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ARTICLE *in* THE JOURNAL OF PHYSICAL CHEMISTRY B · AUGUST 2007

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A Monte Carlo Study of Weak Polyampholytes: Stiffness and Primary Structure Influences on Titration Curves and Chain Conformations[†]

Serge Ulrich,* Marianne Seijo, and Serge Stoll

Department of Inorganic, Analytical, and Applied Chemistry, University of Geneva, Sciences II, 30 quai Ernest-Ansermet, CH-1211 Geneva 4, Switzerland

Received: December 22, 2006; In Final Form: February 12, 2007

The conformation and titration curves of weak polyampholytes are examined using Monte Carlo simulations with screened Coulomb potentials in the Grand Canonical ensemble. Two different types of monomers are considered. Depending on the solution pH, monomers A are weak acidic sites that can either be negatively charged or uncharged (as carboxylic groups), whereas monomers B are weak basic sites that can either be positively charged or uncharged (as amino groups). The influence of the chain stiffness, primary structure, and ionic concentration on the acid/base properties of the polyampholyte chains are systematically investigated. By adjusting the pH values, titration curves and then the fractions of positively and negatively ionized charged monomers are calculated. Stiffness influence is estimated by comparing two models of chain: a fully flexible and a rod-like polyampholyte. Different primary structures such as statistical (diblock, octablock, and alternating) and random polyampholytes are also considered. We demonstrate that the primary structure plays important roles in the acid/base properties as well as the charge distribution along the polymer backbone of a statistical rod-like polyampholyte. When flexible polyampholytes are considered, polyampholyte conformations promote the attractive electrostatic interactions between positively and negatively charged monomers, hence leading to more or less compact conformations and acid/base properties relatively different in comparison to the rod-like polyampholytes. Various conformations such as extended, globular, and pearl-necklace conformations are found in good agreement with the literature by adjusting the interaction parameter between monomers and monomer stoichiometry.

Introduction

Charged polymers receive nowadays a lot of attention due to their strong adsorption onto oppositely charged surfaces and important conformational changes in solutions.^{1–6} They are largely encountered in nature as proteins, polysaccharides, and polypeptides and reveal outstanding physical and chemical behaviors to fit the physicochemical properties of living materials to their biological functions. In common terminology, charged polymers are classified as polyelectrolytes (PEs) and polyampholytes (PAs): PEs exhibit one single type of charge, either negative or positive, whereas PAs are copolymers containing both positive and negative charges. Many charged polymers found in nature, including proteins, are in fact PAs. Synthetic PAs are also of interest as they provide simple but useful models to investigate the folding of proteins and properties of biopolymers.⁷

Experimentally,^{8–10} it was shown that the solution behavior of PAs is essentially controlled by their net electrical charge. The net charge $\delta\alpha$ of the chain is generally defined as the absolute value of the difference between the fractions of negatively (α_-) and positively (α_+) charged monomers. It was found that conductivity, viscosity, as well as coil size of PAs had a minima at the isoelectric conditions (i.e., when $\delta\alpha = 0.00$) where most of PAs precipitate.^{8–15} At the isoelectric conditions, viscosity and coil size were also found to increase with the

increase of ionic concentration, suggesting the formation of more open structures.^{11,15} On the other hand, when the net charge of PAs is large, viscosity and coil size are expected to decrease by increasing the ionic concentration, which promotes the chain collapse. In such conditions, PAs having a strong net charge behave like PEs.

To clarify the complexity of the interplay between the repulsive and attractive interactions found on PAs, both analytical models^{16–19} and computer simulations^{20–28} were largely used. The conformations of PAs were first theoretically investigated by Edwards, King, and Pincus.¹⁶ The authors showed that a randomly charge-balanced PA collapses into a globule. Then, Higgs and Joanny¹⁷ investigated the case of a randomly charged PA in the globular state. Charged monomers into the globule were considered to be similar to that of charges in a small volume of a simple electrolyte. They showed that each charge is surrounded by a shell of charges of the opposite sign and suggested that the PA collapses into a globule having a radius of gyration significantly smaller than its value in the absence of charges. As a result, PAs exhibit a strong tendency of self-neutralization without the help of counterions unlike PEs.

The effect of the net charge change on the conformational properties of PAs was investigated by simulations^{20–27} by mainly focusing on random quenched distributions of positively and negatively charges. Kantor and Kardar^{21–23} investigated the conformational properties of a randomly charged linear PA consisting of N_m monomers of size b and charge $\pm q_0$. The mean PA charge was found to be equal to $Q \sim \pm\sqrt{N_m}q_0$. The overall conformation was also found to depend on the net charge Q .

[†] Part of the special issue "International Symposium on Polyelectrolytes (2006)".

* To whom correspondence should be addressed. E-mail: serge.ulrich@cabe.unige.ch.

When Q is less than a critical value, Q_c , it was found that the PA adopts a globular conformation, whereas, when the net charge Q is larger than Q_c , the globule splits into two smaller globules so as to reduce electrostatic repulsions by analogy with the shape instability of charged drops described by Rayleigh.²⁹ Dobrynin, Rubinstein, and Joanny¹⁹ presented a very useful PA state diagram as a function of the net charge and total fraction of charged monomers: Gaussian coil, spherical globule, pearl-necklace, and stretched conformations were found.

Properties of PAs in solution depend not only on the fraction of positively and, respectively, negatively charged monomers but also on their distribution along the chain backbone. Random and block PAs can exhibit contrasting behaviors, and it was shown that PAs are also sensitive to the primary structure and the stoichiometry of the different monomer types.^{18,20,30} Wittmer and co-workers¹⁸ discussed the influence of the primary structure by comparing random and alternating PAs and showed that alternating PAs are more soluble than random distributions. Then, Victor and Imbert²⁰ studied the effect of primary structure on the collapse of charge-balanced PAs using lattice Monte Carlo simulations. Alternating PAs were found to behave like hydrophobic polymers with short-range interactions, and a collapse transition was found similar to the coil–globule transition of a neutral polymer. Sequence influence on PA conformations was investigated by Srivastava and Muthukumar.²⁴ Twenty different linear neutral PAs with positively charged, negatively charged, and neutral monomers randomly distributed along the chain were considered, and the overall composition ratio was the same in each case. Clear differences in the mean-square radii of gyration were observed due to the differences in the location of charges along the chain. The authors showed that the PA radii of gyration depends on the intrachain energy that arises from the electrostatic repulsions between same charges and electrostatic attractions between opposite charges at low temperature.

On the other hand, considerable experimental work has been devoted to the potentiometric titration of charged polymers in aqueous solution.^{31–33} The continuous increase of the apparent pK of a polymeric acid with the degree of ionization was found to be one of the most remarkable features of the dissociation equilibrium of weak PEs in aqueous solution. More recently, titration of PEs have been also largely investigated by computer simulations.^{34–41} In some circumstances, remarkable similarities are found between the different conformations of PAs and those of PE chains in a poor solvent. Indeed, by adjusting the solvent quality for polymer backbone and $pH-pK_a$ value, it was shown that a PE can exhibit various different conformational states that are also observed for PAs: coil, collapsed spherical globule, stretched chain, cigar-shape-like aggregate, and pearl-necklace conformations.^{34,42}

More specific conformations of a diblock PA with increasing degree of ionization were experimentally described in light of viscosity data. It was found that pairing of oppositely charged monomers leads to a kind of cross-linked structure.⁴³ Wang and Rubinstein⁴⁴ recently investigated the conformational properties of symmetric flexible diblock PAs by scaling theory and simulations. They demonstrated that, in some conditions, the electrostatic attraction causes the chain to fold through the overlap of the two blocks and each block is slightly stretched by self-repulsion.

Acid dissociation constants of alternating PAs made of acrylic acid (AA) and 4-vinylpyridine (4VP) were determined using pH titration methods by Masuda and co-workers.⁴⁵ It was shown that the concentration of the protonated form of the alternating

copolymer exists in the lower pH range and decreases with the increase of solution pH until $pH = 6$ and the deprotonated form begins to appear around $pH = 9$. On the other hand, it was found that the neutral forms were present over a wide range of pH, in equilibrium with zwitterionic molecules. Neutral molecules were largely predominant over the zwitterionic molecules. The authors compared these pH distribution curves with those of mixtures of AA and 4VP monomers in which zwitterionic and neutral molecules coexisted in a limited range of pH with predominance for the zwitterionic molecules. The paper clearly shows the influence of polymerization on acid/bases properties of a PA.

The ionic equilibrium in aqueous solutions of PAs made of acrylic acid and 2-methyl-5-vinylpyridine of various compositions was experimentally investigated.¹¹ The protonation degree of base and dissociation degree of the acid groups and the ionization constant of methylvinylpyridine groups for the isoelectric conditions were assessed spectrophotometrically and via viscometric titration. It was found that the basicity of methylvinylpyridine groups increases in proportion to the content of acid groups.

The aim of the present paper is to explore PA conformations and investigate in a systematic way the influence of the PA primary structure, stoichiometry, solution ionic concentration, and stiffness on the acid/base properties of PAs. For that purpose, Monte Carlo simulations will be used. Because the knowledge of protein structure is essential for a number of applications, and because proteins bear a structural resemblance to PAs having a distribution of neutral and charged amino acids, two monomer types are considered in our PA model. The nature of each monomer is identified from the mean pK_a value of amino and carboxyl groups found in proteins. It is assumed that the first type of monomer is representative for the mean acid/base properties of carboxylic groups (monomer A), whereas the second type is chosen so as to be representative of the acid/base properties of amino groups (monomer B).

Considering two different monomers A and B, when the monomer distribution along a linear chain is correlated, the PA is referred to as statistical PA. On the other hand, when there are no correlations in the monomer distribution, the PA is denoted random. We will consider two sections: In section I, statistical PAs will be first investigated by considering diblock, octablock, and alternating PAs, whereas, in section II, random PAs will be considered. In all cases, PAs are composed of a fixed distribution of monomer sequence. Nonetheless, it should be noted that the charge distribution is annealed.

Model Description

An isolated linear polyampholytes (PA) is simulated with the assumption of a very dilute solution. The PA chain is represented as a succession of N_m freely jointed spheres of radius R_m . The usual interaction parameter u is defined as

$$u = \frac{l_B}{2R_m} \quad (1)$$

where l_B represents the Bjerrum length, which is equal to 7.14 Å at $T = 298$ K in water. Hard-sphere repulsions between monomers are described using hardcore interactions. Stiffness influence follows from the direct comparisons of two chain models (Figure 1): (i) a rod-like chain that cannot change its conformation during simulation (model 1) and (ii) a flexible chain (model 2).

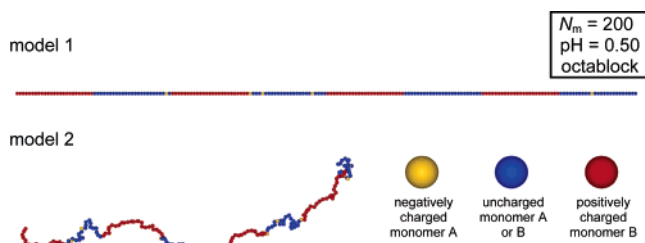


Figure 1. Two models of chains were considered to investigate chain flexibility influence. Model 1 consists of a rod-like chain, whereas model 2 is a flexible chain. The total number of monomers is set to $N_m = 200$ in all simulations. The rod-like cannot change its conformation during simulations. Negatively charged monomers A are represented by yellow spheres, whereas positively charged monomers B are represented by red spheres. Both non-charged monomers A or B are represented by blue spheres. The case of the octablock polyampholyte chain at $\text{pH} = 0.50$ was arbitrarily chosen here.

The long-range repulsive electrostatic potential along the distance r_{ij} between charged monomers i and j is described via a screened Debye–Hückel potential:⁴⁶

$$u_{\text{el}}(r_{ij}) = \frac{z_i z_j e^2}{4\pi\epsilon_r \epsilon_0 r_{ij} k_B T} \frac{\exp[-\kappa(r_{ij} - (R_i + R_j))]}{(1 + \kappa R_i)(1 + \kappa R_j)} \quad (2)$$

where e is the elementary charge ($e = 1.6 \times 10^{-19}$ C), ϵ_0 the permittivity of the vacuum ($\epsilon_0 = 8.85 \times 10^{-12}$ C V⁻¹ m⁻¹), and z_i the amount of charge on the monomer i . R_i represents the radius of the spherical monomer i . The solvent is treated as a dielectric continuum of a given permittivity $\epsilon_r = 78.5$ equal to that of water at $T = 298$ K. The overall effect of free ions on interactions are described via the dependence of the inverse Debye screening length κ .

The chemical equilibrium of a charged polymer with hydrogen ions in aqueous solution is determined by the intrinsic dissociation of the various ionizable groups. Our chain model considers two types of monomers: monomers A and monomers B (Figure 1). The total number of monomer is set to $N_m = 200$. The total number of monomer A is noted N_A and the total number of monomer B is noted N_B . The ratio $\eta = N_B / N_A$ is introduced here to describe the stoichiometry of a chain. A balanced stoichiometry is reached when $\eta = 1.00$.

Each of the N_A monomers represents a weak acidic site that can either carry a negative charge $z_m = -1$ on its center or be uncharged. The dissociation of an isolated acid monomer (HA) in an aqueous solution is given by



According the law of mass action, the equilibrium constant is

$$K_a^A = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]} \quad (4)$$

The $\text{p}K_a^A$ value was arbitrarily set to 2.17 in order to simulate the mean acid/base property of a carboxylic group in amino acids.

On the other hand, each of the N_B monomers represents a titrating site that can either carry a positive charge $z_m = +1$ on its center or be uncharged. The dissociation of an isolated base monomer (BH^+) is given by



with an equilibrium constant given by

$$K_a^B = \frac{[\text{B}][\text{H}^+]}{[\text{BH}^+]} \quad (6)$$

The $\text{p}K_a^B$ value was arbitrarily set to 9.53 in order to simulate the mean acid/base properties of an amino group in amino acids. Thus, it is assumed that the carboxyl groups (monomers A) are protonated (neutral monomers) when $\text{pH} < \text{p}K_a^A$ and deprotonated when $\text{pH} > \text{p}K_a^A$ (negatively charged). On the other hand, the amino groups (monomers B) are protonated (positively charged) when $\text{pH} < \text{p}K_a^B$ and deprotonated (neutral monomers) when $\text{pH} > \text{p}K_a^B$. Hence, positive and negative monomers will coexist when $\text{p}K_a^A < \text{pH} < \text{p}K_a^B$, whereas mainly positively (negatively) and neutral monomers will be present when $\text{pH} < \text{p}K_a^A$ ($\text{pH} > \text{p}K_a^B$) (see Figure 2a).

In the absence of electrostatic interactions, according to the solution pH, the fraction α_- of negatively charged monomers is defined as

$$\alpha_- = \left(\frac{N_A}{N_m} \right) \left(1 + \frac{[\text{H}^+]}{K_a^A} \right)^{-1} \quad (7)$$

On the other hand, the fraction α_+ of positively charged monomers is defined as

$$\alpha_+ = \left(\frac{N_B}{N_m} \right) \left(1 + \frac{K_a^B}{[\text{H}^+]} \right)^{-1} \quad (8)$$

Subsequently, the fraction α_0 of neutral monomers is described as

$$\alpha_0 = \left(\frac{N_A}{N_m} \right) \left(\frac{[\text{H}^+]}{[\text{H}^+] + K_a^A} \right) + \left(\frac{N_B}{N_m} \right) \left(\frac{K_a^B}{K_a^B + [\text{H}^+]} \right) \quad (9)$$

The condition $\alpha_- + \alpha_+ + \alpha_0 = 1.00$ is then always respected. Curves calculated from eqs 7 to 9 are considered as ideal curves and are presented in Figure 2b when $\eta = N_B / N_A = 1.00$ (balanced stoichiometry, i.e., when the number of monomers A is equal to the number of monomers B).

Monte Carlo simulations were performed according to the Metropolis algorithm. On the one hand, chain conformations are sampled to obtain a reasonably low energy conformation. To generate new conformations, the monomer positions are randomly modified by elementary random movements: end-bond, kink-jump, and pivot. On the other hand, to simulate the titrating behavior, a Grand Canonical ensemble with a fixed bulk chemical potential for the protons is used to generate reversible protonation/deprotonation processes: at regular simulation steps, monomers are chosen randomly in the limit of $N_m/4$ monomers and their charge states are modified. In order to achieve an efficient conformational relaxation of the chain after switching on or off charged monomers, the protonation/deprotonation procedure is less frequent than that of the monomer movements.

The acceptance of each “trial” is related to the Monte Carlo Metropolis selection criterion. The energy variation associated with the probability for accepting a new charge state is the sum of the change in the electrostatic interaction ΔE_c and a term that corresponds to the change in free energy of the intrinsic association reaction of a monomer^{47,48}

$$\Delta E_{\text{tot}} = \Delta E_c \pm \chi \ln(10)(\text{pH} - \text{p}K_a^i) \quad (10)$$

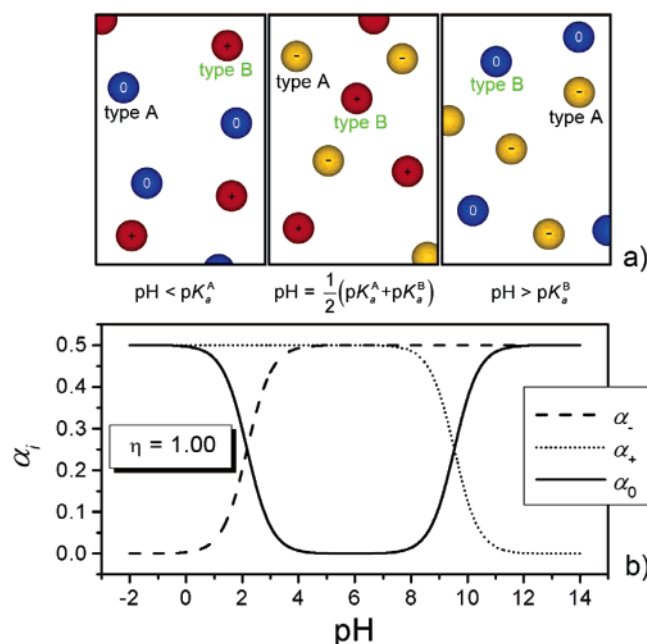


Figure 2. (a) Schematic representation of the species present at different pH conditions. When $\text{p}K_a^A < \text{pH} < \text{p}K_a^B$, both monomer types are expected to be charged. When $\text{pH} < \text{p}K_a^A$, only monomers B are charged, whereas when $\text{pH} > \text{p}K_a^B$, only monomers A are charged (ideal conditions). (b) Ideal titration curves in absence of electrostatic interactions. Fractions of positive α_+ , negative α_- , and neutral α_0 monomers with $\alpha_+ + \alpha_- + \alpha_0 = 1.00$ are represented as a function of the solution pH. A balanced stoichiometry is imposed.

where pH is an imposed input parameter. When the monomer is protonated, the plus sign is used in eq 10 (conversely, when the monomer is deprotonated, the minus sign is required). The constant χ is equal to +1 or −1 when monomer A ($\text{p}K_a^i = \text{p}K_a^A$) or B ($\text{p}K_a^i = \text{p}K_a^B$) is, respectively, considered.

Results and Discussion

I. Statistical Polyampholytes. In this section, we discuss simulation results by considering independently three different primary structures $[A_n B_m]_m$: (i) a diblock PA with $n = 100$ and $m = 1$, (ii) an octablock PA with $n = 25$ and $m = 4$, and (iii) an alternating PA with $n = 1$ and $m = 100$. A balanced stoichiometry is imposed because $\eta = 1.00$ in all cases and the interaction parameter u is set to 1.00.

In this section, for the sake of clarity all titrating curves of polyampholytes (PAs) are compared with the corresponding ideal curves.

A. Rod-like Polyampholyte. The influence of the primary structure on the acid/base properties behavior of a rod-like PA (model 1) that cannot change its conformation during simulations is first investigated. The ionic concentration is fixed to $C_i = 0.001$ M to enhance the effects of the electrostatic interactions between the monomers. The corresponding titration curves are presented in Figure 3.

Considering first the diblock PA (Figure 3a) and the fraction of charged monomers A, as expected when $\text{pH} < \text{p}K_a^A$, α_- is close to zero because most of the monomers A are uncharged. By increasing the pH value, the variation of α_- as a function of the pH largely differs from the ideal case. The titration curve is shifted to the right of the ideal curve, suggesting that higher pH values are required to obtain a given value of α_- . In other words, to minimize electro-repulsive interactions between the negatively charged monomers A inside the A block, the charging

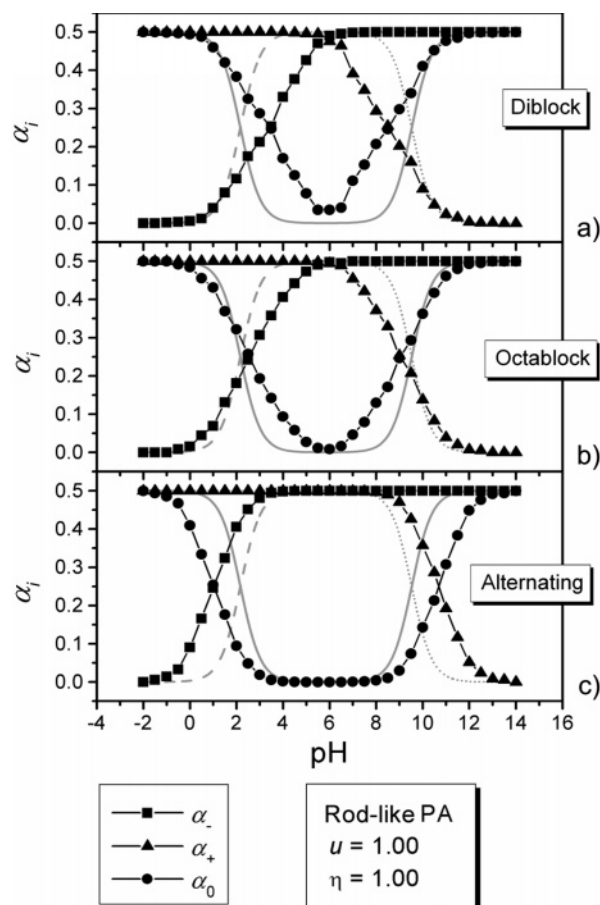


Figure 3. Titration curves of rod-like polyampholytes. The primary structures strongly influence the acid/base properties of the rod-like polyampholyte. Ideal titration curves are also represented to make comparison with titration curves. By comparison with the ideal titration curves, it is shown how the PA structures influence the acid/base properties of the PAs. In particular, alternating structure promotes the coexistence domain of both negative and positive charges.

process of monomers A is strongly shifted to higher pH values. Symmetrically, to reduce electro-repulsive interactions of the positively charged monomers B inside the B block, the neutralization process of monomers B is strongly shifted to lower pH values. Owing to the connectivity between the monomers, monomers charging process is hence strongly reduced, and a small fraction of neutral monomers is still present when $\text{pH} = 1/2(\text{p}K_a^A + \text{p}K_a^B)$. As monomer ionization is not promoted, the domain of existence of neutral monomers is larger than the ideal case.

For the sake of clarity for the interpretation and discussion of titration curves, we define $\Delta\alpha_i$ as

$$\Delta\alpha_i = \omega(\alpha_i^{\text{ideal}} - \alpha_i^{\text{chain}}) \quad (11)$$

where α_i^{ideal} is the fraction of ionized monomers in the ideal case and α_i^{chain} is the fraction of ionized monomers in the polymeric chain at a given pH. When i is negative (positive), then $\omega = -1$ (+1). As a result, when $\Delta\alpha_i > 0$, the inversion of monomer state of charges is promoted, whereas, when $\Delta\alpha_i < 0$, the inversion of monomer state of charges is not promoted. The variations of $\Delta\alpha_i$ as a function of the pH are presented in Figure 4. In the case of the rod-like diblock PA, when $0.50 < \text{pH} < 6.50$, then $\Delta\alpha_- < 0.00$ (Figure 4a). The shift is connected with the increasing difficulty to remove protons from the A block with the increase of negatively charged groups.^{31,38} It

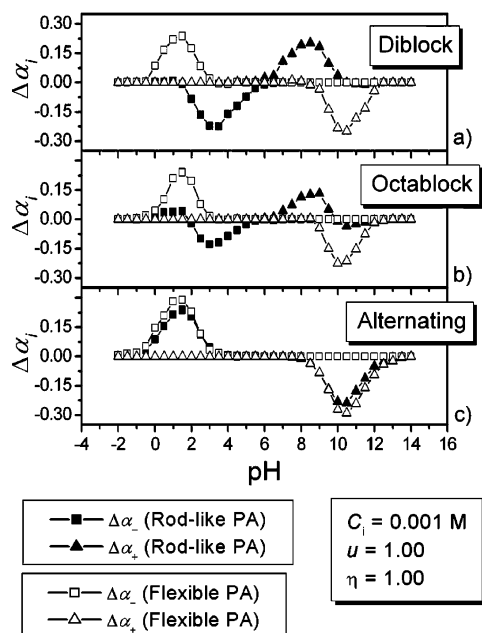


Figure 4. Variation of $\Delta\alpha_i$ as a function of the solution pH. Both rod-like and flexible polyampholytes are considered. When $\Delta\alpha_i > 0.00$, the inversion of monomer state of charge is promoted, whereas it is not promoted when $\Delta\alpha_i < 0.00$. It is shown here how (i) the primary structure and (ii) the chain flexibility promotes (or not) the charging process of monomers A and B.

should be noted that $\Delta\alpha_- = 0.00$ when $\text{pH} < 0.50$ and $\text{pH} > 6.50$. Thus, in such a pH domain, the PA behaves like the ideal case. The variation of $\Delta\alpha_+$ as a function of the pH, on the other hand, indicates that $\Delta\alpha_+ \geq 0.00$ when $\text{pH} < 11.00$ because monomers B are mainly surrounded by monomers having the same charge. Moreover, $\Delta\alpha_+$ is equal to zero when $\text{pH} > 11.00$.

Two particular points have to be considered here when $\text{pH} = 0.50$, where $\Delta\alpha_-$ is positive and when $\text{pH} = 11.00$ where $\Delta\alpha_+$ is negative. These behaviors are due to the heterogeneous charging process along the diblock PA. For the sake of clarity, the mean degree of ionization of a monomer $\langle\alpha_i(j)\rangle$ as a function of its position j on the polymer backbone is presented in Figure 5 for different pH values. The variation of $\langle\alpha_i(j)\rangle$ as a function of j with $1 \leq j \leq 100$ indicates that a uniform distribution is observed when $\text{pH} = -2.00$. Then, by increasing pH, it is clearly demonstrated that charges accumulate preferentially near the already charged B block and at the end of the chain. This inhomogeneous distribution disappears when the block becomes fully charged at $\text{pH} \approx 6.00$, i.e., when the A block is close to be fully charged. Symmetric observations can be made by considering the deprotonation of monomer B with $101 \leq j \leq 200$. Figure 5b demonstrates that neutral monomers preferentially appear in the central part of the B block with the increase of pH.

Considering the titration curves of an alternating rod-like PA (Figure 3c), by increasing the pH value, the titration curve of monomer A is shifted to smaller pH values. The ionization of monomer A is clearly here made easier by the presence of neighboring oppositely charged monomers B and with regard to the variation of $\Delta\alpha_-$ as a function of pH in Figure 4c ($\Delta\alpha_-$ is found ≥ 0.00). On the other hand, at low pH, the fraction of positively charged monomers α_+ is identical to the ideal case. By furthermore increasing the solution pH, the titration curve is shifted to larger pH; i.e., the neutralization of monomers B surrounded by two oppositely charged monomers A is not favorable. As a result, the variation of $\Delta\alpha_+$ as a function of the pH (Figure 4c) shows that $\Delta\alpha_+ \leq 0.00$ in the whole pH range.

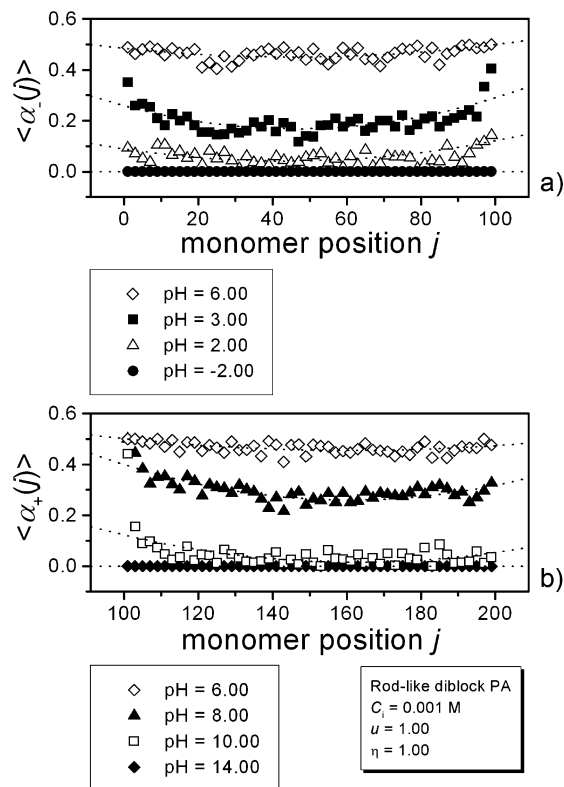


Figure 5. Mean degree of ionization $\langle\alpha_i(j)\rangle$ of a monomer j . A diblock rod-like polyampholyte is here arbitrarily considered. (a) Mean degree of ionization of a monomer A $\langle\alpha_-(j)\rangle$ as a function of its position j when $\text{pH} = -2.00, 0.00, 2.00, 3.00$, and 6.00 . (b) Mean degree of ionization of a monomer B $\langle\alpha_+(j)\rangle$ as a function of its position j when $\text{pH} = 6.00, 8.00, 10.00$, and 14.00 . $\langle\alpha_i(j)\rangle$ is rather uniform at small (symmetrically large pH values) and when pH is close to $1/2(\text{p}K_a^A + \text{p}K_a^B)$. However, accumulation of charge toward PA extremities as well as at the block junction is observed at intermediate pH conditions.

It should be observed that, in the case of an alternating rod-like PA, in good agreement with experimental observations,⁴⁵ the net charge is found to be equal to zero in a large range of pH. Moreover, the domain of existence of neutral monomers is smaller than the ideal case.

Considering the case of the octablock PA (Figures 3b and 4b), intermediate trends are observed: at small pH values, $\Delta\alpha_-$ increases with the increase of the solution pH, then decreases to reach the 0 value at $\text{pH} \approx 2.00$ (hence, at this point, the acid/base properties of monomers are similar to the ideal case) and achieve negative values. Symmetrically, $\Delta\alpha_+$ increases with the increase of the solution pH, decreases to reach the 0 value, and then becomes negative. In the case of an octablock rod-like PA, the net charge is found to be equal to zero in a large range of pH. Moreover, the domain of existence of neutral monomers is larger than the ideal case.

Such behaviors clearly demonstrate that (i) the monomers of one type (A or B) close to charged monomers of the other type on the PA backbone are preferentially ionized and (ii) charged neighboring monomers of the same type tend to preferentially be uncharged.

B. Flexible Polyampholyte. To determine the influence of conformational changes on titration curves, simulations are carried out at $C_i = 0.001, 0.01$, and 0.1 M using flexible PAs. Experimentally, viscosity as well as coil size of PAs had a minima at the isoelectric conditions due to attractive interactions. On the other hand, out of the isoelectric conditions, both were found to increase with the increase of net charge because of the electrostatic repulsions.^{8–15} The effects of the primary

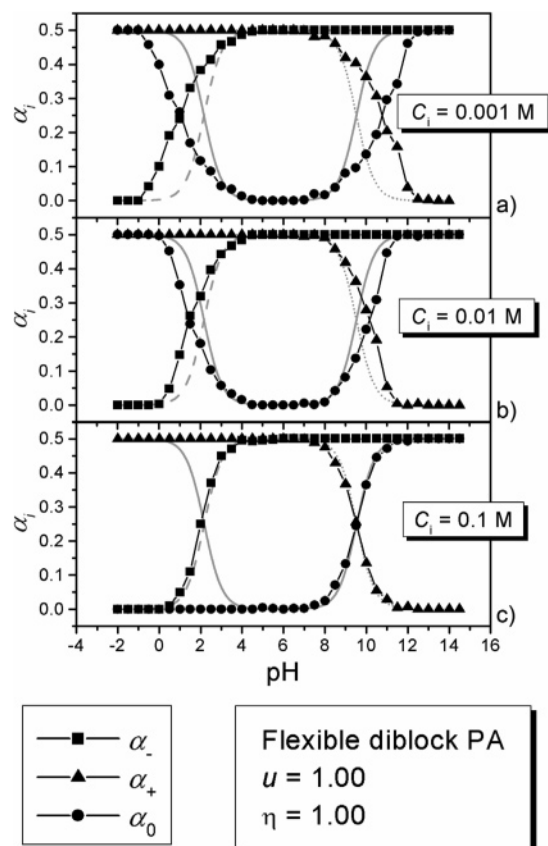


Figure 6. Titration curves of flexible diblock polyampholyte at various ionic concentration (a) $C_i = 0.001$, (b) $C_i = 0.01$, and (c) $C_i = 0.1$ M. As the importance of the electrostatic interactions are controlled by the ionic concentration, the increase of charge screening makes the difference between titration curves of PAs and the ideal curves less important.

structure are also investigated by considering independently the case of the diblock, octablock, and alternating flexible PAs.

The titration curves of a flexible diblock PA are presented in Figure 6. Chain flexibility influence is clearly observed by comparison with Figure 3a at $C_i = 0.001$ M (Figure 6a). When the flexible model is considered, the ionization of monomers A and B is clearly promoted at a given pH value. Hence, the variation of $\Delta\alpha_i$ as a function of pH for model 1 is very different from model 2 (Figure 4a).

It should be observed that, whatever the primary structure, flexibility allows the PAs to adopt conformations that optimize the attractive electrostatic interactions. As a result, all the $\Delta\alpha_i$ variations as a function of pH are analogous to the variation of the alternating rod-like PA. When the pH increases, the inversion of monomer charge state is promoted until isoelectric conditions are reached. Then, by furthermore increasing the solution pH, the inversion of monomer state of charges is made more difficult. Small differences between the diblock, octablock, and alternating structures are observed and arise from the different primary structures, which allow more or less conformational changes.

To get an insight into the PA structures at various pH and primary structures, equilibrated conformations are presented in Table 1 as a function of the pH. It is observed here that important conformational changes arise with the pH and charge fraction of the PAs. Indeed, extended as well as coil and collapsed conformations are observed. To quantitatively characterize flexible PA conformational changes with the pH, the mean-square radius of gyration $\langle R_g^2 \rangle$ is calculated and presented in Figure 7a.

TABLE 1: Equilibrated Conformations of Flexible Polyampholytes at Ionic Concentration $C_i = 0.001$ M, $\eta = 1.00$, and $u = 1.00$ as a Function of Solution pH^a

		Primary structure		
		diblock	octablock	alternating
pH	-2.00			
	0.00			
	2.00			
	4.00			
	6.00			
	8.00			
	10.00			
	12.00			
	14.00			

^a The primary structure has important effects on the polyampholyte conformation. In particular, when a diblock is considered, the uncharged block has a coiled structure, whereas the charged block has an extended conformation. This is not the case for the alternating polyampholyte where the homogeneous distribution of charges leads to the formation of extended conformations. At intermediate pH, the presence of both positive and negative charges promotes the formation of more compact conformations. In good agreement with previous works,^{43,44} at pH = 0.00 and pH = 2.00, the two blocks overlap each other and they are stretched by electrostatic repulsions between monomers of same signs.

When $\text{pH} < \text{pK}_a^A$, the monomers B are fully charged, whereas the monomers A are not charged. Regarding the flexible diblock PA, the charged block adopts a stretched conformation, whereas the second uncharged block adopts a self-avoiding walk (SAW) conformation (same situation is symmetrically observed when $\text{pK}_a^B > \text{pH}$). By increasing the pH, because the fraction of monomers A is also increasing, to promote from a conformational point of view the electrostatic interactions via ion pairing, the diblock PA is broken in half through the overlap of the two blocks and each block is stretched by self-repulsion^{30,43} (see Table 1, pH = 0.00).

On the other hand, regarding the flexible octablock PA, the repulsions between blocks force the uncharged block to be more stretched. Then, when only positive or negative monomers are present, the radii of gyration are larger when octablock and alternating PA are considered.

In good agreement with experimental observations^{8–11} and Higgs and Joanny results,¹⁷ chain size is found to be at a minimum when only positive and negative monomers are present. The electrostatic interactions create correlations between charged monomers of opposite signs, and a shell of charges of the opposite sign tends to appear to surround each charge. The

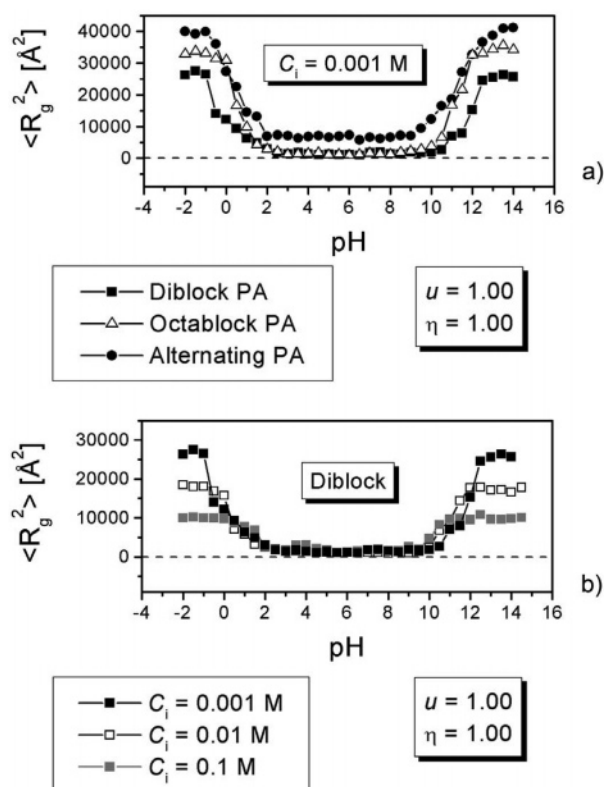


Figure 7. (a) Mean-square radius of gyration $\langle R_g^2 \rangle$ of the diblock, octablock, and alternating polyampholytes as a function of pH for flexible polyampholyte with $N_m = 200$ and $u = 1.00$. (b) Mean-square radius of gyration $\langle R_g^2 \rangle$ as a function of pH for a flexible diblock polyampholyte with $N_m = 200$ and $u = 1.00$. At low and high pH values, the PAs achieve stretched conformations, whereas, at intermediate pH values, polyampholytes achieve more compact structures. Little influence of ionic concentration is observed in that regime for the diblock structure.

radii of gyration of the di- and octablock PAs are equivalent at the isoelectric point.

When block PAs are considered, it is generally accepted that globular conformations are achieved when $\delta\alpha$ is close to 0. In such conditions, the collapsed volume of the di- and octablock PAs, V_{block} , is found to be equal to $2.45 \times 10^5 \text{ \AA}^3$ from our simulations. V_{block} is larger than the volume of the completely close-packed monomers $V_{\text{close-packed}}$ (theoretically estimated with $N(2R_m)^3 = 7.28 \times 10^4 \text{ \AA}^3$) but smaller than the Gaussian volume V_{Gaussian} (theoretically estimated with $N^{3/2}(2R_m)^3 = 1.03 \times 10^6 \text{ \AA}^3$). As $V_{\text{close-packed}} < V_{\text{block}} < V_{\text{Gaussian}}$, di- and octablock PAs conformations are termed as “dilute” globules in good agreement with ref 17.

On the other hand, for the alternating PA, the radius of gyration is found larger than the di- and octablock PAs at the isoelectric condition with $V_{\text{Gaussian}} < V_{\text{alternating}} = 2.19 \times 10^6 \text{ \AA}^3$. The subtle balance between attractive and repulsive electrostatic interactions results in the swelling of the alternating PA chain compared to the di- and octablock PAs.

By arbitrarily considering the case of a flexible diblock PA, the influence of ionic concentration on titration curves and conformations is here shortly discussed. In Figure 6 are presented the corresponding titration curves at different ionic concentrations. At low ionic concentration, titration curves change appreciably from the ideal curves because of the importance of the electrostatic interactions. By increasing the ionic concentration and thus screening effects, the shifts that we discussed above (i.e., when $C_i = 0.001 \text{ M}$) are attenuated.

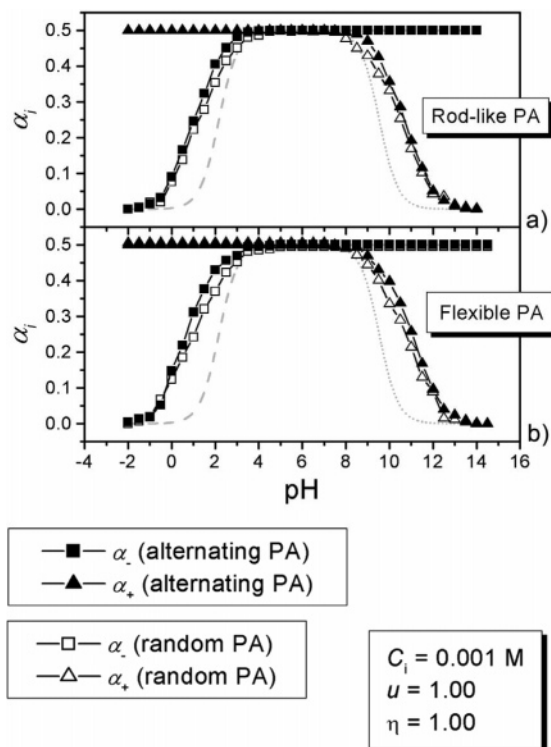


Figure 8. Titration curves of charged balanced ($\eta = 1.00$) (a) rod-like alternating and random polyampholytes and (b) flexible alternating and random polyampholytes. Random and alternating polyampholytes are compared. In both cases, ionization of both monomers is made easier for the regularly alternating polyampholytes.

As a result, when $C_i = 0.1 \text{ M}$, the titration curves of the diblock flexible PA lie close to the ideal curves.

The mean-square radius of gyration $\langle R_g^2 \rangle$ of the flexible diblock PA is calculated and presented as a function of pH in Figure 7b for different ionic concentration. When only positive or negative monomers are present, it decreases with the increase of the ionic concentration. On the other hand, when only positive and negative monomers are both present, the chain adopts “dilute globule” conformations. It was shown theoretically and confirmed experimentally that the chain expansion of polyampholytes takes place at the isoelectric conditions with increasing ionic concentration.^{11,15} In such conditions, Higgs and Joanny¹⁷ found that the chain conformation is only significantly affected by the increase of ionic concentration if the salt concentration is higher than the concentration of polymeric charges. At pH = 6.00, in our case, because the concentration of diblock polymeric charges is equal to 1.35 M, the mean-square radius of gyration $\langle R_g^2 \rangle$ is not significantly affected by the variation of the ionic concentration; i.e., $0.001 \text{ M} \leq C_i \leq 0.1 \text{ M}$. This is clearly demonstrated in Figure 7b.

II. Random Polyampholytes. In this section, we carried out simulations by considering the case of PAs having a randomly distribution of A and B monomers to investigate the influence of the monomer stoichiometry. In the first part, a balanced stoichiometry ($\eta = 1.00$) is imposed, whereas the stoichiometry is varied in the second part. The influence of the interaction parameter u is also investigated by considering two values; i.e., $u = 1.00$ and $u = 3.57$.

A. Balanced Stoichiometry. The obtained titration curves are very similar whatever the random distribution of monomer type when $C_i = 0.001 \text{ M}$, $u = 1.00$, and $\eta = 1.00$. Titration curves of an arbitrarily chosen random PA are presented in Figure 8 when (a) a rod-like and (b) a flexible PAs are, respectively,

TABLE 2: Equilibrated Conformations of Flexible Polyampholytes at Ionic Concentration $C_i = 0.001$ M and $\text{pH} = 6.00^a$

		Interaction parameter u	
		1.00	3.57
η	1.00		
	11/9		
	3/2		
	7/3		
	4.00		

^a The monomer distribution is random. The polyampholyte composition $\eta = N_B/N_A$ is adjusted to 1.00, 11/9, 3/2, 7/3, and 4.00. Two interaction parameters u are considered with $u = 1.00$ and 3.57. By increasing the charge asymmetry, the repulsions between the excess of charges result in the chain extension, and depending on the interaction parameter, globular, pearl-necklace, and extended conformations are observed.

considered. They are compared with the titration curves of regularly alternating PAs in the same conditions. The differences between the random and alternating PAs are expected to arise from the random distribution of A and B monomers along the PA backbone. Considering random or alternating PAs, both titration curves of monomers A are shifted to smaller pH values and the ionization of monomer A is made easier. On the other hand, both titration curves of monomers B are shifted to larger pH values meaning that the neutralization of monomers B is not favorable. Nonetheless, it should be noted that these effects are clearly more pronounced when an alternating PA is considered owing to the regular positive and negative monomer type distribution, which promotes “short range” electrostatic interactions.

On the other hand, flexibility clearly allows the chain to adopt conformation to optimize the “long range” attractive electrostatic interactions by promoting compact conformations.

B. Unbalanced Stoichiometry. Five different compositions of flexible random PAs and two interaction parameters u are considered here: $\eta = 1.00$, 11/9, 3/2, 7/3, and 4.00; $u = 1.00$ and $u = 3.57$. It should be noted that the total number of monomer N_m is equal to 200 for any values of η . Moreover, at a given ratio η , the randomly monomer type distribution is the

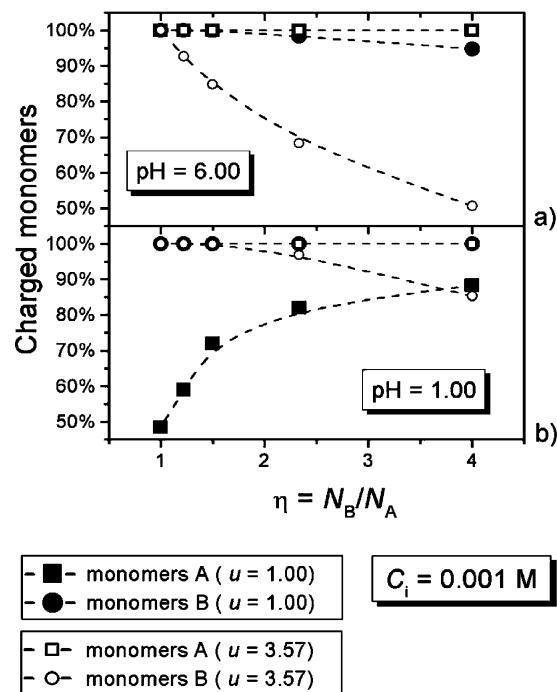


Figure 9. Variation of the percentage of negatively and positively charged monomers as a function of ratio $\eta = N_B/N_A$ when a flexible random polyampholyte is considered. It is clearly observed that the charging process of a weak random PA chain strongly depends on the solution pH, the interaction parameter u , and the stoichiometry. When an excess of monomer B is considered, the corresponding percentage of charged monomers is decreasing, whereas the percentage of charged monomers A is observed to increase.

same whatever the interaction parameter u . Equilibrated conformations at $\text{pH} = 6.00$ are presented in Table 2.

In qualitatively good agreement with Dobrynin, Rubinstein, and Joanny,¹⁹ when $\eta = 1.00$ and $u = 1.00$, PAs adopt close-to-Gaussian coil conformations. By increasing the charge asymmetry, the repulsions between the excess of charges stretch the chain to form extended conformations. By increasing the interaction parameter to $u = 3.57$, when $\eta = 1.00$, the chain adopts a more spherical globular shape. When $\eta = 11/9$, the pearl-necklace conformation is observed. Then, by furthermore increasing the charge asymmetry, the PA chain stretches again.

The variation of the percentage of charged monomers A and B as a function of η is presented in Figure 9a at $\text{pH} = 6.00$ and $u = 1.00$. When $\eta = 1.00$, all the monomers, A or B, are charged. Figure 9a demonstrates that monomers of type A are fully charged at $\text{pH} = 6.00$ for every investigated value of η . On the other hand, due to the importance of both electrostatic repulsion forces between monomers B and electro-attractive forces between monomers A–B, the percentage of charged monomers B slightly decreases when η increases. Due to the increase of electrostatic interactions, this effect is more pronounced when $u = 3.57$ and the percentage of charged monomers B dramatically decreases with the increase of the ratio η . Nonetheless, the increase of u does not change the percentage of charged monomers A.

By considering now the pH of the solution equal to 1.00, the variation of the percentage of charged monomers A and B as a function of η is presented in Figure 9b. When $u = 1.00$ and $\eta = 1.00$, all monomers B are charged, whereas less than 50% of monomers A are charged. By adjusting the η value, Figure 9b shows that monomers of type B are fully charged for every investigated value of ratio η . On the other hand, due to electro-attractive effects and the decrease of the total number of

monomers A, the percentage of charged monomers A increases when η increases. This is in good agreement with the experimental work that investigated the potentiometric behavior of several PAs with different compositions of 2-vinylpyridine and methacrylic acid.¹² It was found that increasing the acid content caused a larger dissociation of the basic groups.

When $u = 3.57$, electro-attractive effects are strong and all the monomers A are charged in the whole investigated range of η . Once again, because charge distances are decreased, hence promoting repulsive electrostatic effects, the percentage of charged monomers B decreases when η increases. It is then clearly demonstrated that the charging process of a weak random PA chain strongly depends on (i) the solution pH, (ii) the interaction parameter u , and (iii) the stoichiometry. McCormick and Salazar¹³ similarly showed that the effects of composition on the viscosity depend of the ionic concentration. Indeed, significant differences due to composition were found at low ionic concentration, where the effect of the electrostatic balance is strong.

Conclusions

In this paper, the acid/base properties and titration curves of a weak polyampholyte chain were investigated using Monte Carlo Simulations and a coarse-grained model. The coarse-grained model used here has no direct connection to any specific polyampholyte. It is a generic model retaining only features common to a class of polyampholytes. Two different types of monomers were considered: a weak acid (type A with $pK_a^A = 2.17$) and a weak base (type B with $pK_a^B = 9.53$). Depending on the solution pH, monomers A were either negatively charged or uncharged, whereas monomers B were positively charged or uncharged.

Considering rod-like polyampholytes, primary structures were found to play a key role in the acid/base properties of the chains. A heterogeneous charging process along the rod-like polyampholytes was put in evidence, and it was clearly demonstrated that charges accumulate preferentially near already charged monomers of opposite charges and at the chain or block extremities. It was shown that flexibility allows the polyampholytes to optimize ion pairing by adopting dense conformation in the isoelectric conditions. Ionization of monomers was observed to be promoted, and only small differences between the different primary structures of polyampholytes were noted. It was clearly demonstrated that the charging process of a weak polyampholyte chain strongly also depends on the interaction parameter and monomer stoichiometry. By increasing the charge asymmetry, the repulsions between the excess of charges resulted to the chain extension, and depending on the interaction parameter, cross-linked and pearl-necklace conformations were observed.

It is shown that computer simulations can isolate, in good agreement with experimental and analytical theory, the factors that control the acid/base properties of polyampholyte chains and, thus, help to address the optimization of polyampholyte solutions where polyampholytes electric properties and conformations are expected to play a key role. Two monomer types having characteristic pK_a values were used, but the model could be extended to consider several types of monomers with specific pK_a values so as to mimic the behavior of biopolymers.

Acknowledgment. We express our thanks to Professor M. Borkovec, Professor J. Buffle, Dr. A. Laguecir, and Dr. N.

Parthasarathy for their encouragements and stimulating discussions. We also gratefully acknowledge the financial support received from the Fond National Suisse (200020-101974/1).

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