

Synthesis and characterization of a novel versatile poly(amic acid) derived from ethylenediaminetetraacetic dianhydride

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ABSTRACT

The polycondensation reaction between ethylenediaminetetraacetic dianhydride and 1,4-diaminobutane in various aprotic polar solvents is being exploited to create a novel linear aliphatic polymer poly(amic acid) (PAA). PAA samples were characterized by Fourier transform infrared, Proton nuclear magnetic resonance and Carbon nuclear magnetic resonance spectroscopy resulting in the identification of characteristic absorption bands and thereby verifying successful synthesis. Gel permeation chromatography confirmed narrow molecular weight distributions with polydispersity indices ranging from 1.2 to 2.2 and reported low number average molecular weights ranging from 4000 to 6000 g mol⁻¹. X-ray photoelectron spectroscopy and energy dispersive X-ray analysis showed the presence of nitrogen on the surface and also found nitrogen to be homogeneously distributed throughout the bulk of the PAA samples.

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1. Introduction

Poly(amic acids) (PAAs) are a class of polymers that are generally formed through a polycondensation reaction between a dianhydride and a diamine [1]. Possessing amides and carboxylic acid groups in the polymer backbone, PAAs have many interesting potential materials applications. However, they are often overlooked and are recognized as intermediate polymers towards the formation of polyimides. In contrast to polyimides, particularly the aromatic polyimides, PAAs are soluble in a range of dipolar aprotic solvents and can easily be processed. In addition, PAAs have the option to form polyimides through a condensation reaction. Over the years, numerous applications of polyimides have been reported [2–6]. Problems of poor solubility and tractability [7,8], often associated with polyimides, have limited their use as potential medical materials. Compared to polyimides, little work has been reported on PAAs as a potentially useful class of materials. There are a few reports describing PAAs application as an interphase in high performance thermoplastic composites [9] and its use for liquid crystal orientation [10]. However, the majority of emphasis in recent years has been placed on PAAs usefulness as a precursor for heat-resistant thin nonplanar polyimide moldings [11] with high refractive index [12] or as a photosensitive polyimide precursor

[13]. We are especially interested in PAA's potential as a material for biomedical applications. Carefully tailored, PAAs may prove to be worthy materials on their own, thereby providing a wide range of material properties. PAAs reported in the literature are mainly composed of aromatic dianhydrides and aromatic diamines [14]. Representative aromatic dianhydrides have included 1,2,4,5-benzene tetracarboxylic dianhydride, 3,3',4,4'-biphenyl tetracarboxylic dianhydride, 3,3',4,4'-benzophenone tetracarboxylic dianhydride, 2,3,6,7-naphthalene tetracarboxylic dianhydride etc. and examples of aromatic diamines have included paraphenylenediamine, 4,4'-diaminodiphenylether, 4,4'-diaminodiphenylmethane, etc. We chose to focus on the use of an aliphatic dianhydride and an aliphatic diamine as monomers in PAA synthesis as an alternative to traditional monomers used in PAA synthesis. To date, there have been few reports on this type of PAA and its consideration for materials applications.

In our work on the synthesis and characterization of aliphatic poly(amic acid), the monomers of choice are ethylenediaminetetraacetic dianhydride (EDTAD) and 1,4-diaminobutane (DAB) commonly known as putrescine. EDTAD is biodegradable, often recognized as a chelator and is well known to complex with metal ions [15]. Furthermore, EDTAD has been reported to exhibit very little toxicity since the only reactive group introduced into the polymer backbone is a carboxyl group [16]. Recently, EDTAD has been used in the modification of various hydrogels for drug delivery applications [17]. Similarly, DAB, one of the simplest polyamines found in millimolar concentrations in mammals is produced by the breakdown of amino acids (decarboxylation of ornithine by the enzyme ornithine decarboxylase or decarboxylation of arginine by

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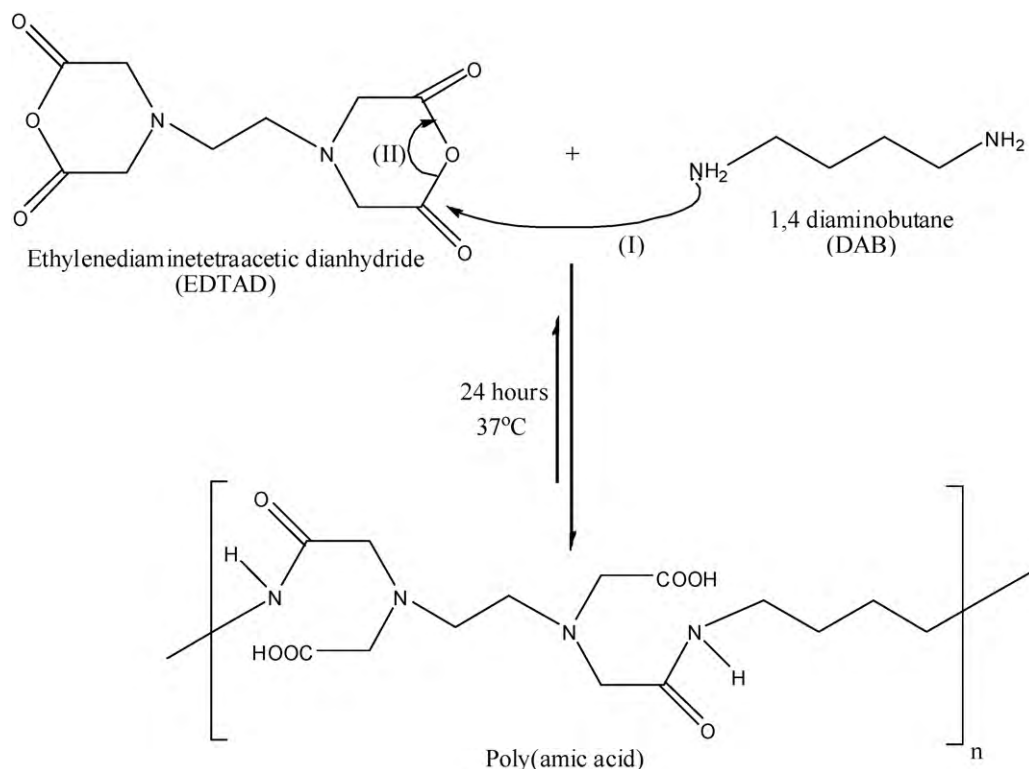


Fig. 1. Synthesis of poly(amic acid); (I) Nucleophilic amine from the DAB attacks the carbonyl groups of the EDTAD. (II) Opening of the anhydride ring which forms the amic acid group.

the enzyme L-arginine decarboxylase) in both living and non-living organisms [18,19]. In general polyamines have been investigated for anticancer therapy [20]. Putrescine in particular has been shown to be non-toxic, anti-mutagenic and effective in reducing mutation frequency, suggesting further that it plays a vital role in DNA synthesis [21]. Both EDTAD and DAB are soluble in aqueous solutions and their structures predict minimal toxicity.

The use of synthetic polymers for medical devices is presently a targeted area in materials research. The aim of this study was to synthesize, characterize and investigate the relationships between the molecular structure and physical properties of linear PAA.

2. Experimental

2.1. Materials

High purity monomers [1,4-diaminobutane (DAB) and ethylenediaminetetraacetic dianhydride (EDTAD)] were purchased from Sigma–Aldrich and used as received. Solvents N-methyl-2-pyrrolidone (NMP), N,N dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and N,N-dimethylacetamide (DMAc) were also purchased from Sigma–Aldrich in sealed vials and either used directly after opening or were dried over molecular sieves having a nominal pore diameter of 3 Å and filtered prior to use. Additional solvents, anhydrous methanol, anhydrous acetone and ethyl ether were purchased from VWR International. All materials required for phosphate buffer solution (PBS) [potassium hydrogen phosphate (K₂HPO₄) and potassium dihydrogen phosphate (KH₂PO₄)] were purchased from Fisher Scientific.

2.2. Synthesis of novel poly(amic acid) films

Poly(amic acid) (PAA) polymers comprising of amide and acid end-groups were synthesized through a condensation polymerization reaction using aliphatic monomers in various aprotic solvents (Fig. 1). A 1 mol equivalent of DAB was placed into a 100 mL, three-necked round bottomed flask and dissolved in an aprotic solvent at a temperature varying from 20 to 37 °C. The apparatus consisted of a condenser, heating element, water bath, stirring bar and magnetic stirrer. A solution containing 1 mol equivalent of EDTAD dissolved in an aprotic solvent was then added to the DAB solution. The PAA polymers were synthesized using four different aprotic solvents (DMF, DMAc, DMSO and NMP). The concentration of PAA solution was varied between 8% and 12% by weight. The temperature of the reaction solution was maintained at 25, 30 or 37 °C (depending on trial) and polymerization was conducted

in a nitrogen atmosphere and duplicated for reproducibility. All experiments were conducted at 24 h or until the viscosity of the polymer's solution increased to the point that uniform stirring of the solution could not be achieved. The synthesized PAA solution was stored at 4 °C in the refrigerator until further use.

2.2.1. Washing, casting and drying

Samples were removed from the refrigerator, precipitated by the addition of methanol, filtered over a Buchner funnel and cast into smooth, circular, glass petri dishes having a diameter of 4 cm. Samples were placed into the fumehood overnight to evaporate the remaining solvent, and then placed into the vacuum oven at 30 °C for 24 h. The dried films or powders were removed from the petri dish, washed three times with methanol and placed into the oven for an additional 72 h.

2.3. Characterization

2.3.1. Fourier transform infrared spectroscopy (FTIR)

Infrared measurements were performed with an attenuated total reflectance (ATR) attachment (Pike Technologies Inc., Madison, WI) using a diamond crystal on a Bruker Vector 22 Fourier Transform Infrared (FTIR) spectrometer (Milton, ON). Spectra were recorded with 256 scans, 4 cm⁻¹ resolution and displayed in absorption mode. The spectra were baseline corrected using OPUS-NT 3.1 software.

2.3.2. Nuclear magnetic resonance (NMR)

Proton nuclear magnetic resonance (¹H NMR) and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on an INOVA 600 (Varian 600 MHz). The spectra were obtained by dissolving samples in either deuterated dimethylsulfoxide (DMSO-*d*₆) or deuterium oxide (D₂O) and by using tetramethylsilane (TMS) as the internal standard (TMS = 0 ppm). The relaxation delay and the angle pulse used for both the ¹H NMR and ¹³C NMR spectra were 1 s and 45°. ACD Labs software was used to process NMR data. In the analysis, phasing parameters and baseline points were determined on the first transformed spectrum. Data transformation and peak height measurements were automated and integration was performed manually.

2.3.3. Scanning electron microscopy (SEM) and energy dispersive X-ray (EDX) analysis

SEM and EDX measurements of the PAA films were obtained using the LEO-Zeiss 1540XB FIB/SEM which was equipped with an EDX Si-detector (Oxford Instruments). An accelerating voltage of 8 kV was used. During EDX analysis, much care was taken to limit the electron radiation damage on the surface of the polymer sample.

Table 1

Gel permeation chromatography data on poly(amic acid) at varying temperatures and monomer concentrations.

	M_n (g mol ⁻¹)	M_w (g mol ⁻¹)	PDI	Temp (°C)	M [] (mol L ⁻¹)	Reaction time (h)	Solvent	Monomer addition
PAAa	4483	6124	1.366	37	0.20	24	DMF	EDTAD into DAB
PAAb	4716	6147	1.303	37	0.15	24	DMF	EDTAD into DAB
PAAc	4312	5402	1.253	37	0.10	24	DMF	EDTAD into DAB
PAAd	5417	6503	1.201	25	0.20	24	DMF	EDTAD into DAB
PA Ae	5304	6416	1.210	25	0.15	24	DMF	EDTAD into DAB
PAAf	5310	6410	1.207	25	0.10	24	DMF	EDTAD into DAB
PAA11	2018	4257	2.110	30	0.20	24	DMF	DAB into EDTAD
PAA12	4509	9676	2.150	25	0.20	24	DMF	DAB into EDTAD

M_n : Number average molecular weight, M_w : Weight average molecular weight, PDI: Polydispersity Index = M_w/M_n , Temp: Temperature, M []: Monomer concentration

2.3.4. X-ray photoelectron spectroscopy (XPS)

XPS measurements were acquired on an AXIS ULTRA spectrometer (Kratos Analytical Inc., New York, NY) utilizing a 210 W Al K α monochromatic X-ray source. Samples were tested in hybrid mode (slot) with a 90° take-off angle. The pass energy of the survey scan was 160 eV and the high-resolution scan was 20 eV. Multi-peak fitting and data analysis was performed using CasaXPS software.

2.3.5. Gel permeation chromatography (GPC)

GPC characterization was carried out using an Agilent 1200 Series GPC-Size Exclusion Chromatography (SEC) analysis system equipped with a refractive index, ultraviolet detector and two PL aquagel-OH (300 mm \times 7.5 mm, 8 μ m pore size, mixed bed) columns. A flow rate of 0.8 mL min⁻¹ was set and a 0.1 M phosphate buffer solution was used as the eluent. The GPC-system was calibrated with 10 PEG/PEO standards having molecular weights ranging from 232 to 1,010,000 g mol⁻¹. Data acquisition and GPC data analysis was performed using Agilent ChemStation with integrated GPC-SEC data analysis software.

3. Results and discussion

3.1. Polymer synthesis and solubility

Adapting a procedure reported by Imai on polyamide synthesis [22], a novel linear PAA polymer resulting from a ring-opening polycondensation reaction of a tetracarboxylic dianhydride (EDTAD) with a diamine (DAB) in various dipolar organic solvents (DMF, DMAc, NMP and DMSO) was synthesized (Fig. 1). PAA was formed via an uncatalyzed mechanism by which the nucleophilic amine from the DAB attacked the carbonyl groups of the cyclic anhydride (EDTAD). This was followed by the opening of the anhydride ring which formed the amic acid group. Successful synthesis was not only dependent on the solvent used, but also the reactivity of the monomers which played an important role in PAA synthesis since the reaction rate was primarily governed by the electrophilicity of the carbonyl groups of the dianhydride and the nucleophilicity of the amino nitrogen atom of the diamine. In this reaction, no condensation molecule was eliminated and rather the anticipated by-product (carboxyl leaving group) remained chemically bonded. In addition to maintaining a 1:1 stoichiometric monomer molar ratio, the sequence of monomer addition (EDTAD into DAB solution versus DAB into EDTAD solution) into the system was explored in order to develop the highest PAA molecular weight achievable. Synthesis of PAA was first investigated by the addition of EDTAD into DAB and then by the addition of DAB into EDTAD. The addition of EDTAD into DAB solution over the addition of DAB into EDTAD gave rise to low molecular weight PAA samples having narrow distributions which were reproducible. This was observed by the increase of solution viscosity, verified by GPC and was consistent with other PAA systems [23]. In contrast, the addition of DAB into EDTAD led to a less viscous solution with polymers having broad molecular weight distributions. This was observed by GPC (Table 1). This notable change was probably due to the presence of water in the reaction. Water was a source of impurity among the monomers and the solvents used and most probably hydrolyzed the anhydride group in EDTAD which ultimately formed an ortho dicarboxylic group. As a result, the ortho dicarboxylic group formed the end group in PAA and consequently affected the molecular weight dis-

tribution of the polymer [24]. Since polycondensation reactions are equilibrium limited (reversible in nature) and thus susceptible to hydrolysis, a nitrogen environment in addition to using an aprotic solvent for polymerization was implemented to prevent moisture from entering into the reaction vessel. The addition of EDTAD into the DAB solution (consisting of DAB in one of the aprotic solvents) resulted in the instantaneous increase of polymer solution viscosity and depending on monomer concentration appeared as either a viscous clear solution or a viscous pale yellowish solution. The newly synthesized PAA was readily soluble in water, D₂O, DMF and DMSO but insoluble in many non-polar solvents such as acetone, ethyl ether and methanol.

3.2. Structural characterization

3.2.1. Fourier transform infrared spectroscopy (FTIR)

One of the greatest advantages of such a novel polymer was the presence of cleavable bonds and reactive functional groups such as the acid (COOH) and the amide (-CO-NH-) in the backbone of the polymer chain. This attribute enhances the properties of the polymer by allowing for chemical cross-linking and thus foreseeing the polymers potential versatility. Polymer samples were characterized by ATR-FTIR spectroscopy to identify functional groups in PAA, thereby giving insight to its molecular structure. The spectra of PAA (samples a \rightarrow f) displayed several sharp peaks in Fig. 2; ν 1660 cm⁻¹ (amide I; C=O stretch = C-O + C-N), ν 1540 cm⁻¹ (amide II; C-N-H stretch = N-H + C-N), ν 3290 cm⁻¹ (-NH), and ν 2930 cm⁻¹ (-CH) which was consistent with absorption bands found in similar PAA systems [25,26]. The presence of the OH vibration at a wavelength

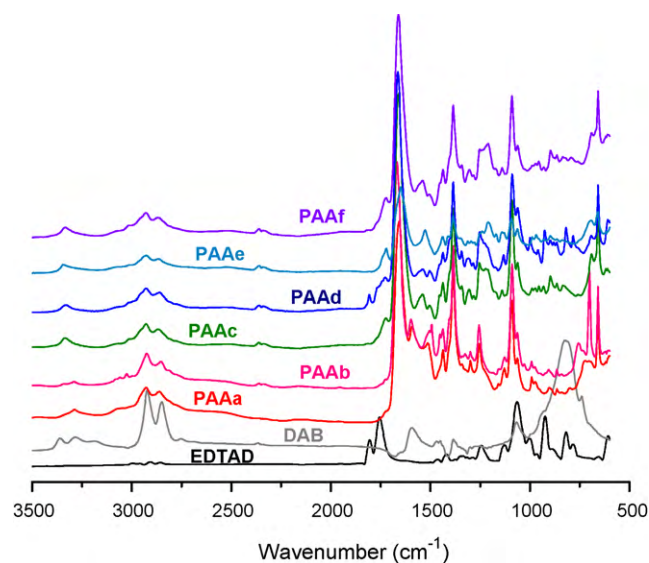


Fig. 2. FTIR spectra of poly(amic acid)s, 1,4-diaminobutane and ethylenediaminetetraacetic dianhydride.

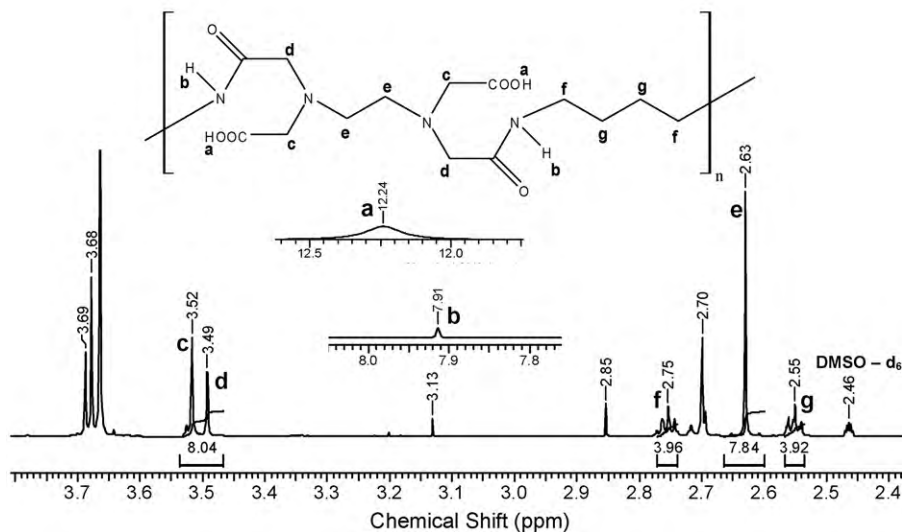


Fig. 3. ^1H NMR spectrum of poly(amic acid).

of 3400 cm^{-1} was difficult to clearly identify as a result of the overlapping peaks associated with NH and OH vibrations.

3.2.2. Proton nuclear magnetic resonance (^1H NMR)

High resolution ^1H NMR and ^{13}C NMR spectra provided support to the FTIR results and in addition showed valuable information on molecular structure. PAA samples were dissolved in $\text{DMSO-}d_6$ (Fig. 3) for ^1H NMR. Peaks observed on the ^1H NMR spectrum (600 MHz, $\text{DMSO-}d_6$, 1 wt%): δ (ppm) 2.52–2.57 (triplet, 2 H); 2.62–2.66 (singlet, 8 H); 2.73–2.79 (triplet, 2 H); 3.47–3.5 (singlet, 2H); 3.51–3.58 (singlet, 2H) 7.91 (singlet, 2H); and 12.24 (singlet, 2H) confirmed the structure of PAA. The majority of the EDTAD monomer was seen at 2.63 ppm and 3.67 ppm. The spectrum was compared with the EDTAD monomer. The ^1H NMR spectrum clearly showed the distinction between methylene protons f and g and its integration values were found to be in agreement with the

chemical formula of the repeating unit of PAA. The spectrum displayed two singlet peaks between 3.45 and 3.75 ppm as a result of chemically equivalent protons. In general, downfield chemical shift changes were seen more often when using $\text{DMSO-}d_6$ (2.47 ppm) for methylene group hydrogens compared to other deuterated solvents. Since DMSO was a strong hydrogen bond acceptor, using $\text{DMSO-}d_6$ resulted in a more dramatic downfield shift for hydroxyl signals (from alcohols and acids) as a result of hydrogen bonding. A broad peak at 12.24 ppm represented the acidic hydrogen from the carboxylic acid. The singlet at 3.13 ppm was the result of the methyl group from the methanol washing and the singlets at 2.85 ppm and 2.70 ppm were the result of the methyl groups from the reaction solvent (DMF) within the sample. Deuterium exchange between the acidic proton and deuterium remained a concern only when D_2O was used as the NMR solvent. Amide protons exchange slowly with deuterated solvents and as a result the proton peak is usu-

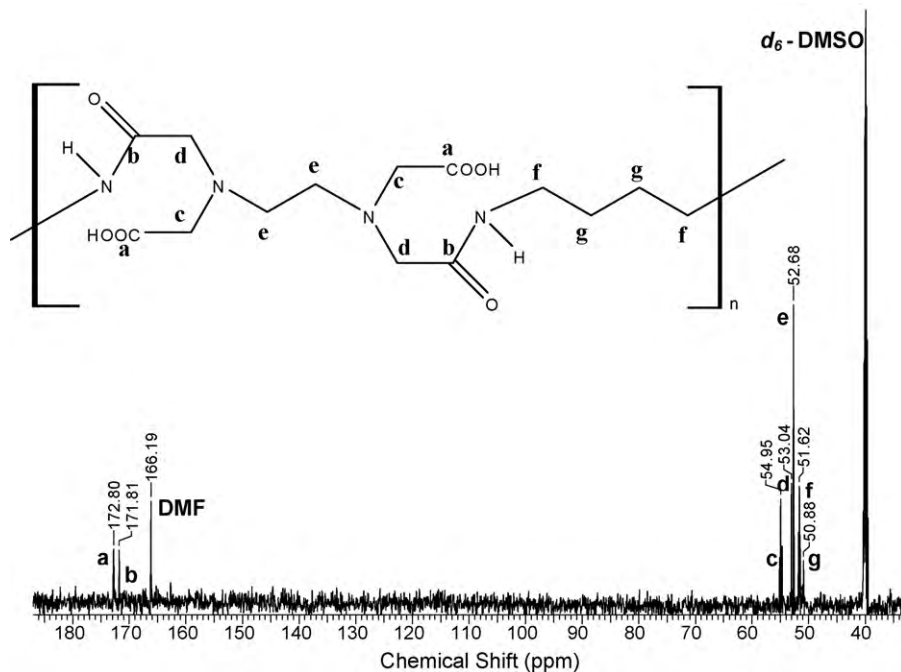


Fig. 4. ^{13}C NMR spectrum of poly(amic acid).

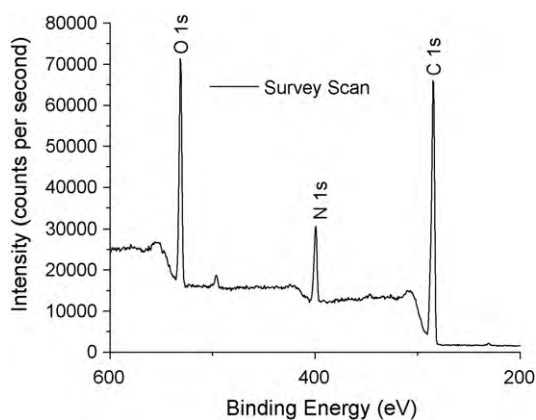


Fig. 5. X-ray photoelectron spectroscopy (XPS) survey scan of poly(amic acid).

ally observed. In general, accurately identifying peak intensities in hydrogen exchange experiments especially in the aliphatic region of the proton spectrum is rather difficult due to the overlapping peaks. In addition to using DMSO- d_6 , samples were also prepared in D $_2$ O. However, samples dissolved in D $_2$ O resulted in chemical shifts of the different methylene groups ($-CH_2-$) as being similar and consequently it was difficult to integrate and accurately quantify any of the protons present.

3.2.3. Carbon nuclear magnetic resonance (^{13}C NMR)

The ^{13}C NMR spectrum (Fig. 4) displayed seven different carbon atoms as expected for the polymer structure. ^{13}C NMR definitively confirmed the repeating structure. Peaks observed on the proton coupled ^{13}C spectrum (600 MHz, DMSO- d_6 , 1 wt%): δ (ppm) 50.88

(2C, C $_g$); 51.62 (2C, C $_f$); 52.68 (2C, C $_e$); 53.04 (2C, C $_d$); 54.95 (2C, C $_c$); 171.81 (2C, C $_b$) and 172.80 (2C, C $_a$) supported structural information provided by 1H NMR. Trace amounts of EDTAD monomer were also present at 52.66 and 50.58 ppm. The additional peaks at 40 and 166 ppm represent DMSO- d_6 and DMF, respectively.

3.2.4. X-ray photoelectron spectroscopy (XPS)

Since the N–H peak was not clearly visible in the 1H NMR spectrum, XPS and EDX were carried out on five polymer samples to determine the elemental composition of the constituting atoms on the surface and in the bulk of the polymer samples. This was done by accurately identifying the number of carbon's, nitrogen's and oxygen's present in each sample. XPS analysis showed the presence of nitrogen at 400 eV on the surface, whereas EDX analysis found nitrogen to be distributed throughout the bulk of the PAA samples (Figs. 5–7). Quantitative results were obtained using XPS by identifying the peak position and fitting the shape of the curves with respect to the C 1s = 285 eV (Fig. 6). The high-resolution C 1s spectrum of the PAA film was fitted with four peak components using CasaXPS (Casa Software Ltd.) based on the built in Marquardt–Levenberg optimization algorithm [27] with binding energies (BE's) at 284.6 eV for the C–H and C–C species, at 285.9 eV for the C–N species, at 287.9 eV for the C=O species, and at 289.2 eV for the O=C–OH species. The N 1s core-level spectrum was curve-fitted with three peak components, with BE's at 399.8 eV for the N–C species, at 400.5 eV for the N–C=O species and at 401.4 eV for the N–H species. The O 1s core-level spectrum was also curve-fitted with three peak components, with BE's at 530.9 eV for the O=C–N species, at 531.9 for the O–(C=O*) and at 533.5 eV for the O*–(C=O) species. In addition to identifying the BE's, the chemical compositions of five polymer samples (atomic concentration percentages of oxygen, nitrogen and carbon) were determined from

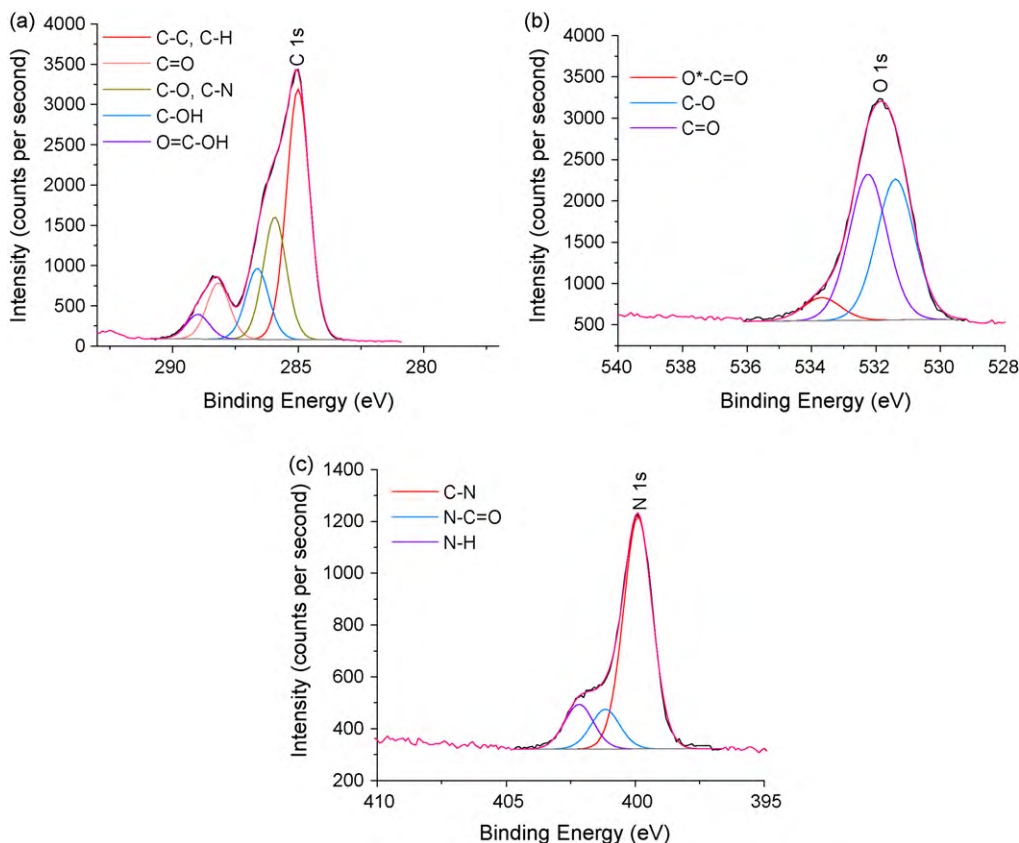


Fig. 6. Core-level spectrums of (a) Carbon (C), (b) Oxygen (O) and (c) Nitrogen (N) for poly(amic acid). Note: The chemical formula with an asterisk (*) indicates the specific atom which is being observed. The asterisk is present only when two or more atoms of the same element are present in different bonding situations.

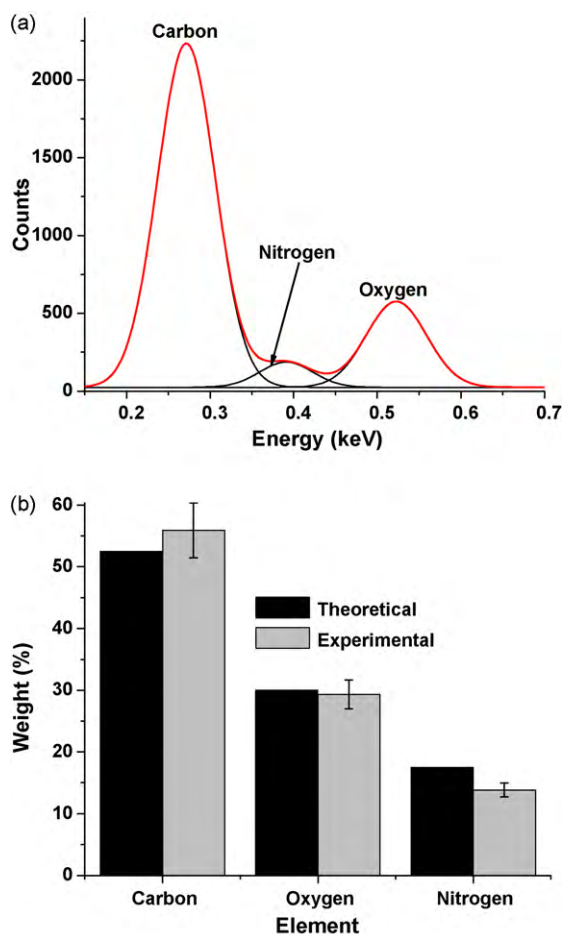


Fig. 7. (a) Energy dispersive X-ray survey scan including peak decomposition and (b) Statistical composition analysis of poly(amic acid).

the survey spectra; % Carbon = 58.0 ± 5.8 , % Oxygen = $27.7 \pm 1.8\%$ and % Nitrogen = 14.3 ± 1.4 . These values were in good correlation with the theoretical values; % Carbon = 52.5, % Oxygen = 30.0 and % Nitrogen = 17.5 which were calculated based on the molecular weight of the repeating unit of PAA. Experimental results showed a higher amount of carbon in the material and a lower amount of oxygen and nitrogen. This higher amount of carbon was most probably due to contamination by other carbon rich compounds in the experimental environment.

3.2.5. Energy dispersive X-ray (EDX) analysis

The percent compositions of the bulk polymer samples were determined using EDX and compared to the compositions of the surface as determined by XPS and were found to be in good agreement (Fig. 7). Quantitative analysis for the experimental compositions of the atoms were determined for five polymer samples; % Carbon = 56.0 ± 4.7 , % Oxygen = 30.5 ± 1.4 and % Nitrogen = 13.3 ± 2.3 . These values were relatively close to both the XPS data and theoretical percent compositions stated above. The percent compositions for both carbon and nitrogen were statistically significant (t -test; $p < 0.05$) this was most probably due to radiation damage by the electron beam and surface charging of the samples.

3.2.6. Gel permeation chromatography (GPC)

GPC in combination with ultraviolet and differential refractive index (RI) detectors were used to determine the molecular weights and molecular weight distributions of PAA. The number average molecular weights (M_n), weight average molecular weights (M_w)

and polydispersity indices (PDI)s where $PDI = M_w/M_n$, for all the poly(amic acid) samples based on PEG/PEO standards are illustrated in Table 1. Polymerization led to low molecular weight PAA samples having M_n values ranging from 4000 to 6000 g mol^{-1} within 24 h and PDI values averaging close to 1.3. Table 1 displays some expected trends; the higher the reaction temperature and concentration, the higher the molecular weight but the broader the molecular weight distribution. A narrow distribution is plausible at an optimal temperature of 25 °C, a reaction time of 24 h and a monomer concentration of 0.20. Polymerization with monomer concentration greater than 0.20 was never conducted since dissolving EDTAD in a polar aprotic solvent was rather difficult. In general all samples were of relatively low molecular weights compared to the molecular weights of polymers synthesized by the traditional condensation polymerization methods. Samples having low molecular weights in the past have often been attributed to water residue inside the reaction vessel, monomer concentration, reaction time and reaction temperature. However, in this particular reaction the 1:1 stoichiometric ratio of the monomers also had a significant impact on the molecular weights of the polymer samples. Despite every effort to change the above factors, polymer samples remained below 10,000 g mol^{-1} . At this molecular weight range, perhaps the PAA polymer may be suitable for use as a coating material for medical devices such as a coronary stent to improve biocompatibility and in addition when bioactive molecules are conjugated into PAA, act as a drug delivery medium.

4. Conclusions

A series of linear PAA polymers containing acid and amide side chains with a M_n in the range of 4000–6000 g mol^{-1} have been successfully prepared and verified using several analytical tools; FTIR, ^1H NMR, ^{13}C NMR, XPS, EDX and GPC. Chemical structure and physical properties were established. The presence of cleavable bonds (functional groups: $-\text{COOH}-$, $-\text{CO}-\text{NH}-$) in the polymer chain enhanced the properties of the polymer by providing versatility. To investigate the PAA polymer further, cell compatibility studies using aortic endothelial cells are being conducted for its potential use in cardiovascular applications [28]. In addition, chemical cross-linking studies are also underway to obtain high molecular weight PAA polymers.

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