration of 0.5 g/dL in DMF at 25 °C. ^b Measured by GPC in DMF, polystyrene was used as standard.

Table 2. FTIR Characterization of PAIs **6a-e**.

Polymer	Spectra data
6a	FT-IR Peaks (cm⁻¹): 3202 (w), 2957 (m), 1776 (w), 1710 (s, br), 1604 (w), 1500 (s, sh), 1386 (m), 1305 (m), 1222 (m, sh), 1068 (m), 833 (w), 787 (w), 516 (w) cm ⁻¹ .
6b	FT-IR Peaks (cm⁻¹): 3254 (w), 2962 (w), 1774 (w), 1710 (s), 1664 (m, sh), 1591 (m), 1531 (m), 1479 (m), 1386 (m), 1305 (m), 1255 (w), 1188 (w), 1151 (m), 1107 (m), 839 (w), 790 (w), 721 (w), 690 cm ⁻¹ .
6c	FT-IR Peaks (cm⁻¹): 3294 (w), 2876 (w), 1776 (w), 1709 (s, br), 1595 (m), 1535 (m), 1479 (m), 1384 (m), 1302 (m), 1244 (m), 1159 (m), 1149 (m), 995 (w), 784 (w), 746 (w) cm ⁻¹ .
6d	FT-IR Peaks (cm⁻¹): 3344 (w), 2960 (m), 2872 (w), 1774 (w), 1707 (s, br), 1610 (w), 1516 (s), 1386 (m), 1307 (w), 1236 (w), 1192 (m), 853 (w), 790 (w) cm ⁻¹ .
6e	FT-IR Peaks (cm⁻¹): 3236 (w), 2958 (m), 1774 (w), 1709 (s, br), 1610 (w), 1535 (m), 1493 (m), 1386 (m), 1192 (m), 1138 (w), 912 (w), 787 (w), 603 (w) cm ⁻¹ .

The representative FTIR spectrum of PAI **6d** is shown in Figure 4. The polymer exhibited characteristic absorption bands at 1707-1774 cm⁻¹ for the imide ring (asymmetric and symmetric C=O stretching vibration) and 1386 cm⁻¹ (C-N stretching vibration). The absorption bands of amide groups appeared at 3344 cm⁻¹ (N-H stretching).

The ¹H-NMR spectra of polymers **6c** showed some peaks that confirm the chemical structure (Figure 5) of this polymer. The aromatic protons related to diphenyl sulfone appeared in the region of 7.55-7.84 ppm and the peak in the region of 10.23-10.26 ppm was assigned to NH of amide groups in the polymer backbone.

These polymers exhibited number-average molecular weights (M_n) and weight-average molecular weights (M_w) in the range of 1.7-2.2 × 10⁴ and 3.9-5.8 × 10⁴ g/mol respectively, as measured by GPC, relative to polystyrene standards.

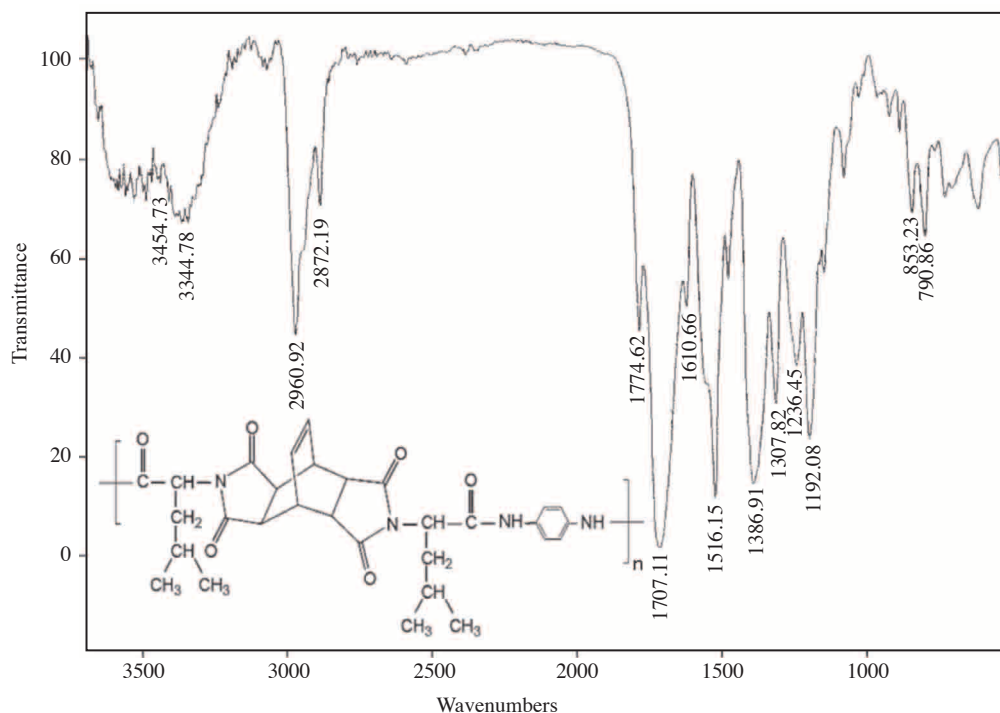


Figure 4. FTIR spectrum of PAI **6d**.

The elemental analyses of the resulting PAIs **6a-e** were in good agreement with the calculated values for the proposed structure.

The solubility of PAIs **6a-e** was investigated by 0.01 g of polymeric sample in 2.0 mL of solvent. All of the polymers are soluble in organic solvents such as N,N-dimethyl acetamide (DMAc), N,N-dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), NMP (N-methyl-2-pyrrolidone), and sulfuric acid, and are insoluble in solvents such as chloroform, methylene chloride, methanol, ethanol, and water (Table 3).

Table 3. Solubility of PAIs **6a-e**

Solvent	6a	6b	6c	6d	6e
H ₂ SO ₄	+	+	+	+	+
DMAc	+	+	+	+	+
DMSO	+	+	+	+	+
DMF	+	+	+	+	+
NMP	+	+	+	+	+
MeOH	-	-	-	-	-
EtOH	-	-	-	-	-
CHCl ₃	-	-	-	-	-
CH ₂ Cl ₂	-	-	-	-	-
H ₂ O	-	-	-	-	-

+, Soluble at room temperature, -, Insoluble at room temperature

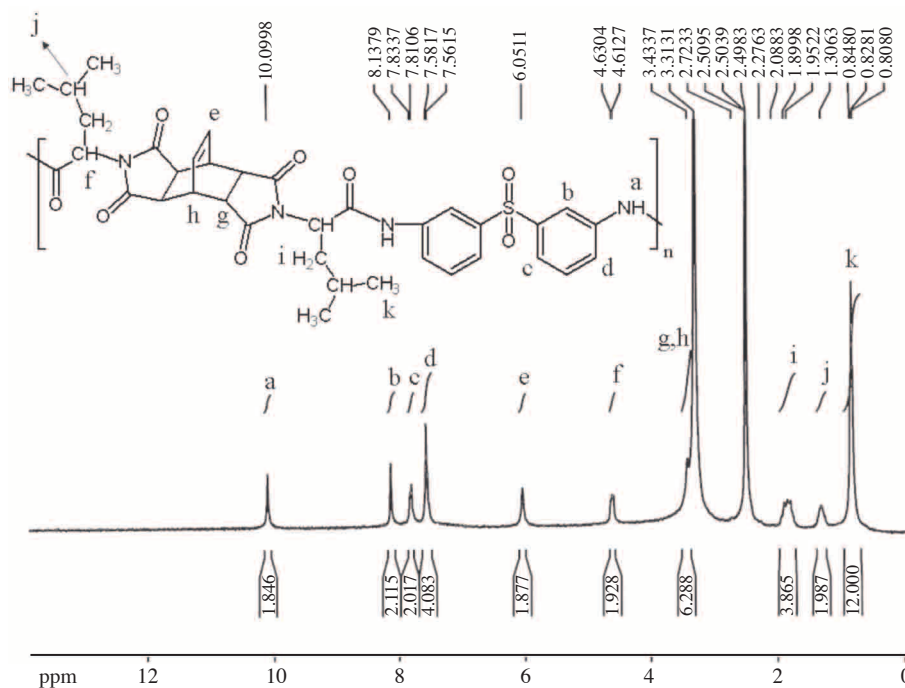


Figure 5. $^1\text{H-NMR}$ spectrum of PAI **6c**.

Thermal properties

The thermal properties of PAIs **6a** and **6b** were investigated by TGA and DTG in a nitrogen atmosphere at a heating rate of $10\text{ }^\circ\text{C}/\text{min}$ as 2 models for the prepared poly(amide-imide)s (**6a-e**) and the thermal data are summarized in Table 5 (Figure 6). The initial decomposition temperatures of 5% and 10% weight losses (T_5 and T_{10}) and the char yield at $600\text{ }^\circ\text{C}$ are summarized in Table 5. These polymers exhibited good resistance to thermal decomposition up to 305 to $385\text{ }^\circ\text{C}$ in nitrogen, and began to decompose gradually above those temperatures. T_5 for these polymers from 305 to $385\text{ }^\circ\text{C}$ and T_{10} for these polymers ranged from 335 to $400\text{ }^\circ\text{C}$, and the residual weights at $600\text{ }^\circ\text{C}$ were 22.09% and 40.32% in nitrogen.

Table 4. Thermal behavior of PAIs **6a** and **6b**.

Polymer	$T_5(^\circ\text{C})^a$	$T_{10}(^\circ\text{C})^b$	Char yield (%) ^c
6a	305-310	335-370	22.09
6b	385-390	400-405	40.32

^{a,b} Temperature at which 5% or 10% weight loss was recorded TGA at a heating rate of $10\text{ }^\circ\text{C}/\text{min}$ in N_2 . ^c weight percentage of material left after TGA analysis at maximum temperature at $600\text{ }^\circ\text{C}$ in nitrogen.

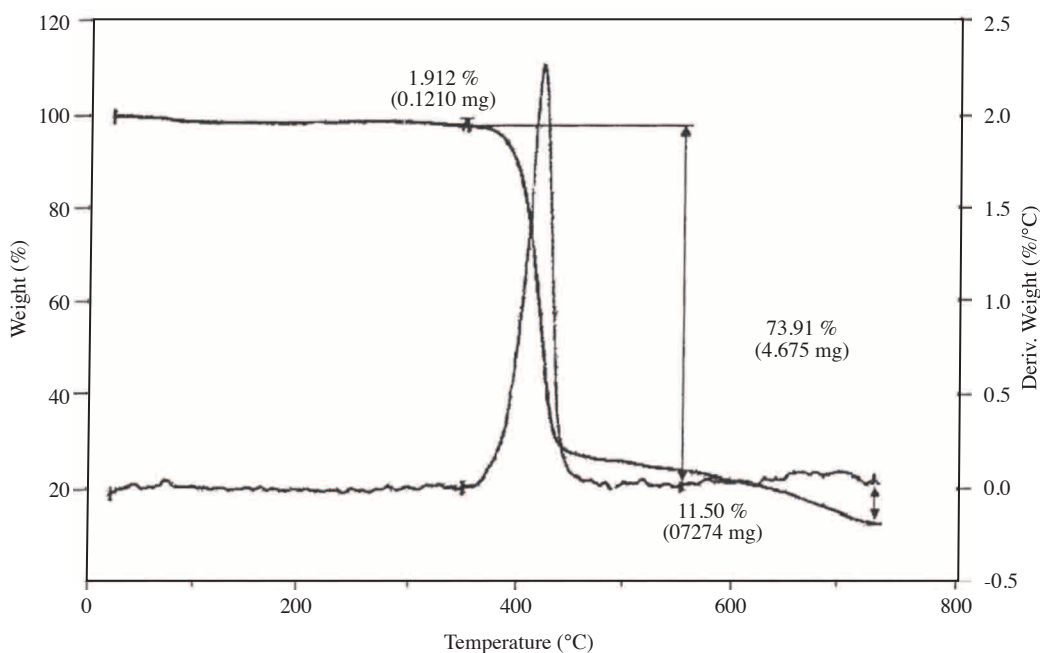


Figure 6. TGA and DTG thermogram of PAIs **6b**.

Conclusions

The present work has shown that N,N-(bicyclo[2,2,2]oct-7-ene-2,3,5,6-tetracarboxylic)bis-L-leucine (**4**) is an interesting monomer that contains both imide groups as well as a chiral L-leucine groups. This compound was used to synthesize a series of new optically active PAIs (**6a-e**) by polycondensation reaction with 5 aromatic diamines (**5a-e**). These PAIs are optically active and soluble in various organic solvents and have good thermal stability. These resulting novel polymers have the potential to be used in column chromatography technique for the separation of enantiomeric mixtures.

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