Synthesis and characterization of piperazine-derived poly(amido-amine)s with different distributions of amido- and amino-groups along the macromolecular chain

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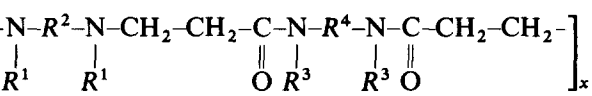
Four poly(amido-amine)s based on piperazine have been synthesized by poly(acylation–addition) reaction of piperazind with various activated derivatives of acrylic acid. In these polymers, amido-, and amino groups are randomly arranged along the macromolecular chain. These polymers have been fully characterized by hydrolytic analysis, ^{13}C n.m.r., and potentiometric techniques.

(Keywords: poly(amide-amine)s random; acryloyl chloride; 1-acryloyl benzotriazole; *N*-acryloxy succinimide; acrylic acid; ^{13}C nuclear magnetic resonance; potentiometric analysis)

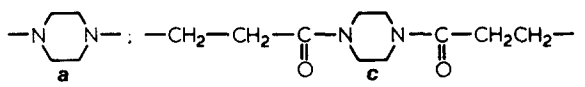
INTRODUCTION

Poly(amido-amine)s having a regular sequence of amido- and amino groups are obtained by polyaddition of primary monoamines, or bis(secondary amine)s, to bis acrylamides[1,2]. These polymers, when derived from bis(secondary amine)s, have the following structure:

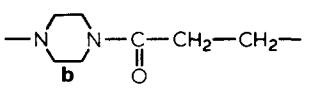


A previous paper[3] reports the synthesis of poly(amido-amine)s having essentially a similar structure, but in which the amido- and amino groups were, in part, irregularly arranged along the macromolecular chain.

In particular, the piperazine-derived 'regular' poly(amido-amine), obtained by polyaddition of piperazine to 1,4 bis-acryloylpiperazine, contains two types of regularly alternating units, of bis-aminic and bis-amidic structure, respectively:



However, the 'irregular' poly(amido-amine), PAA-1A[3], obtained by poly(acylation–addition) reaction of acryloyl chloride with piperazine, contains also a third type of unit, having the structure of a mono-acylated piperazine:



This polymer, however, still had an unexpectedly high degree of chain regularity, showing the following ratio between the repeating units:

$$\mathbf{a}:\mathbf{b}:\mathbf{c} = 42:16:42$$

whereas, if the acylation and addition steps occurred randomly, the expected ratio should have been 25:50:25.

This paper reports the synthesis and characterization of a series of poly(amido-amine)s, obtained by acylation–addition polymerization of piperazine with various activated derivatives of acrylic acid (see Scheme 1). The use of different activation methods results in different distributions of amido- and amino groups along the macromolecular chain. Such distributions have been determined by chemical, ^{13}C n.m.r. and potentiometric methods.

SYNTHESIS

Four different samples of PAA-1 were prepared (Scheme 1). In Scheme 1, PAA-1 A, prepared as described previously[3], is also mentioned.

Firstly, the reaction between acryloyl chloride and piperazine was repeated, following the same technique described previously[3], but inverting the order of reagents addition in the first step, i.e. piperazine (as chloroform solution) was added dropwise to a solution of acryloyl chloride in the same solvent (see Experimental). Using this method PAA-1 B was obtained.

Polymers PAA-1 C and PAA-1 D were obtained by

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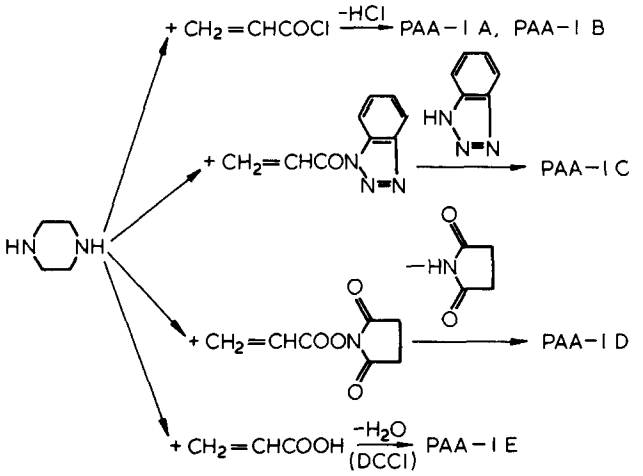
Scheme 1



using two previously described activated derivatives of acrylic acid, i.e. 1-acryloyl benzotriazole (ABT)[4], and *N*-acryloxy succinimide (AOS)[5]. The first reaction step was carried out in a water-soluble solvent (*tert*-butylalcohol), then the reaction mixture was diluted with water, in which polyaddition proceeds faster[6] (see Experimental).

PAA-1 E was obtained from piperazine and acrylic acid, in the presence of *N,N'*-dicyclohexylcarbodiimide, a well known coupling agent, under conditions similar to those used in the case of PAA-1 A. The intrinsic viscosities, and some solubility data of all the polymers obtained are listed in *Table 1*.

Table 1

Polymer	$H_2O/HCONH_2$ (1 : 1) η 30°C (dl g^{-1})	Solubility data[a]
PAA-1A[b]	0.51	S a, g, h S_c f I b, c, d, e
PAA-1B	0.25	S a, h S_c f, g I b, c, d, e
PAA-1C	0.14	S a, b, c, h S_c f, g I d, e
PAA-1D	0.18	S a, b, c, g, h S_c f I d, e
PAA-1E	0.12	S a, b, c, f, g, h I d, e

[a] Solvents used: a = H_2O; b = chloroform; c = methanol; d = ethylether; e = acetone; f = dimethylsulphoxide; g = formamide; h = H_2O/formamide 1 : 1

[b] Data reported in reference 3

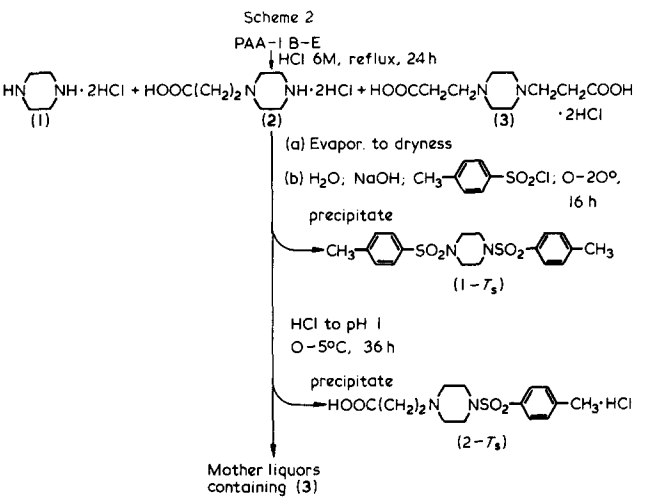
X-ray powder patterns (CuK_α) of the polymers revealed that all samples were partly crystalline, their degree of crystallinity depending more on the working up of the samples than on their origin. The shape of the diffraction pattern was always approximately the same as that of the 'regular' PAA derived from piperazine and 1,4-bis-acryloylpiperazine, i.e., it showed two main reflections at 18° and 23°. D.s.c. measurements showed decomposition between 200° and 250°C, but no clear melting peaks could be detected. I.r. spectra (KBr pellets) were always approximately superimposable on that of 'regular' PAA. For example, *Figure 1* shows the i.r. spectrum of PAA-1 C.

DISTRIBUTION OF AMINO- AND AMINO GROUPS IN THE MACROMOLECULAR CHAIN

Chemical determination

The determination of the relative amounts of the different units in PAA-1 B–E was carried out by hydrolytic analysis, following essentially the same method described in the previous paper[3]. This method is summarized in Scheme 2.

Scheme 2



No quantitative method to isolate (3), the presence of which could be qualitatively detected by t.l.c., was devised. Owing to the polymerization mechanism, however, both

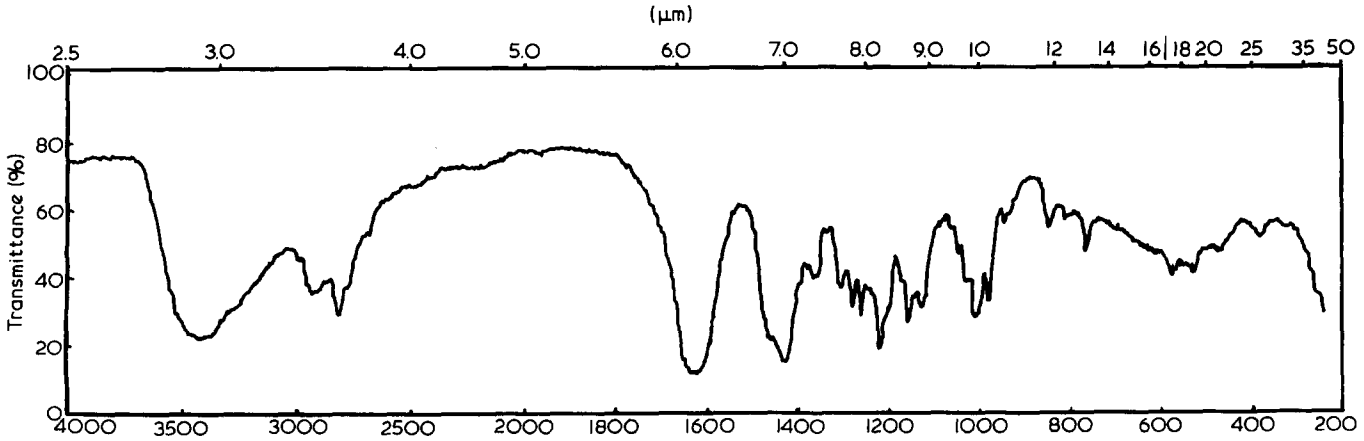


Figure 1 Infra-red spectrum (KBr pellet) of PAA-1 C

Table 2 Relative amounts of units (a), (b), and (c) in PAA 1B–1E determined by different methods[a]

Polymer	Hydrolytic analysis			^{13}C n.m.r.			Potentiometric analysis[b]		
PAA-1B	42	16	42	41	18	41	41.5	17	41.5
PAA-1C	34	32	34	30	40	30	30.5	39	30.5
PAA-1D	31	38	31	27	46	27	21	48	21
PAA-1E	25	50	25	25	50	25	22	46	22

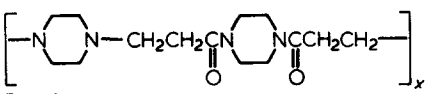
[a] For each method, the three columns give the percents in the polymers of units (a), (b), (c), in the order
[b] By this method, the purity of the polymers could be determined. It was in agreement with the findings of elemental analysis (see Experimental), showing that they tenaciously retain some amount of moisture

(1) and (3), deriving from units (c) and (a), respectively, must be present in equimolecular amounts.

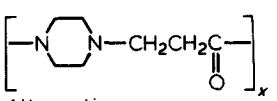
The results are reported in *Table 2*. At high contents of compound (2) in the hydrolytic mixture (i.e. of units (b) in the polymer), the percentage error, though difficult to calculate, may be relatively high, as either precipitation may be incomplete, or some (3) hydrochloride may be included in the precipitate.

^{13}C n.m.r.

The n.m.r. determination of the relative amounts of units (a), (b) and (c) in PAA-1 B–1 E was carried out by taking into account the previously reported spectra of 'regular' PAA, obtained from piperazine and 1,4-bis acryloylpiperazine[7], and of 'alternating' PAA, obtained by self-polyaddition of 1-acryloylpiperazine[8], which has the following structures:



Regular



Alternating

Their ^{13}C n.m.r. spectra (in H_2O with dioxane as internal reference) show carbonyl resonances at 173.4 and 173.0 ppm, respectively. Other differences are present in the chemical shifts of the ring methylene groups attached to the aminic nitrogens.

The spectrum of polymer PAA-1 B and the carbonyl resonances of PAA-1 C–1 E are shown in *Figure 2*. From the intensity ratios of the carbonyl signals the relative amounts of (b) and (c) units could be established, thus allowing the percentages of (a), (b) and (c) in the polymer to be calculated. The results are given in *Table 2**. The experimental mean error could be estimated by obtaining several spectra for each sample, and was between 5 and 15% of the figures shown in the Table, being higher when the content of units (b) was lower.

As in the case of hydrolytic analysis, units (a) could not be directly determined with reasonable accuracy (see previously).

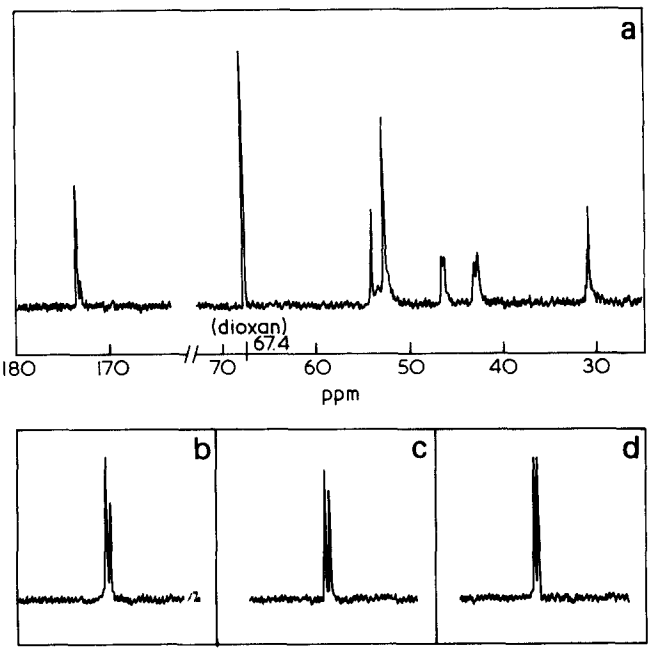


Figure 2 ^{13}C n.m.r. spectrum of PAA-1 B(a) and carbonyl resonances of PAA-1 C (b), PAA-1 D (c), and PAA-1 E (d)

Potentiometric measurements

By considering the structure of the 'regular' PAA's, it is apparent that the two basic nitrogens of units (a), and the basic nitrogen of units (b) are always separated from the basic nitrogens of other units by rings, and at least one amidic CO. These groups have been found to be able to shield the basic groups of a given unit[9], so that their protonation behaviour is independent of the overall degree of protonation of the whole macromolecule[10]. This means that the protonation constants of these polymers are 'real'[11]. As a consequence, the titration of an 'irregular' PAA may be considered as the titration of a mixture of a monoprotic and diprotic weak base[12]. In fact, the basicity constants of the 'regular' PAA, and of 'alternating' PAA, the structures of which have been shown previously, have been found to be 'real' and to have the following values: $\log K_1 = 7.01$; $\log K_2 = 2.98$ ('regular')[7], and $\log K = 5.88$ ('alternating')[13]. These constants have been utilized as the values of the constants of the two basic units present in 'irregular' PAA's, to determine their relative amounts in the macromolecule. The results are reported in *Table 1*. These results have been obtained by taking 15–20 points in each titration curve in a pH range 5.5–7.5.

It is emphasized that the potentiometric method directly determines the amounts of (a) and (b) units, while the amounts of (c) units is considered equal to that of (a) (see previously). In contrast, both with hydrolytic analysis,

* It is noteworthy that, by expanding the scale, the carbonyl bands at 173.4 and 173.0 ppm appear to be actually constituted by poorly-resolved aggregates of bands grouped within a 0.1 ppm interval. This can be reasonably attributed to the influence of different neighbouring units on the chemical shift of the carbonyl group of a given unit. In fact, this multiplicity of bands is particularly evident in polymers PAA-1C, 1D and 1E, in which the content of (b), and (c) units is reasonably close, thus giving similar amounts of different triads

and ^{13}C n.m.r., the amounts of (**b**) and (**c**) are directly determined, while the amount of (**a**) is considered equal to that of (**c**). The fact that the results obtained by the three methods are in reasonable agreement may be considered a further proof of the structure of the polymers.

METHODS OF CALCULATION

Consider the titation of a volume V_0 of a mixture of T_x° mmol of X and T_y° mmol of Y by a strong acid HA of concentration C_H mol l^{-1}. V_i is the volume of acid added at each titration point i and V_e the volume equivalent to the total basicity. (Here and elsewhere charges are omitted for convenience).

The j^{th} overall protonation constant of each of the two bases (which have m and n dissociation steps, respectively) are as follows:

$$B_{jX}=[H_jX]/[X][H^j] \tag{1a}$$

$$B_{jY}=[H_jY]/[Y][H^j] \tag{1b}$$

At any point in the titration, the mass balance equations are:

$$\frac{T_x^\circ}{V_0+V_i}=[X_i]+[HX]_i+\ldots+[H_mX]_i$$

$$=[X_i]\left(1+\sum_{j=1}^{m}B_{jx}[H]_i^j\right)$$

$$=[X_i](1+B_{Xi}) \tag{2a}$$

or

$$[X_i]=\frac{T_X^\circ}{(V_0+V_i)(1+B_{Xi})} \tag{3a}$$

$$\frac{T_Y^\circ}{V_0+V_i}=[Y_i]+[HY]_i+\ldots+[H_nY]_i$$

$$=[Y]_i\left(1+\sum_{J=1}^{n}B_{jY}[H]_i^j\right)=[Y]_i(1+B_{Yi}) \tag{2b}$$

or

$$[Y]_i=\frac{T_Y^\circ}{(V_0+V_i)(1+B_{Yi})} \tag{3b}$$

The charge balance equation is:

$$[OH]_i+\frac{C_HV_i}{V_0+V_i}=[HX]_i+2[H_2X]_i+\ldots$$

$$+m[H_mX]_i+HY_i+2[H_2Y]_i+\ldots+nH_nY_i+H_i \tag{4}$$

Substituting for all forms of H_jX and H_jY:

$$[OH]_i+\frac{C_HV_i}{V_0+V_i}=[H]_i+[X]_iA_{Xi}+[Y]_iA_{Yi} \tag{5}$$

with

$$A_{Xi}=\sum_{J=1}^{m}j[H]_i^jB_{jX} \tag{6a}$$

and

$$A_{Yi}=\sum_{J=1}^{n}j[H]_i^jB_{jY} \tag{6b}$$

and from equations (3a) and (3b):

$$[OH]_i+\frac{C_HV_i}{V_0+V_i}=[H]_i+\frac{T_X^\circ}{V_0+V_i}\frac{A_{Xi}}{1+B_{Xi}}$$

$$+\frac{T_Y^\circ}{V_0+V_i}\frac{A_{Yi}}{1+B_{Yi}} \tag{7}$$

or

$$T_Y^\circ+T_X^\circ\left(\frac{1+B_{Yi}}{1+B_{Xi}}\right)\frac{A_{Xi}}{A_{Yi}}=\frac{1+B_{Yi}}{A_{Yi}}$$

$$\left[([OH]_i-[H]_i)(V_0+V_i)+C_HV_i\right] \tag{8}$$

If

$$Z_i=\left(\frac{1+B_{Yi}}{1+B_{Xi}}\right)\frac{A_{Xi}}{A_{Yi}} \tag{9}$$

and

$$W_i=\frac{1+B_{Yi}}{V_0A_{Yi}}\left[(V_0+V_i)([OH]_i-[H]_i)+C_HV_i\right] \tag{10}$$

equation (7) becomes

$$W_i=T_Y^\circ+Z_iT_X^\circ \tag{11}$$

Z_i and W_i can be evaluated for each point (from the analytical data and the measured pH_i) so that a least squares method can be used to determine T_X° and T_Y° from equation (11).

The use of this method demands consideration of only the points in the titration curve in which both bases protonate at the same time. To fulfil this condition points in the range $7.5<pH<5.5$ (the protonation constants are $\log K_1=7.01$, $\log K_2=2.98$ and $\log K=5.88$ for the di-base and monobase, respectively) have been considered.

To estimate the reliability of the results (together with computing the standard deviations of T_X° and T_Y° and the R factor of the least squares line) the pH at each point is recalculated from the computed T_X° and T_Y° by means of the mass balance equation for the acid, i.e.:

$$C_H=[H^+]+[HX]+2[H_2X]+\ldots+[HY]$$

$$+2[H_2Y]+\ldots \tag{12}$$

From equations (3a) and (3b):

$$C_H=[H^+](1+[X]A_X+[Y]A_Y) \tag{13}$$

and from equations (6a) and (6b):

$$C_H=[H^+]\left(1+\frac{T_X^\circ}{1+B_X}A_X+\frac{T_Y^\circ}{1+B_Y}A_Y\right) \tag{14}$$

i.e.

$$[H^+]=C_H\Big/\left(1+\frac{T_X^\circ}{1+B_X}A_X+\frac{T_Y^\circ}{1+B_Y}A_Y\right) \tag{15}$$

As A_X and A_Y depend on [H], equation (15) is solved iteratively starting from the measured pH at each point.

The mean error on pH never exceeds 0.01, which implies a mean error on the measured e.m.f. of ≈ 0.5 mV.

EXPERIMENTAL

Instruments

^{13}C n.m.r. spectra were obtained at 25.16 MHz using a

Varian XL-100 FT spectrometer in H_2O solution with dioxan as internal standard.

Wide-angle X-ray powder diffraction spectra were obtained using a Philips PW 1050 counter diffractometer, using CuK_α radiation.

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

Potentiometric measurements were carried out by using a digital PHM-84 radiometer potentiometer, an Ag–AgCl reference electrode and an Orion 91-01-00 glass electrode. All the titration operations were automatically governed by a Rockwell AIM 65 minicomputer.

Synthesis

PAA-1 B. To a 1.2635 M solution of acryloylchloride in anhydrous (CaH_2) alcohol-free chloroform (126 ml, 0.159 mol), a solution of piperazine (13.71 g, 0.159 mol) in the same solvent (60 ml) was added dropwise under vigorous stirring. The temperature of the reacting mixture was maintained at -15 ± 5°C by means of a dry-ice/acetone bath. A white precipitate was formed. After addition, the mixture was stirred for 2 h, while warming to room temperature. The solvent was then thoroughly eliminated *in vacuo* at room temperature, and the residue (22.13 ml, 0.159 mol) was dissolved in water (50 ml). Triethylamine (19.5 ml, 140.4 mmol) was added, and the reaction mixture was maintained 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 = 21.77 g (97.7%).

Analysis: C, 55.97; H, 8.38; N, 18.46 wt% (determined); calculated wt% for $(C_7H_{12}N_2O\cdot0.5\ H_2O)_x$: C, 56.35; H, 8.78; N, 18.77. No presence of Cl^- ions was found by qualitative analysis.

PAA-1 C. 1-acryloylbenzotriazole (ABT) (2.01 g, 11.61 mmol) was added to a solution of piperazine (1 g, 11.61 mmol) in *tert*-butanol (6 ml), under stirring. The temperature was maintained at ≈10°C by external cooling. The reaction mixture was then allowed to warm to room temperature. A precipitate separated out. After 3 h, water (10 ml) was added and the resulting homogeneous solution extracted with 3×25 ml of ether. The ethereal extracts contained approximately the theoretical amount of benzotriazole. The aqueous phase was left at room temperature for 3 days, then poured into an excess of acetone. The precipitate was extracted with acetone, and ether, and finally dried at room temperature and 13 Pa. Yield = 1.32 g (76.2%).

Analysis: C, 56.27; H, 8.20; N, 18.20 wt% (determined); calculated wt% for $(C_7H_{12}N_2O\cdot0.5\ H_2O)_x$: C, 56.35; H, 8.78; N, 18.77.

PAA-1 D. To a mixed solution of piperazine (1.14 g, 13.23 mmol) and triethylamine (1.84 ml, 13.23 mmol) in *tert*-butanol (7 ml) a solution of *N*-acryloxysuccinimide (2.00 g, 13.23 mmol) in the same solvent (15 ml) was added. The reacting mixture was maintained at ≈10°C by external cooling. After keeping overnight at room temperature, water (≈25 ml) was added to the reaction mixture, which was not homogeneous, and the clear solution obtained was left at room temperature for 3 days. After this time, it was concentrated *in vacuo* to a small volume, and then worked up as in the previous case. Yield = 1.53 g (82.7%).

Analysis: C, 56.56; H, 8.34; N, 18.28 wt% (determined); calculated wt% for $(C_7H_{12}N_2O\cdot0.5\ H_2O)_x$: C, 56.35; H, 8.78; N, 18.77.

PAA-1 E. To a solution of anhydrous piperazine (9 g, 104 mmol) in anhydrous, alcohol-free chloroform (100 ml), dry acrylic acid (7.16 ml, 104 mmol) was added. After cooling at ≈0°C by means of an ice-bath, dicyclohexylcarbodiimide (22 g, 107 mmol) was added under vigoruos stirring. The mixture was then allowed to react for 24 h, while warming to room temperature. The precipitate dicyclohexylurea was filtered out, and the solution was evaporated to dryness *in vacuo*. The residue was dissolved in ≈30 ml of water, filtered, and then allowed to polymerize for 3 days at room temperature. The polymer was then isolated as in previous case.

Yield = 10.62 g (68.47%).

Analysis: C, 57.83; H, 8.49; N, 19.33 wt% (determined); calculated wt% for $(C_7H_{12}N_2O\cdot0.25\ H_2O)$: C, 58.31; H, 8.39; N, 19.43.

Hydrolytic analysis of PAAs 1 B–E was carried out as described previously[3].

Potentiometric analysis

Reagents. A CO_2-free NaOH solution was prepared, stored, and standardized as described elsewhere[14]. Stock solutions of 0.1 M NaCl were prepared from sodium chloride (Erba, ACS grade) and used without further purification as the ionic medium for potentiometric and calorimetric measurements.

Electromotive force measurements. All potentiometric measurements were carried out at 25°C in 0.1 M NaCl.

The obtained data (titrant (ml) added at each step and the corresponding average of output voltages) were automatically printed and stored on a floppy disk for further processing. The titrant vessel was thermostated at 25.0 ± 0.1°. A stream of nitrogen presaturated with water vapour by bubbling through a 0.1 M NaCl solution was passed over the surface of the solution to be titrated. For the titrations the NaOH or HCl solutions were dispensed from a Metrohom 655 Dosimat piston buret governed by the minicomputer. Buret and $E°$ calibrations were carried out before and after each titration. The concentration of hydrogen ion was calculated from the e.m.f. values (mV) by means of the formula:

$$[H^+]=\exp(E-E°)/25.693$$

No attempt was made to correct the data to zero ionic strength or to apply activity coefficient corrections as under the conditions used the bases do not contribute very much to the ionic strength, and ionic strength is relatively high. The experimental details are reported in *Table 3*.

ACKNOWLEDGEMENTS

Thanks are due to the Highfield NMR Service of CNR (Bologna) for obtaining the ^{13}C n.m.r. spectra, and to the Italian Ministry of Education for financial support.

Table 3 Experimental details of the potentiometric measurements at 25°C in 0.1 M NaCl

Sample	Potentiometric vessel			Titrant added			
	Weight (mg)	H^+ (mmol)	Vol[a] (ml)	Vol[b] (ml)	CH^{+c}	pH range	Data points
PAA-1	101.3	–	104.02	7.0	0.1018	7.8–2.8	350
PAA-1	101.3	0.7126	111.02	8.0	–0.1001	2.8–9.6	400
PAA-2	108.8	–	103.03	7.9	0.1024	8.1–2.8	395
PAA-3	110.2	–	99.94	6.6	0.1022	8.4–3.2	330
PAA-4	108.6	–	99.84	7.0	0.1020	7.8–3.0	350
PAA-5	53.6	–	99.55	6.72	0.0890	8.4–2.6	168
PAA-5	31.8	–	99.98	3.88	0.1050	8.5–2.7	97

[a] Initial volume
[b] Total volume added stepwise
[c] Negative value refers to the concentration of the NaOH solution used as titrant

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