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Conformational Behavior of Poly(*N*-vinylimidazole). Potentiometric Titration, Viscosity, and Proton Nuclear Magnetic Resonance Studies

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ABSTRACT: The effect of protonation on the conformation of poly(*N*-vinylimidazole) was studied by potentiometry, viscometry, and ^{1}H NMR spectroscopy. The polymer coil contracts during the initial stages of protonation but then expands upon further protonation. The conformational changes are discussed in terms of competition between an internal hydrogen bonding between protonated and nonprotonated rings and charge repulsion. The initial contraction requires that the hydrogen bonding involves non-nearest-neighbor imidazole rings.

The catalytic properties of imidazole-containing polymers have interested a number of workers.[1] Some of these polymers show unusual specificity to the substrate in their catalytic action and so have been considered as possible models for enzymes.[2] Several of these polymers also bind metals very strongly[3–5] and, in that sense, might be analogous to the metal-containing enzymes, where the imidazole group is found in the histidyl residue.

It is believed that the conformations of imidazole-containing polymers play an important role in their catalytic behavior.[6] The ability to form complexes with transition-metal ions also presumably depends on the ability of the polymer to assume a conformation which facilitates chelation. Nevertheless, relatively few details of the conformational behavior of poly(*N*-vinylimidazole) have been investigated.[7]

Information about the conformation of ionizable polymers in solution is often obtained from potentiometry and viscosity measurements.[8–11] Such methods are useful in drawing conclusions about whether the overall conformation of the polymer is extended or contracted, and changes in conformation induced by changes in pH, ionic strength, and temperature, for example, can often be detected. Details about the nature of the conformation or conformational transitions at a local level are much more difficult to obtain.

NMR spectroscopy has been a powerful tool for the determination of conformations of small molecules[12] and has the potential for giving information about the local conformation of polymers.[13] It was our hope that, by combining potentiometric titration, viscosity, and NMR techniques, we could obtain a more complete conformational description of poly(*N*-vinylimidazole) than with any single method. Even if the NMR chemical shift and coupling parameters could not be precisely interpreted in terms of the polymer conformation, the fact that they are

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sensitive to conformational features on a local level gives us a broader means of detecting changes in conformation induced in the polymer than when bulk methods alone are used.

We were particularly interested in the effects of pH, ionic strength, counterions, and solvent on the conformation of poly(*N*-vinylimidazole). A detailed characterization study of the polymer and its quaternized form is to be reported elsewhere.[14]

Experimental Section

Poly(*N*-vinylimidazole) was synthesized from *N*-vinylimidazole by aqueous polymerization at 95 °C under nitrogen, with 4,4'-azobis(4-cyanovaleric acid) as the initiator. The polymer was purified by a ten-turnover diafiltration in distilled water, using a polysulfone 20KPS membrane (20 000 molecular weight permeation limit). Polymer samples used in this report were from the whole polymer. The weight-average molecular weight, as determined by intrinsic viscosity and the Mark–Houwink relation,[14] was 210 000. The polymer was dried in vacuo at 80 °C to constant weight before preparation of solutions.

For all of the solutions the degree of neutralization, α, was defined as $[C_{PVI^+}]/[C_{PVI}]$, where $[C_{PVI}]$ is the concentration of polymer in monomol/L and the molarity of the neutralized imidazole, $[C_{PVI^+}]$, was taken to be equal to the amount of acid titrant added. No correction was made for the amount of free acid or base resulting from incomplete reaction, but the error from such an assumption should be small and does not affect the conclusions.

Potentiometric Titration. The potentiometric titrations were done with a Metrohm Model 436 automatic potentiograph equipped with a microburet which delivers the acid titrant at 0.5 mL/min. The pH and potentials were monitored by a Beckman glass electrode and a saturated calomel reference electrode pair. For the nonaqueous titrations, the aqueous KCl solution in the reference electrode was replaced with 0.1 M tetramethylammonium chloride in methanol. Polymer solutions were prepared at 0.013 monomol/L (M) (or 0.12 g/dL) unless otherwise stated.

For the nonaqueous titrations, the ionic strength was not held constant, owing to the addition of titrant (equal to 0.01 M salt at the end of the titration). In some cases tetramethylammonium bromide (TMAB) or the tetramethylammonium (TEA) salts of chloride, iodide, nitrate, or perchlorate were added at the start of the titration at concentrations from 0.01 to 0.5 M. For the aqueous titrations, TMAB at concentrations of 0.18, 0.88, and 3.0 M or the TEA salts of perchlorate or iodide were added at the start of the titrations to allow us to observe the effect of added salts.

Viscosity. Viscosities were measured as a function of the degree of neutralization in various ionic-strength media by using Ubbelöhde viscometers at 25.00 °C. Since the plots for inherent viscosity ln η_r/C_p vs. C_p (where η_r is the relative viscosity and C_p is the polymer concentration in g/dL) were linear with negligible slopes, only the inherent viscosity data at C_p = 0.01 M (0.094 g/dL) in aqueous media and at C_p = 0.05 M in organic media are presented in this work. Since constant pH cannot be maintained upon dilution without altering the total acid present, intrinsic viscosity was not used.

The degree of neutralization, α, was varied by the addition of aqueous HCl in experiments run in aqueous solutions and methanolic HCl in those run in organic media. The ionic strength was controlled by the total amount of acid and TMAB present. The aqueous solutions were clear throughout the whole range of α, whereas the solutions in methanol and in methanol/acetonitrile (1/1, v/v) were turbid between α = 0.2 and 0.4 and between 0.2 and 0.3, respectively, at ionic strengths greater than 0.05. Viscosity measurements were not made for the turbid samples.

^{1}H NMR Spectra. Samples for NMR spectroscopy were prepared at 1 and 0.1 g/dL in the stated solvent. The degree of neutralization was varied by the addition of aqueous or methanolic HCl (100% deuterated). For the organic solutions a trace of tetramethylsilane was added to give a reference NMR signal; the aqueous solutions were run without reference. Spectra were taken on a Bruker WH-270 spectrometer in the Fourier transform mode with quadrature detection at about 31 °C. For the 1-g/dL solutions, 100 transients were averaged before Fourier transformation with a spectral width of 3012 Hz in 16K data points. For the 0.1-g/dL solutions ~500 transients were averaged. When necessary, a 180–90° sequence was used to null interfering solvent signals.[15] Partly relaxed spectra were also obtained with 180–90° sequences.

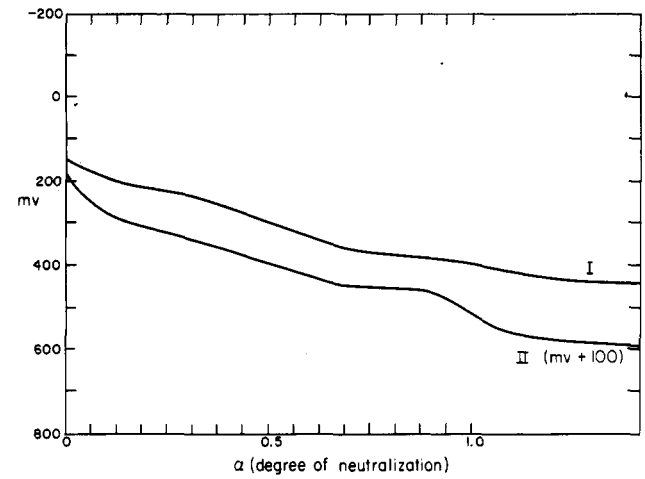

Figure 1. Potentiometric titration curves of poly(*N*-vinylimidazole) (C_p = 0.12 g/dL) with perchloric acid titrant (0.1 M) in (I) methanol and (II) methanol/acetonitile (1/1, v/v) (scale displaced +100 mV).

Results

Potentiometric Titration. The potentiometric titration curves for poly(*N*-vinylimidazole) in methanol and in methanol/acetonitrile (1/1, v/v) with perchloric acid titrant are shown in Figure 1. Two inflection points are obvious. The equivalence end point is shown at α = 1.0. The inflection point at the lower degree of neturalization ($\alpha \cong 0.5$) is unusual and will be discussed later in relation to conformational change of the polymer during the course of titration.

For titrations with perchloric acid at concentrations of polymer above 0.05 g/dL in the organic solvents, turbidity was observed at $\alpha > 0.2$ during the titration, indicative of a condition below the Θ point. At concentrations below 0.05 g/dL polymer, no turbidity was observed although the inflections near α = 0.5 and 1.0, as shown in Figure 1, persisted. Addition of supporting electrolyte caused greater turbidity which obscured the end-point inflection. Titrations with hydrochloric acid titrant in organic solvent in the absence of supporting electrolyte produced only the inflection at α = 1.0. Titrations with HCl titrant in the presence of 0.01 M perchlorate or iodide gave inflections near α = 0.5 accompanied with slight turbidity, identical with the titrations with perchloric acid titrant. However, titrations with HCl titrant in the presence of 0.01 M chloride, bromide, or nitrate gave no inflection near α = 0.5. When the bromide concentration was increased to 0.04 M or higher, the inflection was again observed with no accompanying turbidity. Turbidity became noticeable with bromide concentrations much above 0.05 M, and the inflections near α = 0.5 and 1.0 persisted.

In aqueous solutions without added supporting electrolyte and with hydrochloric acid titrant, no inflection points corresponding to either a conformational change or the equivalence point were observed (Figure 2, curve I). The addition of high concentrations of bromide or nitrate resulted in an obvious equivalence end point (Figure 2, curves II–IV). However, in the presence of 0.01 and 0.02 M perchlorate, an inflection was observed near α = 0.4 (Figure 3, curve II), similar to the inflection observed in organic solvent. At higher concentrations of perchlorate,

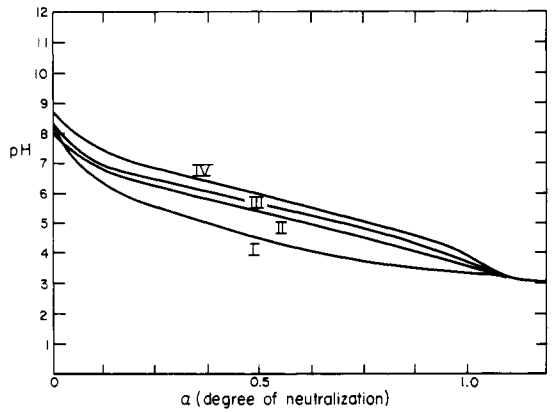

Figure 2. Potentiometric titration curves of poly(*N*-vinylimidazole) (C_p = 0.12 g/dL) in water with HCl titrant (0.1 M): (I) no added electrolyte; (II) 0.18 M TMAB; (III) 0.88 M TMAB; (IV) 3.0 M TMAB.

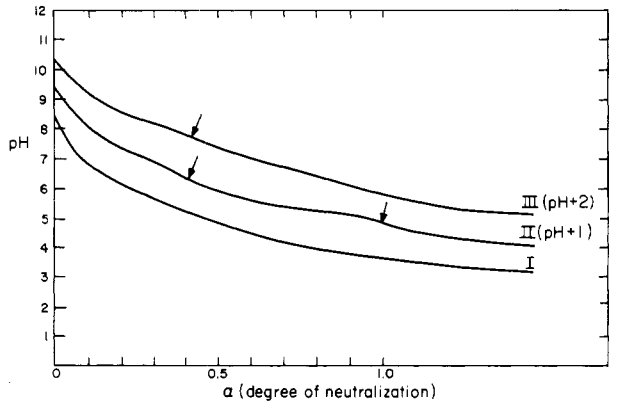

Figure 3. Potentiometric titration curves of poly(*N*-vinylimidazole) (C_p = 0.12 g/dL) in water with HCl titrant (0.1 M): (I) no added electrolyte; (II) 0.01 M TEAP (pH scale displaced +1 unit); (III) 0.04 M TEAI (pH scale displaced +2 units).

turbidity or precipitation occurred, obscuring the end-point inflection. At concentrations below 0.01 M perchlorate, no distinct inflections were observed. In the presence of 0.04 M iodide an inflection appeared near α = 0.4, but no distinct end-point inflection was observed (Figure 3, curve III).

Inherent Viscosity. The effect of protonation on observed inherent viscosities of poly(*N*-vinylimidazole) in water and in organic solvents is shown in Figure 4. In methanol or methanol/acetonitrile (Figure 4, curves V and VI), addition of acid initially led to a sharp reduction of the inherent viscosity, followed by an increase to the equivalence point. By contrast, in water, the initial decrease in viscosity occurred only when the ionic strength was high. When the ionic strength was low (0.01 M, curve I), there was only a very sharp increase in the inherent viscosity with added acid. Curve I continued to increase monotonically up to α = 1.0 (not shown in Figure 4). Increase in ionic strength in aqueous media broadened the minimum region (curves II–IV) and decreased the sensitivity of viscosity to α.

Turbidity was observed for the methanol solutions in the range from α = 0.2 to 0.4 and for the methanol/acetonitrile solutions in the range from α = 0.2 to 0.3 (curves V and VI, respectively, in Figure 4), indicative of a condition below the Θ point. Clear solutions would have been obtained if the total ionic strength had been kept lower in these runs. Nevertheless, a minimum is obvious in the plot of inherent viscosity vs. α for this polymer in organic media.

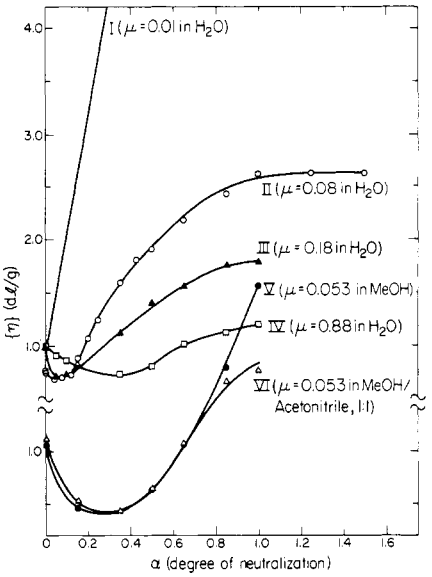

Figure 4. Inherent viscosity (dL/g) vs. α (degree of neutralization) of poly(*N*-vinylimidazole) at ionic strengths, μ, as shown.

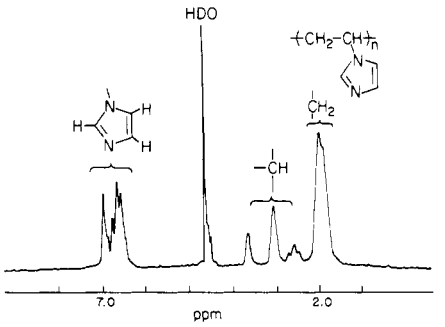

Figure 5. ^{1}H NMR spectrum of poly(*N*-vinylimidazole) in D_2O. The chemical shift scale has been placed somewhat arbitrarily, as no internal reference was used.

NMR Spectroscopy. The 270-MHz proton NMR spectrum of poly(*N*-vinylimidazole) in water is shown in Figure 5. The high degree of complexity in the aromatic region of the spectrum results from tacticity effects on chemical shifts and not from spin–spin coupling effects. In related compounds such as 1-methylimidazole and imidazole itself we have found that couplings are often unresolved and are apparently quite small. Essentially the same pattern in the aromatic region for the polymer was observed at 100 MHz as at 270 MHz. Very different patterns would have resulted if spin–spin couplings were involved.

Tacticity effects also account for the appearance of the three groups of methine signals. Although the central methine peak presumably results from protons in the center of heterotactic triads, the assignment of the outer peaks to isotactic and syndiotactic sequences is at present uncertain. The relative proportions of the three resonances confirm that this is essentially an atactic polymer, however. Although there is also some fine structure in the methylene region of the spectrum, we have not been able to make assignments to specific structural features for that region.

The separation of the resonances for the different tactic triads (1.03 ppm) in the methine region for this polymer is unusually large.[16] This difference in chemical shift presumably is determined by the orientations of the aromatic rings relative to the methine protons. If the chemical shifts could be analyzed in detail, they might tell us something about the conformations involved. More simply, changes in conformation caused by temperature or pH

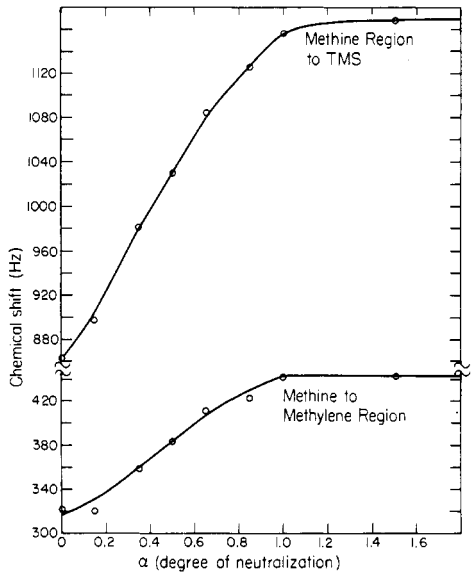

Figure 6. Chemical shift vs. α for poly(*N*-vinylimidazole) in methanol/acetonitrile (1/1, v/v).

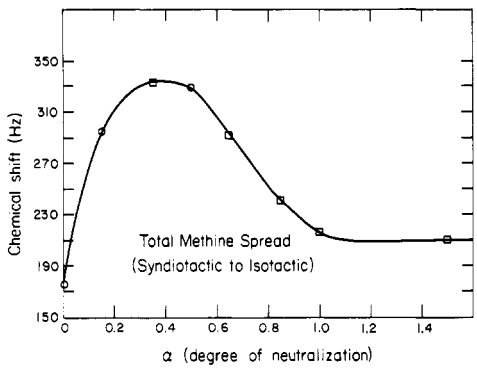

Figure 7. Chemical shift (total methine spread) vs. α for poly(*N*-vinylimidazole) in methanol/acetonitrile (1/1, v/v).

changes may be detected by variations in the methine chemical shifts. Thus, we might reasonably expect that the conformational changes which appear to occur during titration will be reflected in the NMR spectrum.

Two chemical shift influences must be considered during titration. The first is the inductive effect caused by the introduction of positive charge into the imidazole ring. The second is a result of conformational changes in the polymer. We can use the separation of the center of the methine region from either the methylene region or a reference peak as a qualitative measure of the first effect.

We assume initially that the inductive effect influences each of the methine signals equally. Although this assumption cannot rigorously be justified (see Discussion), it does allow us to consider that chemical shift changes within the methine region result from conformational changes of the polymer during protonation. We concern ourselves with the "spread" in the methine region, defined as the chemical shift between the most deshielded peak on the left and the center of the small group of three peaks on the right.

The effects of protonation on poly(*N*-vinylimidazole) in methanol-d_4/acetonitrile-d_3 (1/1, v/v) are shown in Figures 6 and 7. The separation from the center of the methine region to the methylene region or Me_4Si peak increased smoothly with the degree of neutralization and then leveled off beyond $\alpha = 1.0$. On the other hand, the spread of the methine region resonances went through a maximum at about $\alpha = 0.35$ and then decreased up to the equivalence

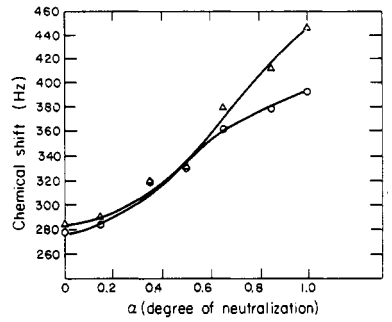

Figure 8. Chemical shift (center of methine to methylene) vs. α in D_2O at ionic strengths 0.01 M (circles) and 0.88 M NaBr (triangles).

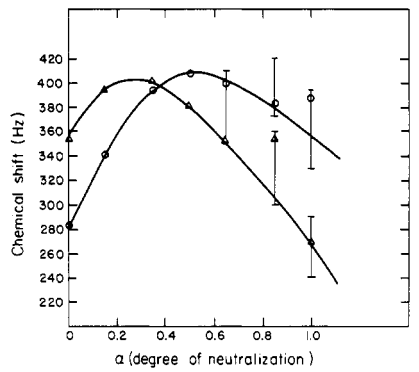

Figure 9. Chemical shift (total methine spread) vs. α for poly(*N*-vinylimidazole) in D_2O at ionic strengths 0.01 M (circles) and 0.88 M NaBr (triangles).

point where there again was a leveling off beyond $\alpha = 1.0$. No control of ionic strength was attempted for the organic solutions, since it is difficult to find a soluble salt which would not give interfering NMR signals. Failure to control ionic strength is assumed to be relatively unimportant for the organic solutions.

The effect of protonation on the separation of the center of the methine resonances from the methylene resonance for an aqueous solution is shown in Figure 8 for two different ionic strengths. For low levels of neutralization, the curves for each ionic strength are similar, whereas there is some divergence at high protonation levels. As Figure 9 shows, a maximum in the chemical shift spread within the methine region occurred for both low and high ionic strength solutions. For the higher ionic strength solutions the maximum was more pronounced, however, and was shifted to a lower degree of neutralization.

Changes in conformation could affect NMR relaxation times as well as chemical shifts by changing the internal motions of the polymer chain. Accurate determinations of T_1 values were not possible for our samples because of solvent overlap in some of the spectra. Simple comparisons of partly relaxed spectra at different pH values showed that the proton T_1 values are relatively independent of pH in both water and the organic solvents, however.

On the other hand, an interesting broadening and then resharpening of the aromatic resonances occurred with the addition of acid to the methanol/acetonitrile solution (Figure 10). Since line widths are inversely proportional to T_2 values, we are apparently seeing a decrease and then an increase of the T_2 values during the titration. A similar effect was not observed for the aqueous solutions.

Discussion

The free energy required to ionize a polymer is normally expected to increase with the degree of neutralization, α, because the increasing accumulation of charges repels the

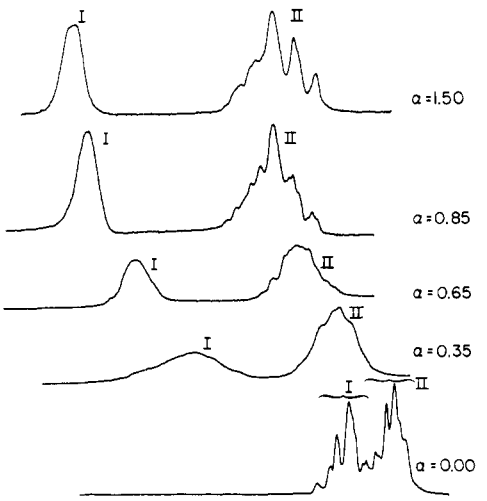

Figure 10. ^{1}H NMR spectra for the aromatic group of poly(*N*-vinylimidazole) in methanol/acetonitrile (1/1, v/v) as a function of α.

incoming ionizing species (H^+ or OH^-). This results in a smooth increase in pH during the course of a potentiometric titration up to the equivalence end point. In the absence of other conformational changes, the polymer dimensions increase with α as a result of repulsion of the charges on the chain. This behavior can be demonstrated, for example, by the monotonic increase in the plots of the apparent pK vs. α or viscosity vs. α for poly(acrylic acid).[11,17]

In some cases, additional conformational changes caused by interactions such as hydrogen bonding or hydrogen-bond breaking and hydrophobic interaction may occur and prevent full coil expansion until the polymer is very highly charged. As a result, abnormal shapes of the pH titration and viscosity curves are found.[8-11] In ideal cases the titration data can be used to calculate a free-energy change for the conformational transition.

Some of the titration curves for poly(*N*-vinylimidazole) do contain an inflection point in addition to the equivalence end point expected for the titration of a weak base. The pK_a of poly(*N*-vinylimidazole) is ~4 at $\alpha = 0.5$ in the absence of added salt.[14] Protonation presumably occurs on the 3-position of the ring. A second end point indicative of a conformational transition has also been observed for another basic polymer, atactic poly(2-vinylpyridine), but the nature of the transition was not explored.[18]

Both the equivalence end point and the inflection for the conformational transition are particularly pronounced for the organic solvents. By contrast, the aqueous titration curves are rather featureless in the absence of supporting electrolytes. With chloride, bromide, or nitrate electrolyte, it is only at high ionic strength that even the end-point inflection is observed. Apparently the screening effect of these anions within the polymer coil reduces the electrostatic repulsion to incoming hydrogen ions, leading to a better defined end point.

The inflection point indicative of a conformational transition occurred for the aqueous solutions only in the presence of perchlorate or iodide, even though the concentrations of these ions were rather low (0.01 to 0.04 M) (Figure 3).

The overall results demonstrate the strong influence of the nature of the counterion and solvent on the titration behavior and chain conformation. The strength of counterion binding increases in the order $Cl^- < Br^- < NO_3^- < I^- < ClO_4^-$, based on our titration results on the minimum concentrations of these ions required for the observation of the inflection and turbidity in organic or aqueous media. It is apparent that the stronger screening effect provided by the counterions, according to the above order, also facilitates conformational changes in the polymer during protonation.

The viscosity data provide additional information about the nature of the conformational changes brought on by acid titration. Initially, in the un-ionized polymer solutions, we expect the polymers to exist in a random, loosely coiled conformation. The viscosity data show that the addition of acid led first to a contraction of the polymer followed finally by expansion. This was most pronounced in the organic solvents. In the aqueous solutions the contraction occurred only when the ionic strength was high.

An increase in viscosity is normally expected for a polymer during ionization if charge repulsion is the only source for chain expansion. Our viscosity results suggest that we are dealing with two competing processes: one which initially leads to contraction and the other which leads to expansion.

One possible source of contraction of the chain is hydrogen bonding among the pendant groups. This force would be maximized when only some of the imidazole rings are protonated. The hydrogen bonds may be formed between two imidazole rings which are either adjacent to each other or are more distant neighbors. The end-to-end distance is expected to decrease when hydrogen bonding occurs among nonnearest neighbors and results in a decrease in viscosity. Contrariwise, the end-to-end distance would increase upon hydrogen bonding between the adjacent pairs of imidazole rings. This can be rationalized by a simple freely jointed chain model.[19] The square of the end-to-end distance of a freely jointed chain containing n segments with segmental length l is nl^2. If the adjacent pair of segments were hydrogen bonded with a segmental length of $(l^2 + l^2 - 2l^2 \cos 109°)^{1/2} = 1.63l$, the square of the end-to-end distance would be $(n/2)(1.63l)^2 = 1.33nl^2$. This distance is larger than the value for the unbonded, freely jointed chain. Consequently, any restriction in the motion of the pendant groups as imposed by its nearest neighbors would extend the chain and increase the viscosity.

We think, therefore, that the initial contraction occurs because of hydrogen bonding between protonated and unprotonated imidazole rings at sites which are far enough apart on the backbone to require chain coiling. Hence, viscosity decreases with α. Further protonation reduces the overall amount of hydrogen bonding by leaving most rings protonated and at the same time increases the importance of charge–charge repulsion. Eventually the polymer opens up into a highly extended chain, leading to large viscosity values. In aqueous media, the high dielectric constant of water favors separation of the ionic sites of the polymer and less counterion binding. This separation works against the contraction caused by hydrogen bonding. Hence, a much shallower minimum in the viscosity plots (or earlier rise in chain dimensions) was observed than was seen for the organic solvents.

The initial contraction resulting from long-range hydrogen-bonding effects may not be significant in raising the potential for further protonation. On the other hand, charge repulsions which lead to chain expansion do increase the potential for further protonation. Thus, the inflection in the potentiometric titration curve comes at a higher degree of neutralization than does the minimum in the inherent viscosity.

In aqueous solutions of high ionic strength or with stronger binding counterions such as ClO_4^- and I^-, the

charges on the protonated chain are shielded by the counterions present. Thus, when the ionic strength is high, the chain collapses more easily upon protonation, allowing the non-nearest-neighbor hydrogen bonding between the protonated and unprotonated imidazole groups to occur. Therefore, the conformational transition is more identifiable for the solutions having high ionic strength (see viscosity results in Figure 4) or for solutions containing ClO_4^- or I^- (see titration curves in Figure 3). In the presence of a large amount of supporting electrolytes, the coil does not significantly open up, however, even at high levels of protonation.

Viscosity behavior similar to what we observe was reported by Liu and Gregor[20] for the same polymer in aqueous NaBr or $NaNO_3$ solutions but not in aqueous NaCl solutions. Although intramolecular hydrogen bonding or triple-ion ($-N^+Br^-N^+-$) formation was proposed, the separation of bonding sites and its relation to ionic strength or conformational changes were not discussed.

In the nonaqueous media, the counterion screening effect is not very pronounced. Hence, ionic strength plays a less important role than in water. Furthermore, methanol and acetonitrile are weaker hydrogen-bonding reagents than water. Therefore, competition for hydrogen-bonding sites from the solvent molecules is less important, resulting in more intramolecular hydrogen bonds in the polymer. Consequently, the conformational transition in nonaqueous media is more identifiable by viscosity and potentiometric titration measurements, and we were justified in not controlling the ionic strength for the NMR experiments.

With NMR spectroscopy one might hope to obtain additional details about the conformations in this system. For example, the differences in the conformational behavior of isotactic, syndiotactic, and heterotactic triad sequences might be detectable. It is certainly known that polymers of different tacticity have different conformational behavior. For example, different potentiometric titration curves were observed for atactic and isotactic poly(2-vinylpyridine) polymers.[18]

The most informative NMR information about specific conformations would come from a measure of coupling constants for protons on the backbone. For poly(*N*-vinylimidazole) the line widths of the methine protons are too large for coupling constants to be measured, however. The use of deuterated polymers to simplify the coupling patterns and reduce the relaxation mechanisms leading to line broadening might be helpful, but at present the most useful NMR information about conformations of this polymer lies in the chemical shifts. The patterns of change found in the chemical shifts are similar to those found for the other techniques, which suggests that the chemical shifts reflect the same conformational changes.

There is some evidence, however, that basic sites in different tactic sequences may have different proton affinities.[18] Thus, the NMR results may also be explained in terms of preferential protonation first of imidazole groups in either isotactic or syndiotactic sequences. It would be especially helpful to have polymer samples with stereoregular tactic sequences so that we could explore this possibility.

Treloar and co-workers[21] found that NMR line widths could be used to reveal conformational changes during ionization of poly(methacrylic acid) and other polymers. We found that the line widths of the imidazole side-group resonances broaden and then resharpen during acid neutralization in the methanol/acetonitrile solution. A possible explanation of this effect is that the motion of the pendent groups is inhibited in the intermediate titration ranges as a result of the hydrogen bonding. It is interesting that the line-broadening effect is most pronounced for the organic solutions where the other methods also give the most clear-cut indications of the presence of hydrogen bonds which would restrict side-group motion.[22]

Conclusions

Potentiometry, viscometry, and ^1H NMR spectroscopy offer complementary techniques to study conformational behavior of polymers. Our results suggest that the poly(*N*-vinylimidazole) chain contracts and then expands upon protonation. The transition region involves a balance between hydrogen bonding of the protonated and unprotonated imidazole rings and charge repulsion among the protonated imidazole groups. Although both nonnearest-neighbor and nearest-neighbor hydrogen bonds may be present, the former are expected to be predominant in order to allow for chain contraction. High levels of protonation result in polymer expansion because of a decline in the number of hydrogen bonds and an increase in internal charge–charge repulsion. The ability of this polymer to form long-range hydrogen bonds may be helpful in explaining how metal complexation by poly(*N*-vinylimidazole)[4,23] and related polymers[24] occurs.

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(22) This broadening could also result from slow exchange of a proton between protonated and unprotonated imidazolyl groups. Such broadening would reasonably be maximized when there were equal amounts of the two types of ring. For sufficiently slow exchange, the separate species would even

give rise to individual signals in the NMR spectrum. We have not observed such separated resonances, even in spectra acquired at −23 °C. Nevertheless, an exchange process remains an interesting possibility to explain the observed results. We are grateful to Dr. F. A. Bovey for pointing out this idea.

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Proton Magnetic Resonance Study of Linear Sarcosine Oligomers

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ABSTRACT: A high-resolution proton NMR study of a series of monodisperse N- and C-protected sarcosine (*N*-methylglycine) peptides has been carried out. The compounds of the series *t*-Boc(Sar)$_n$OMe, where *t*-Boc is *tert*-butoxycarbonyl, OMe denotes the methyl ester, and n = 1–5, give well-resolved spectra in Me_2SO-d_6. The cis and trans conformers at the peptide bonds (and at the N-terminal urethane bond) are in sufficiently slow exchange that each exhibits separate CO_2CH_3, NCH_2, NCH_3, and *tert*-butyl proton resonances. Their chemical shifts also vary with the amino acid position in the chain. The result is that the spectra become very complex as n increases and cannot be fully interpreted beyond n = 2. The N-terminal urethane bond shows a weak preference for the cis state, while the C-terminal peptide bond exhibits a ca. 3:1 preference for trans. The other peptide bonds appear to have substantial proportions of both conformers. In contrast to the known behavior of L-proline oligomers [and poly(amino acids) generally], the sarcosine oligomers show no tendency to assume a regular structure as the chain is lengthened. Similar behavior is observed in D_2O and $CDCl_3$. Polysarcosine ($\overline{DP} \simeq 68$) is likewise random in conformation.

High-resolution proton magnetic resonance (^{1}H NMR) is a valuable and widely employed technique in the conformational analysis of linear oligopeptides in solution. Local environments of individual NH and α-CH (or α-CH_2) protons can be probed, and from this information one can deduce subtle structural characteristics of oligopeptides. Goodman, Bovey, Toniolo, Pysh (now Stevens), and co-workers have reported ^{1}H NMR studies of several series of monodisperse fully protected homopeptides derived from N-unsubstituted α-amino acids, including those from γ-alkyl esters of L-glutamic acid,[1-4] L-alanine,[5-7] L-norvaline,[8] L-valine,[7] L-isoleucine,[4,6] and L-methionine.[9-11] Jardetzky and co-workers[12] have examined in detail the glycine series and Shoji et al.[13,14] some C-protected L-alanine oligomers.

Less attention has been paid to homopeptides derived from *N*-alkyl α-amino acids, mainly because few are available. Blout and co-workers[15] have analyzed the proton spectra in chloroform of *t*-Boc(L-Pro)$_n$OX, where n = 2–6 and X is H or benzyl (*t*-Boc is *tert*-butyloxycarbonyl). They reported that the lower oligomers contain nearly random distributions of cis and trans peptide bonds but that the peptides abruptly assume an all-trans helical structure when n = 5 in the *O*-benzyl series and n = 6 in the OH series. A ^{1}H NMR study of the α-CH resonances of *t*-Aoc(L-Pro)$_n$OH (n = 2–6, 8; *t*-Aoc is *tert*-amyloxycarbonyl) in acetic acid has indicated that the peptides larger than the tetramer increasingly adopt the trans tertiary amide conformation with increasing chain length.[16] Rothe and co-workers[17] have shown by proton spectroscopy that all members of the series H_2^+(L-Pro)$_n$O$^-$ (with n from 2 to 40) which they examined have the trans conformation in acetic acid and trifluoroacetic acid. A distinct dependence of the cis–trans isomerism on chain length in other solvents—water, methanol, and trifluoroethanol—has been verified, diproline behaving differently from the higher oligomers. Only in methanol solution is the all-cis configuration attained by the higher oligoprolines (n > 10). Chao and Bersohn[18] observed the ^{1}H and ^{13}C spectra of H_2^+(L-Pro)$_n$O$^-$ (n = 2–4, 6) and reported that the percentage of trans peptide bonds increases substantially from dimer (65% trans) to trimer (90% trans), thereafter remaining more or less constant. A high salt concentration was shown to cause conformational randomization.

Only few and scattered ^{1}H NMR results have been described on homopeptides derived from sarcosine (*N*-methylglycine). They include the following: (i) the crystallizable oligomer Z-(Sar)$_3$OMe (Z is benzyloxycarbonyl) at −70 °C in a halogenated hydrocarbon shows only one isomer, each amide bond being in a single conformation, cis or trans.[19] As the temperature is increased, the 100-MHz ^{1}H NMR spectrum becomes more complex due to cis–trans isomerism of the peptide bonds. On the other hand, the noncrystallizable Z-(Sar)$_7$OMe exhibits a complex ^{1}H NMR spectrum even when dissolved at low temperature. (ii) The 220-MHz ^{1}H NMR spectrum of the *N*,*N*-dimethylamide derivative of a *polydisperse* oligosarcosine with $\overline{DP} \simeq 5$ shows that the ratios of trans–cis conformers in $CDCl_3$ and D_2O are similar (about 2:1).[20]

In this paper we discuss the results of a high-resolution ^{1}H NMR investigation of a homologous series of monodisperse linear sarcosine peptides having the general formula *t*-Boc(Sar)$_n$OMe (n = 1–5) as a function of solvent and temperature. The C-deblocked monomer and dimer and the corresponding homopolymer have also been examined for comparison, the two oligomers by changing solvent, concentration, and pH.

Among the vast body of conformational calculations of the sarcosyl residue and poly(Sar)[20-33] it has been reported that (i) in a linear oligosarcosine of at least four residues the cis conformation of the peptide bond is energetically preferred.[28] However, because the effect of solvation was not included in these calculations, these results are most

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