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Estimation of the Cooperative Unit Size in Conformational Transitions of Hydrophobic Polyacids

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ABSTRACT: A method for estimating the cooperative unit size in conformational transitions of hydrophobic polyacids from potentiometric titration data is developed. The cooperative unit is considered to be an intramolecular micelle. Two cases are considered: one in which the macromolecule is small enough to form a single micelle, the other in which the macromolecule is very large compared to the micelle size so that it may contain many micelles. The results are applied to the conformational transition of a hydrolyzed copolymer of maleic anhydride and butyl vinyl ether in 0.2 M LiCl, where the micelle is found to comprise 18 repeat units.

Introduction

It has been shown that the hydrolyzed 1:1 copolymer of maleic anhydride and butyl vinyl ether undergoes a conformational transition upon ionization which appears to be cooperative and of a two-state nature.[1-3] At high degrees of ionization the polyacid exhibits a random coil conformation typical of ordinary polymers and polyelectrolytes. At low degrees of ionization the polyacid exists in a hypercoiled conformation,[1] which may be ascribed to intramolecular micelle formation caused by hydrophobic interactions.[4] An initial analysis of potentiometric titration data suggests that high molecular weight polyacid molecules do not form single large micelles but consist of a number of relatively small micelles.[5,6] In this paper we intend to develop a method for estimating the size of these micelles from potentiometric titration data.

The thermodynamics of micelle formation has been extensively discussed in the literature.[7-9] It appears that the formation of small micelles cannot be described by two parameters alone, one relating to nucleation and the other to growth, as is done in the treatment of helix–random coil equilibria. The stability of micelles is governed by a combination of the hydrophobic effect, which tends to minimize the interface between water and hydrocarbon, the water affinity of the polar groups, and geometrical constraints involving the relative sizes of hydrophilic and hydrophobic groups. These effects impose a limit on the growth of the micelles.[9] For this reason quantitative estimates predict a very narrow size distribution for small micelles.[7-10]

It is difficult to assess the modifications necessary for the treatment of micelle formation when it occurs as an intramolecular process in a macromolecule. A number of differences between ordinary and intramolecular micelle formation may be envisioned. Thus, the net changes in the interactions between the micelle-forming entities might be smaller, while the geometrical constraints affecting micelle formation might be larger for the intramolecular process. Furthermore, the possibility of interactions, both attractive and repulsive, between micelles is enhanced when the micelles are contained in the same macromolecule.

Since our objective is limited to developing a method for estimating the micelle size from experimental data, we shall start out by ignoring these possible complications and by making the following simplifying assumptions. First, the micelles will be considered monodisperse. Second, the micelles will be assumed to form from sequences of adjacent segments in the polymer chain. Third, interactions between micelles will be neglected.

We divide the treatment into two parts. In the first part we consider the simple case where the polyacid molecule can exist either as a random coil or as a single micelle. With the help of the results thus obtained we treat, in the second part, the more complex case of multiple micelle formation in large polyacid molecules. The results of this treatment will be applied to potentiometric titration data obtained with the copolymer of maleic anhydride and butyl vinyl ether.

Theory

Single Micelle Formation. Consider a polyacid molecule with n repeat units and N ionizable groups so that the number of ionizable groups on one repeat unit, $\alpha_{\max}$, equals N/n.

Following a previous treatment[3] the ionization of this polyacid molecule may be described by the equations

$$\mathrm{AH}_N = \mathrm{AH}_{N-i}{}^{-i} + i\mathrm{H}^+ \qquad i = 1, 2, ..., N \tag{1}$$

In a constant excess concentration of simple electrolyte the activity coefficients may be considered to remain constant, and overall dissociation constants may be defined by the relations

$$\beta_i = [\mathrm{AH}_{N-i}{}^{-i}]/h[\mathrm{AH}_N] \qquad i = 1, 2, ..., N \tag{2}$$

where brackets denote concentrations of the species and h is the reciprocal of the hydrogen ion activity.

If we define the quantity $\sum_N$ by the equation

$$\textstyle\sum_N = 1 + \sum_{i=1}^{N} \beta_i h^i \tag{3}$$

it can be shown[11] that the degree of ionization, α, defined to go from 0 to $\alpha_{\max}$, is given by the expression

$$\alpha = \frac{1}{n}\,\frac{\mathrm{d}\ln \sum_N}{\mathrm{d}\ln h} \tag{4}$$

and the free energy of ionization per mole of polyacid, ΔG_{ion}, from zero charge ($\alpha = 0$, $h = 0$) to any value of h by

$$\Delta G_{\text{ion}} = -RT \ln \textstyle\sum_N \tag{5}$$

Equations 1–5 apply not only to the polyacid under consideration but also to its hypothetical completely micellar and completely random coil forms, for which the symbols β_i, $\sum_N$, and α are annotated with subscripts m and r, respectively. In what follows we shall use the equations in these forms, but for conciseness of presentation we do not explicitly rewrite them here for each form separately.

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The standard free energy of transition per mole of polyacid from micellar to random coil form, at any value of h, $\Delta G°(h)$, is given by the identity

$$\Delta G°(h) = \Delta G°(0) + \Delta G_{\mathrm{r,ion}} - \Delta G_{\mathrm{m,ion}} \qquad (6)$$

This equation derives from a stepwise process in which the micellar form is discharged ($-\Delta G_{\mathrm{m,ion}}$), the transition carried out at zero charge ($\Delta G°(0)$), and the random coil form is charged ($\Delta G_{\mathrm{r,ion}}$). Applying eq 5 to the last two terms in eq 6, differentiating eq 6 with respect to ln h, and applying eq 4, we obtain

$$\frac{1}{RT}\frac{\partial \Delta G°(h)}{\partial \ln h} = -n(\alpha_{\mathrm{r}} - \alpha_{\mathrm{m}}) \qquad (7)$$

Since each whole polymer molecule must be in one or the other conformation, we have

$$\Delta G°(h) = -RT \ln [\theta/(1-\theta)] \qquad (8)$$

where θ is the fraction of residues in the random coil form. It has been shown[1] that θ can be obtained from the experimental data by the relation

$$\theta = (\alpha - \alpha_{\mathrm{m}})/(\alpha_{\mathrm{r}} - \alpha_{\mathrm{m}}) \qquad (9)$$

Inserting eq 8 into eq 7 and rearranging terms, we obtain

$$n = \frac{1}{\alpha_{\mathrm{r}} - \alpha_{\mathrm{m}}}\frac{\mathrm{d} \ln [\theta/(1-\theta)]}{\mathrm{d} \ln h} \qquad (10)$$

Equation 10 has been given previously[12] and represents the classical way of obtaining the size of the cooperative unit in conformational transitions when there is only one such cooperative unit in the macromolecule.

Multiple Micelle Formation. Consider a polyacid molecule with M repeat units. Assume that W micelles, each micelle consisting of n adjacent repeat units, are present. The remaining J ($=M - Wn$) repeat units are in random coil form and are distributed without regard to sequence length. The relative probability of this state is

$$Q_W = \frac{(J+W)!}{J!W!}\exp(W\Delta G°/RT) \qquad (11)$$

where $\Delta G°$ is the negative standard molar free energy of forming a micelle from n adjacent monomer units. The partition function is the sum of Q_W over all possible values of W consistent with the fixed values of M and n. If we assume that M is much larger than n, we may replace the sum by its maximum term. Applying Stirling's formula and differentiating with respect to W at constant M and n, we obtain, after simplification,

$$\left(\frac{\partial \ln Q_W}{\partial W}\right)_{M,n} = \ln\frac{W}{J+W} - n\ln\frac{J}{J+W} - \frac{\Delta G°}{RT} = 0 \qquad (12)$$

Since, by the definition of θ, $J = \theta M$ and $W = (1-\theta)M/n$, eq 12 can be simplified to yield

$$\ln\frac{1-\theta}{n\theta + (1-\theta)} - n\ln\frac{n\theta}{n\theta + (1-\theta)} = \Delta G°/RT \qquad (13)$$

We now differentiate with respect to ln h and obtain, after simplification,[13]

$$\frac{\mathrm{d}\ln[\theta/(1-\theta)]}{\mathrm{d}\ln h} = -\frac{n\theta + (1-\theta)}{nRT}\frac{\partial \Delta G°}{\partial \ln h} \qquad (14)$$

Since $\Delta G°$ applies to the equilibrium between a micelle and n repeat units in the random coil conformation treated in the first part of this paper, we may apply eq 7, which results in

$$\frac{\mathrm{d}\ln[\theta/(1-\theta)]}{\mathrm{d}\ln h} = [n\theta + (1-\theta)](\alpha_{\mathrm{r}} - \alpha_{\mathrm{m}}) \qquad (15)$$

If we define n' by the relation

$$n' = \frac{1}{\alpha_{\mathrm{r}} - \alpha_{\mathrm{m}}}\frac{\mathrm{d}\ln[\theta/(1-\theta)]}{\mathrm{d}\ln h} \qquad (16)$$

i.e., the value of n that we would obtain if we incorrectly applied eq 10 to this case, eq 15 simplifies to

$$n = \frac{n' - 1}{\theta} + 1 \qquad (17)$$

which gives the size of the cooperative unit, i.e., the micelle, from potentiometric titration data of polyacids whose molecules are very large compared to the micelle.

Application

We have applied this method to estimate the cooperative unit size for the hydrolyzed alternating copolymer of maleic anhydride and butyl vinyl ether in 0.2 M LiCl at 30 °C. This butyl copolymer was our laboratory sample B-II prepared by Dubin.[1] Its weight-average degree of polymerization was determined by light scattering to be 1980 by Yang.[14] The potentiometric titration technique and the method for determining α have been described previously.[3] The results are presented in Table I.

The first two columns give interpolated values of α and pH for the butyl copolymer. The third and fourth columns give α_{r} and α_{m}, respectively, corresponding to the pH values in the second column. The α_{r} values are obtained from the potentiometric titration curve of the propyl copolymer (our sample Pr-I[15]), which has a random coil conformation for all values of α. The pentyl and hexyl copolymers (our samples P[15] and C,[1] respectively) have compact conformations over the pH range covered in Table I, and their values of α coincide within 0.01 unit. Their averages are therefore considered to adequately represent the hypothetical compact form of the butyl copolymer and are taken as the values of α_{m} given in Table I. The values of θ in the next column are obtained by means of eq 9. The derivative in the seventh column is calculated by linear regression from the data in the row of interest and the rows immediately preceding and following it. The values of n' and n in the last two columns are obtained by means of eq 16 and 17, respectively.

It is instructive to consider the cause of the difference between n' and n. The value of n' is the value of n obtained by eq 10 for the case where the macromolecule is the size of a micelle. This equation would also apply to the hypothetical case of a macromolecule much larger than the micelle if there were barriers separating groups of n repeat units so that micelles could not span these barriers. Let us compare this hypothetical macromolecule with the actual macromolecule that has no such barriers. We examine first the case where only one micelle of n repeat units exists on the macromolecule with M repeat units. The hypothetical macromolecule has M/n compartments in which this micelle can form and thus has M/n ways of forming the micelle. The actual macromolecule can form the first micelle in $M - n + 1$ ways. For $M \gg n$, the second of these numbers exceeds the first by a factor of n. On a logarithmic scale the difference is relatively small, which explains why, according to eq 17, n' and n approach one another as θ approaches unity. Next let us consider the case near $\theta = 0$ where the first micelle breaks up into n random coil units. Again, for the hypothetical macromolecule this can happen in M/n ways. However, for the actual macromolecule this can happen in the number of ways in which $M/n - 1$ micelles can be permuted with n

Table I
Determination of Micelle Size for Butyl Copolymer

α	pH	α_r	α_m	θ	$\log \frac{\theta}{1-\theta}$	$\frac{d \log \frac{\theta}{1-\theta}}{d(pH)}$	n'	n
0.325	3.800	0.513	0.283	0.183	−0.651			
0.350	3.865	0.547	0.299	0.206	−0.587	1.06	4.3	17.0
0.375	3.923	0.577	0.314	0.232	−0.520	1.23	4.7	16.8
0.400	3.975	0.604	0.328	0.261	−0.452	1.42	5.1	16.9
0.425	4.021	0.627	0.341	0.294	−0.381	1.81	6.3	19.1
0.450	4.059	0.645	0.352	0.335	−0.299	2.26	7.7	21.0
0.475	4.094	0.661	0.362	0.378	−0.216	2.29	7.7	18.6
0.500	4.128	0.677	0.372	0.420	−0.141	2.14	7.0	15.4
0.525	4.163	0.692	0.382	0.461	−0.068	2.34	7.6	15.2
0.550	4.194	0.704	0.391	0.508	0.014	2.85	9.1	16.9
0.575	4.223	0.714	0.399	0.559	0.103	3.52	11.2	19.2
0.600	4.247	0.722	0.406	0.614	0.201	4.13	13.1	20.6
0.625	4.270	0.732	0.413	0.665	0.297	4.41	13.8	20.3
0.650	4.294	0.740	0.420	0.719	0.408	4.42	13.8	18.8
0.675	4.320	0.750	0.428	0.767	0.518	4.55	14.1	18.1
0.700	4.347	0.759	0.437	0.817	0.649	4.59	14.3	17.2
0.725	4.379	0.770	0.448	0.860	0.789	3.86	12.0	13.8
0.750	4.419	0.784	0.462	0.894	0.928	2.67	8.3	9.1
0.775	4.472	0.802	0.481	0.916	1.037			

nonmicellar units, which is $(M/n - 1 + n)!/[(M/n - 1)!n!]$. The ratio of the second to the first of these numbers is approximately $(Me/n^2)^{n-1}$, which is quite substantial and far from negligible on a logarithmic scale. These statistical effects make it easier for the micelles to break up in the actual than in the hypothetical macromolecule, and therefore the conformational transition is spread out over a larger pH range. The application of eq 17 corrects for this effect.

The value of n is seen to be reasonably constant from $\alpha = 0.35$ to $\alpha = 0.70$. Over this range its average value is 18, with a standard deviation of 2. Since n was assumed to be constant in the derivation, its constancy in the results satisfies the condition of self-consistency for the applicability of eq 17.

One can speculate concerning the geometry of the micelles. It can be seen rather easily that a liquid micellar core consisting of 18 butyl groups cannot be spherical. Using Tanford's method of estimation,[7,16] we find that a butyl group has a length of 5.30 Å and a volume of 108 Å^3. The volume of the core will then be 1944 Å^3, while a sphere with a radius of 5.30 Å has a volume of only 622 Å^3. To give a sample of the dimensions of various conceivable shapes fitting the above volume and having at least one dimension equal to the length of two butyl groups, a cylinder in which the butyl groups are perpendicular to the axis would be 22.1 Å long with a diameter of 10.6 Å; a similar cylindrical shape with the same diameter but with hemispherical ends would have a length of 25.6 Å, while a cylindrical disk with the butyl groups arranged parallel to the axis would have a thickness of 10.6 Å and a diameter of 15.3 Å. These shapes should be regarded as highly idealized. The restraints imposed by the polymer chain to which the butyl groups are attached are expected to interfere with such an efficient packing and to result in less-ordered micellar structures.

Concluding Remarks

The chief result of this paper is the development of a method for estimating the size of small micelles in large hydrophobic polyacid molecules from the pH dependence of their conformational transition. The method was successfully applied to a high molecular weight copolymer of maleic acid and butyl vinyl ether. The results were consistent with the assumption of noninteracting micelles of constant size during the major portion of the transition.

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