Synthesis of tertiary poly(amido-amine)s with amido- and amino-groups randomly arranged along the macromolecular chain

L. Rusconi and M. C. Tanzi
Istituto di Chimica Industriale del Politecnico, Piazza L. da Vinci 32, 20133 *Milano, Italy*

and P. Ferruti and L. Angiolini
Istituto di Chimica degli Intermedi dell'Università, Viale Risorgimento 4, 40136 *Bologna, Italy*

and R. Barbucci and M. Casolaro
Istituto di Chimica Generale dell'Università, Pian dei Mantellini 44, 53100 *Siena, Italy*
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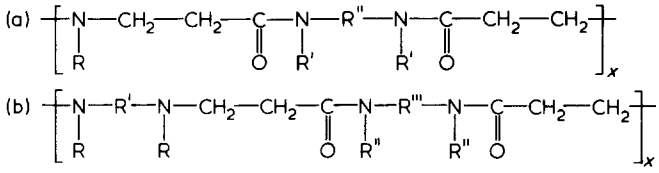
A new synthesis of poly(amido-amine)s from bis(secondary amine)s and acryloyl chloride has been studied, leading to polymers in which the amido- and amino-groups are randomly arranged along the macromolecular chain. A poly(amido-amine) based on piperazine, chosen as the mother compound, has been fully characterized by ^{13}C n.m.r. as well as by identification and quantitative evaluation of its hydrolysis products.

Keywords Poly(amido-amine)s; tertiary; random; bis (secondary amines); acryloyl chloride; ^{13}C nuclear magnetic resonance

INTRODUCTION

Linear poly(amido-amine)s are usually obtained by polyaddition of primary monoamines, or bis-(secondary amine)s, to bis-acrylamides. The reaction takes place readily in water or alcohols, at room temperature, and without added catalysts. Aprotic solvents are not recommended, if high molecular weight products are desired. This method is a general one, as far as aliphatic or cycloaliphatic amines are concerned[1].

The poly(amido-amine)s prepared by this method have the following structures:



referring to poly(amido-amine)s derived from primary monoamines, and bis(secondary amine)s, respectively. Both are characterized by a regular structure, in which amido- and tertiary amino groups are regularly arranged along the macromolecular chain.

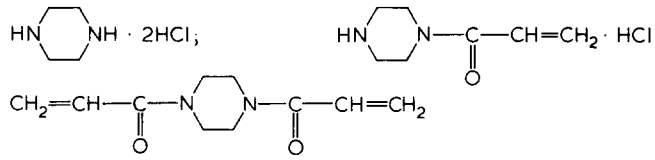
Poly(amido-amine)s, as a class, show interesting behaviour, as far as their protonation and complex formation with heavy metal ions are concerned. In particular, their repeating units behave independently in these respects, which appears to be quite unusual in the polymer domain[2-7]. Furthermore, many poly(amido-amine)s form stable complexes with heparin in aqueous solution, and therefore are potentially useful in the biomedical applications[8-11].

As a further development in the poly(amido-amine)s chemistry, we thought it interesting to study a synthetic route to polymers having essentially the same composition as the poly(amido-amine)s deriving from bis (secondary amine)s and bisacrylamides, but in which the amido- and tertiary amino groups had no regular sequence along the macromolecular chain. This was done in order to determine the influence of chain regularity on the peculiar properties of this family of polymers. The aim of this report is to relate the first results obtained in this work.

SYNTHESIS OF AN 'IRREGULAR' POLY(AMIDO-AMINE) BASED ON PIPERAZINE

The general synthetic pathway devised to synthesize 'irregular' poly(amido-amine)s involves the reaction of a bis-(secondary amine) with an equimolecular quantity of an activated acrylic acid derivative, able to act both as an acylating agent, and as substrate for a Michael-type hydrogen transfer addition. The reaction of piperazine with acryloyl chloride was considered first.

The reaction was performed in two steps. In the first step, a solution of acryloyl chloride in anhydrous chloroform was added under stirring to a cooled solution of anhydrous piperazine in the same solvent. The resulting mixture presumably contained three products: piperazine dihydrochloride, 1-acryloylpiperazine hydrochloride, and 1,4-bis-(acryloyl)piperazine:



Little or no Michael addition should take place at this stage. The solvent was then eliminated under vacuum, the reaction mixture was dissolved in water, which according to previous data is the most suitable solvent for this kind of polyaddition[12], and a tertiary amine was added in slight excess over the hydrochloric acid resulting from the acylation reaction. At this point, heat was evolved, and the polyaddition started, as evidenced by a gradual increase of viscosity.

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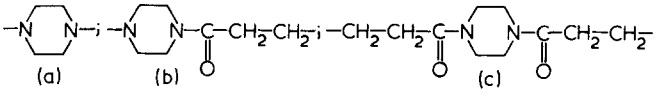
According to the reaction scheme, the polymer (PAA-1) should contain the following units:



It is apparent that amido- and tertiary amino groups must be present in equal numbers in the macromolecular chain, provided the molecular weight of the polymer is sufficiently high. This seems to be the case, since the intrinsic viscosities of different samples of PAA-1, obtained as above, ranged between 0.50 and 0.55 dl/g (see *Table 1*).

DETERMINATION OF THE CHEMICAL STRUCTURE OF PAA-1

^{13}C n.m.r. studies. N.m.r. analysis of PAA-1 was carried out by comparison with 'regular' poly(amido-amine) obtained from piperazine and bis-acryloylpiperazine[12], the spectrum of which (H_2O, r.t.) shows the expected signals due to the presence of chain methylene groups (at 30.5 and 53.7 ppm for, respectively, carbon atoms in α and β position with respect to the carbonyl group), bis-alkylated piperazine methylene groups (repeating unit (a)) (at 52.3 ppm) and bis-acylated piperazine methylene groups (repeating unit (c)) (at 45.8 and 42.3 ppm).* Besides the above signals, the PAA-1 spectrum also showed a band at 52.9 ppm which was attributed to the mono-acylated piperazine (repeating unit (b)) methylene groups adjacent to the amine nitrogen. A rough estimation based on peak heights gave an amount of unit (b) in the molecule of approximately 20%.

Hydrolytic analysis. In order to determine more exactly the relative amounts of the different units in PAA-1, this polymer was fully hydrolysed with 6M hydrochloric acid.

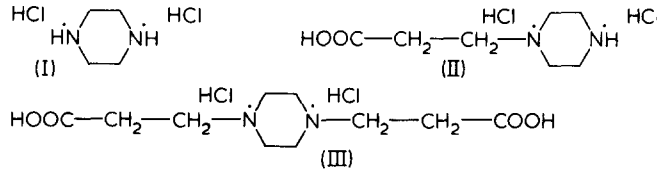
* Two broad bands are observed, due to conformational rigidity caused by restricted rotation around the amide C–N bond. This was confirmed running the spectrum at 80°C and observing coalescence of both signals

Table 1 Viscosities (intrinsic) and solubility data for PAA samples

Polymer	$[\eta]$ (dl/g)*	Aspect	Solubility data**
PAA–1	0.51	White solid	S a, g, h S_c f I b, c, d, e
PAA–2	0.28	White solid	S a, c, g, h S_c f I b, d, e
PAA–3	0.10	Pale yellow viscous liquid	S a, b, c, e, g, h Sc f I d
PAA–4	0.15†	Yellow viscous liquid	S b, c, e, g, h S_c f I a,d

* In H_2O/formamide 1:1 by volume, where not otherwise indicated
** Solvents tried: a = H_2O; b = chloroform; c = methanol; d = ethylether; e = acetone; f = dimethylsulphoxide; g = formamide; h = H_2O/formamide 1:1
† In aqueous 0.1 *M* HCl/0.5 M NaCl

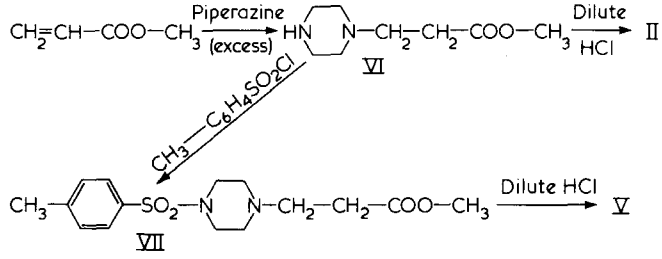
According to the probable structure of PAA-1, by evaporating the resulting solution to dryness, a mixture of three products should be obtained, namely the hydrochlorides of piperazine (I), 1-piperazine-β-propionic acid(II), and 1,4-piperazine-di-β-propionic acid(III).



In fact, the presence of only three products was detected by t.l.c., two of which were immediately identified as I and III, by comparison with authentic samples.

In order to separate quantitatively the three products, the overall hydrolysis product was treated in aqueous solution with *p*-toluenesulphonylchloride and sodium hydroxide. 1,4-bis-(*p*-toluenesulphonyl) piperazine (IV) precipitated out, and was collected by filtration. It was identified by comparison with an authentic sample. By acidifying the filtrate with hydrochloric acid to pH $\simeq$ 1, and cooling, a product was obtained whose analytical data were consistent with the hydrochloride of the *p*-toluenesulphonamide of II (V). In the mother liquors no V was revealed by t.l.c., while by the same technique the presence of III could be ascertained, but no simple method to isolate it quantitatively was found.

In order to confirm the identity of II and V, authentic samples were prepared as follows. Methyl acrylate was treated with a large excess of piperazine, thus obtaining the methyl ester of piperazine mono-β-propionic acid (VI). This could be either hydrolysed, thus obtaining II, or *p*-toluene-sulphonated, thus obtaining the methylester of V (VII), which in turn yielded V by hydrolysis.



The identity of this product with that obtained from the hydrolysis of PAA-1 was checked by i.r., t.l.c., m.p. and mixed m.p. Both products could be titrated in aqueous solution with methylred as indicator. In both cases, the alkali consumption was 1 mol mol^{-1}. With phenolphthalein as indicator, the alkali consumption was 2 mol mol^{-1}.

The molar ratio between I and II, isolated as *p*-toluenesulphonamides, was about I:0.38. Since units (a) and (c) must always exist in 1:1 molar ratio, the failure in quantitatively isolating III was considered irrelevant to the purpose of our investigation. Therefore, it may be concluded that in the 'irregular' PAA-1 the distribution of the repeating units is as follows:

(a): 42%; (b): 16%; (c): 42%.

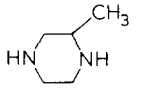
This result is in agreement with the approximate evaluation drawn from ^{13}C n.m.r. spectra (see above).

It may be noted that if the first step of the polymer synthesis, i.e. the acylation step, occurred randomly on the amino groups, the relative ratios would have been different, namely 25:50:25. Our results seem to indicate that, in the conditions we used, and if subsequent exchange reactions during polyaddition are excluded, acylation of the monoacylated piperazine is favoured over that of piperazine.

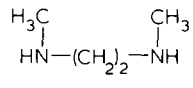
PAA-1 was found to be partially crystalline by X-rays examination. Its main reflections (CuKα) are 18° and 23°. They are the same as those obtained in the case of a 'regular' poly(amido-amine) from piperazine and 1,4-bis(acryloyl) piperazine[12]. However, the peaks of the latter polymer are far sharper, thus indicating a higher degree of crystallinity. While in the case of the 'regular' polymer a melting point of about 270° (with decomposition) could be determined[12], no defined melting point was shown from PAA-1 either by polarizing microscopy or by d.s.c. By the same techniques it was found that PAA-1 decomposes in air above 250°.

SYNTHESIS OF POLY(AMIDO-AMINE)S FROM ACRYLOYL CHLORIDE AND BIS-SECONDARY AMINES OTHER THAN PIPERAZINE

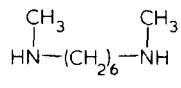
The reaction pathway studied in the case of piperazine was extended to other bis-(secondary amine)s, namely:



2-methyl-piperazine



1,2-bis(methylamino) ethane



1,6-bis(methylamino) hexane

The resulting PAA's 2, 3 and 4 were obtained in good yields. Their intrinsic viscosities and solubility data are given in *Table 1*, together with those of PAA-1. PAA's 3 and 4 are highly viscous liquids, while PAA-2 is a solid product, which is practically amorphous by X-ray examination.

It may be noted that the intrinsic viscosities of PAA's 2, 3 and 4 are considerably lower than that of PAA-1; even so, however, the synthetic method described in this report seems to be a general one. The exact determination of the chemical structures of PAA's 2, 3 and 4, together with the protonation and heavy metal ions complexing behaviour of 'irregular' poly(amido-amine)s of different structures, are presently under examination, and will be the object of forthcoming papers.

EXPERIMENTAL

^{13}C n.m.r spectra were run at 25.16 MHz on a Varian XL-100 FT spectrometer in H_2O solution with dioxane as internal standard.

Wide angle X-ray powder diffraction spectra were run on a Philips PW 1050 counter diffractometer, using CuKα radiation.

I.r. spectra (KBr pellets, where not otherwise indicated) were run on a Perkin Elmer 456 spectrophotometer.

All m.p.'s are uncorrected. The m.p.'s of non-macromolecular compounds were determined by a usual capillary-tube apparatus.

T.l.c.'s were run on Merck 60 Silicagel plates.

Authentic samples of 1,4-piperazine di-β-propionic acid dihydrochloride (III), and 1,4-bis-(*p*-toluenesulphonyl)piperazine (IV) have been prepared as described previously[13,14]. Commercial acryloylchloride was doubly-distilled immediately before use, b.p. 75°–76°C. Anhydrous piperazine was a commercial product (Fluka, puriss.). The same applies for 2-methyl piperazine, 1,2-bis(methylamino)ethane and 1,6-bis(methylamino)-hexane.

PAA-1. PAA-1 was prepared as follows. To a solution of piperazine (11.52 g, 133.7 mmole) in anhydrous (CaH_2), alcohol-free chloroform (50 ml), 100 ml of a 1,3372 M acryloylchloride solution in the same solvent was added dropwise under vigorous stirring. The temperature of the reacting mixture was maintained at $-15 \pm 5°$ by means of a dry-ice/acetone bath. A white precipitate was formed. After addition, the mixture was stirred for 2 hours, while rising to room temperature. The solvent was then thoroughly eliminated under vacuum at room temperature, and the residue was dissolved in water (50 ml). Triethylamine (19.5 ml, 140.4 mmole) was added, and the reaction mixture was kept at room temperature for three days. After this time, the very viscous solution was poured into 500 ml acetone containing 15 ml triethylamine.

The gummy precipitate was dissolved in water, reprecipitated again into the same mixture, and finally thoroughly extracted with acetone. Yield = 17.4 g (93%). Analysis: found % C 54.26; H 8.21; N 18.27; Ctd % for $(C_7H_{12}N_2O \cdot 0.75\ H_2O)_x$: C 54.70; H 8.85; N 18.23. I.r, ^1H n.m.r. spectra were consistent with the proposed structure. No presence of Cl^- ions was found by qualitative analysis.

Hydrolysis of PAA-1. PAA-1 (9 g) was treated with 6M HCl (120 ml), and the mixture was refluxed for 24 h. After this time, the solution was evaporated to dryness *in vacuo*. Yield = 13.5 g (100%), calculated on the partially hydrated product (see above).

By t.l.c. (CH_3OH/aq.conc.NH_3 95:5) gave three spots (R_f's = 0.09, 0.19 and 0.55). The R_f's of authentic samples of piperazine dihydrochloride and 1,4-piperazine di-β-propionic acid dihydrochloride were: 0.09, and 0.55. No additional spots were found by chromatographing a mixture of these compounds with the hydrolysis product.

p-*Toluenesulphonylation of the hydrolysis product.* The hydrolysis product (2 g, 8.7 mmole) was dissolved in ice water (20 ml), aq. 5M NaOH (10 ml) was added. To the resulting solution, a solution of *p*-toluenesulphonylchloride (2 g, 10.5 mmole) in dioxan (4 ml) was added under stirring, and the reacting mixture was stirred 4 h, by cooling in external ice bath, then for 12 h while rising to room temperature. During the reaction, IV precipitated out.

At the end of the reaction, IV was collected by filtration, washed on the filter with a small amount of water, and dried to constant weight. Yield: 1.26 g. M.p. 291°–292°C. It gave a single spot by t.l.c. (CH_3OH/ aq.conc. NH_3 95:5), and its i.r. spectrum was identical to that of the authentic sample.

The filtrate was acidified with HCl to pH ~1, kept in refrigerator for 36 h, and then warmed back to the room temperature. A white precipitate of V was collected by filtration. This treatment was applied in order to recover the product quantitatively, and to free it from III, which

coprecipitates with V when the acidic solution is cooled to 0°–5°C but re-dissolves at room temperature. Yield: 0.46 g. M.p. 235°–240°C. The i.r. spectrum of the product shows characteristic bands at 1720, 1595, 1350 and 1160 cm^{-1}, which have been attributed to the CO group, to the aromatic ring, and to the sulphamido group, respectively. By t.l.c. (MeOH/aq.conc. NH_3 95:5) the product gave a single spot with $R_f = 0.8$.

Preparation of authentic samples of II and IV. To a solution of 10 g (116 mmole) piperazine in 30 ml MeOH, 2.5 ml (23 mmole) methyl acrylate (Merck) were added dropwise. The reaction solution was left at room temperature for ~4 h, then it was thoroughly evaporated to dryness *in vacuo*, and the residue redissolved with 280 ml $CHCl_3$.

One half of this solution was treated with water (5.8 ml) under stirring and cooling to 0°C with an ice-bath. Piperazine hexahydrate precipitated almost quantitatively and was eliminated by filtration. The filtrate was evaporated to dryness *in vacuo*, and the residue (1.15 g) was purified by column chromatography (SiO_2, methanol). The methyl ester of II, so obtained as free base, failed to crystallize. Yield: 0.96 g (48%, based on methyl acrylate). The dihydrochloride was prepared by treating a MeOH solution of the free base with conc. HCl, and cooling. M.p. (MeOH) 218°–223°C. Analysis: found % C 37.47; H 7.67; N 11.22; calculated % for $C_8H_{18}N_2O_2Cl_2 \cdot 0.5\ H_2O$; C 37.81; H 7.55; N 11.02.

A sample of the methyl ester of II (0.5 g) was dissolved in 3M hydrochloric acid (50 ml). The solution was refluxed for 4 h and then evaporated to dryness *in vacuo*. The residue was crystallized from MeOH containing about 2% water. Yield: 0.32 g (68%). M.p. 213°–216°C. Analysis: found % C 34.82; H 7.28; N 11.54. calculated % for $C_7H_{16}N_2O_2Cl_2 \cdot 0.5\ H_2O$; C 35.01; H 7.14; N 11.67.

To the second half of the original chloroform solution, 15.25 ml (109.6 mmole) triethylamine and then 20.89 g (109.6 mmole) *p*-toluene-sulphonlychloride were added under stirring and cooling with an ice-bath. The mixture was left 2 h at room temperature and 15 minutes more at 40°. The precipitated IV was filtered off, the filtrate evaporated to dryness *in vacuo*, and the residue dissolved in 0.2M hydrochloric acid (50 ml). After filtration, the solution was adjusted to pH 9 by addition of 2% aqueous Na_2CO_3, and cooled. Crude VII precipitated out. It was collected and purified by column chromatography (SiO_2 ethylether), and finally by crystallization with a 1:2 ether/n-heptane mixture. Yield: 1.2 g. M.p. 80°–84°C. Analysis: found % C 54.87; H 6.92; N 8.85; calculated % for $C_{15}H_{22}N_2SO_4$: C 55.19; H 6.79; N 8.59.

A sample of VII (0.5 g) was dissolved in 0.2 M hydrochloric acid (30 ml). The solution was refluxed for 2 h, cooled and kept in a refrigerator for 12 h. The precipitated V was collected by filtration and recrystallized from 0.2 M hydrochloric acid. Yield: 0.42 g (79%). M.p. 235°–240°C. Analysis: found % C 47.78; H 6.29; N 8.16; calculated % for $C_{14}H_{21}N_2SO_4Cl$: C 48.20; H 6.07; N 8.03.

Preparation of PAA-2. The same procedure described for PAA-1 was followed, by substituting an equimolecular quantity of anhydrous 2-methyl-piperazine for piperazine. The product was isolated in the same way. Yield: 16.5 g (80%). Analysis: found % C 57.64; H 8.99; N 16.98; calculated for $(C_8H_{14}N_2O \cdot 0.75\ H_2O)_x$: C 57.29; H 9.31; N 16.70. No Cl^- ion was detected by qualitative analysis.

Preparation of PAA's-3 and -4. The same procedure as in the previous case was followed, by substituting equimolecular quantities of anhydrous 1,2-bis(methylamino)ethane or 1,6-bis(methylamino)hexane, respectively, for 2-methylpiperazine. The products were isolated as follows. By pouring the reaction mixtures into an excess of acetone, both polymers precipitated out as partial hydrochlorides. The free bases, in fact, are soluble in acetone (see *Table 1*). The precipitates were then dissolved in 200 ml of a 10% chloroform solution of triethylamine. Finely powdered anhydrous potassium carbonate (~50 g) was then added, and the mixture was stirred for 30 min at room temperature, filtered, evaporated under vacuum to about 40 ml, and treated with a large excess of anhydrous ether. Both products precipitated out as highly viscous liquids and were repeatedly washed with ether and finally dried to constant weight at room temperature and 0.1 mm. Yields: PAA-3: 13.7 g (72%); PAA-4 19.9 (75%). Analyses: PAA-3 found % C 52.69; H 8.94; N 18.27; calculated % for $(C_7H_{14}N_2O \cdot 0.75\ H_2O)_x$; C 53.99; H 10.03; N 17.99. PAA-4 found % N 14.05; calculated % N 14.13.

In both cases, no presence of Cl^- ions was found by qualitative analyses.

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