Equilibrium bundle size of rodlike polyelectrolytes with counterion-induced attractive interactions

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Multivalent counterions can induce an effective attraction between like-charged rodlike polyelectrolytes, leading to the formation of polelectrolyte bundles. In this paper, we calculate the equilibrium bundle size using a simple model in which the attraction between polyelectrolytes (assumed to be pairwise additive) is treated phenomenologically. If the counterions are pointlike, they almost completely neutralize the charge of the bundle, and the equilibrium bundle size diverges. When the counterions are large, however, steric and short-range electrostatic interactions prevent charge neutralization of the bundle, thus forcing the equilibrium bundle size to be finite. We also show that if the attractive interactions between the rods become frustrated as the bundle grows, finite-size bundles can be obtained with pointlike counterions.

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The mean-field Poisson-Boltzmann (PB) theory predicts that two identical macromolecules in any salt solution will repel each other [1]. However, the presence of multivalent counterions can actually induce an *attraction* between like-charged polyelectrolytes (PEs). This has been experimentally observed for several different PEs, including double-stranded DNA [2,3], filamentous actin (F-actin) [4,5], microtubules [4,6], the filamentous bacteriophages fd and M13 [4,7], and the tobacco mosaic viruses [4]. Computer simulations of both homogeneously charged rods [8–11] and realistic DNA molecules [11–13] unambiguously show that attractive interactions can arise solely from counterion correlations not included in the PB theory. Several theories that take these correlations into account—including perturbative expansions of the PB theory [14,15], structural-correlation theory [16–18], and strong-coupling theory [19]—obtain an attractive interaction between two rods. It is still a matter of discussion, however, as to which of these theories is the most appropriate description of the correlation-induced attraction seen in experiments and simulations. Furthermore, it is unknown whether the interactions between multiple rods is pairwise additive or not [17,20,21].

Under experimental conditions in which the interaction between PEs is attractive, the PEs typically form dense, ordered bundles of a well-defined size [2–7], rather than precipitating into a PE-rich phase. In this paper, we theoretically investigate the thermodynamic stability of these bundles (if bundle growth is not limited thermodynamically, then it must be limited by kinetic barriers [21–23]). We assume that the attractive interactions are pairwise additive, but do not specify the precise nature of the counterion correlations. Rather, we simply introduce a phenomenological parameter γ to characterize the attractive energy between two PEs in a bundle.

Consider, then, an aqueous solution of volume V with N identical rodlike PEs of length L, radius a_0, and a uniform linear charge density $-e\lambda_0$ (the aggregation of flexible PEs has been considered in [22]). We treat both the aqueous solution and the rods as a uniform dielectric with dielectric constant ϵ; that is, we ignore all image-charge effects. Positive monovalent and q-valent counterions, as well as negative monovalent co-ions, are present; the entire system is charge neutral and in chemical equilibrium with a salt bath. The correlation-induced attraction between the PEs leads to the formation of PE bundles of some size at equilibrium. For simplicity, we assume that only multivalent ions can enter inside the bundle (the effects of competitive binding with monovalent ions will be discussed in a future paper [23]). Also, we assume that the solution of rods is dilute, i.e., the volume fraction $\phi \equiv N\pi a_0^2 L/V \ll 1$. As a result, we can employ the cell model, where each bundle and its surrounding ions are enclosed in a Wigner-Seitz (WS) cell, and interactions between cells are ignored. We work in the long-rod limit ($L \rightarrow \infty$), so that the translational entropy of the bundles is negligible. Finally, we assume that the equilibrium distribution of bundle sizes is sharply peaked, so that all bundles are approximately the same size. Given these assumptions, the free energy can be written as

$$\beta F = \frac{N}{M}[\beta F_{ent} + \beta F_{ES} + \beta F_{attr}] + N\beta F_{corr}, \quad (1)$$

where M is the number of rods in each bundle and $\beta \equiv 1/k_B T$, k_B being Boltzmann's constant and T the temperature. βF_{ent} includes the entropic and chemical potential terms for the ions in one WS cell; βF_{ES} is the mean-field electrostatic energy of a WS cell; βF_{attr} is the total attractive energy for a single bundle; and βF_{corr} is the correlation energy for ions condensed on one rod.

The ions contained within each WS cell can either be located inside or outside of the bundle. We assume that the former are uniformly distributed in the volume available inside the bundle (the inhomogeneity of this distribution is negligible for large bundles). In order to describe the ion

distribution outside the bundle, we use a modified Debye-Huckel approximation (DHA) similar to Manning's counter-ion condensation theory [24]. It is well known that the DHA is valid sufficiently far from a charged surface, where the electrolytic solution is dilute. However, for highly charged surfaces, the bare charge must be replaced by a renormalized charge due to counterion condensation [25]. To account for this, we allow ions to condense into a Stern layer (of width $w \ll R$) surrounding the bundle. We assume that the ions inside the layer are uniformly distributed. The ion distribution functions $n_s(\vec{x})$ (where $s = \pm 1$, q is the ionic species) outside the layer are determined using the DHA. The width w of the Stern layer is set arbitrarily, and counterion correlations of the ions in the Stern layer are ignored; although these factors will quantitatively affect the amount of condensation, they do not alter the scaling behaviour of the free energy with the bundle size. Assuming the ions are pointlike, and discarding terms that contribute constants to the free energy [26],

$$\beta F_{ent} = \sum_s \left(\frac{n_s}{2} \int_{r>R} d^3 x \left[\frac{n_s(\vec{x})}{n_s} - 1 \right]^2 + n_s \alpha_{st} L \right.$$
$$\left. + \lambda_s^{st} L \left[\ln\left(\frac{\lambda_s^{st}}{n_s \alpha_{st}} \right) - 1 \right] \right) + \lambda_q M L \left[\ln\left(\frac{\lambda_q}{n_q \alpha_b} \right) - 1 \right],$$
$$(2)$$

where n_s is the bulk concentration of ion species s, $\lambda_q L$ is the number of multivalent ions condensed on each rod in the bundle, $\alpha_b M L = \pi M L (a^2 - a_0^2)$ is the volume available to the ions inside the bundle ($2a$ being the center-to-center spacing of the rods in the bundle), $\lambda_s^{st} L$ is the number of s-valent ions in the Stern layer, and $\alpha_{st} L \approx 2\pi R w L$ is the volume of the Stern layer.

In order to calculate the mean-field electrostatic energy of the system, we model each bundle as a homogeneously charged cylinder of radius $R \approx a\sqrt{M}$ (so that $V_{cyl} \approx V_{bundle}$), and the Stern layer as a uniform surface charge (i.e., we set $w = 0$). That is, $-en_b(\vec{x}) = -\theta(R-r)e\lambda/\pi a^2$ and $en_{st}(\vec{x}) = \theta(R-r)e\lambda_{st}/2\pi R$ are the charge distributions of a bundle and its Stern layer, respectively, where $-e\lambda \equiv -e(\lambda_0 - q\lambda_q)$ is the renormalized linear charge density of one rod in the bundle and $e\lambda_{st} \equiv e(\lambda_1^{st} + q\lambda_q^{st} - \lambda_-^{st})$ is the linear charge density of the Stern layer. The electrostatic free energy is given by

$$\beta F_{ES} = \frac{l_B}{2} \int \int \frac{d^3 x d^3 x'}{|\vec{x} - \vec{x}'|} n_{tot}(\vec{x}) n_{tot}(\vec{x}'), \qquad (3)$$

where $l_B = e^2/\epsilon k_B T$ is the Bjerrum length ($l_B \approx 7.1$ Å in water) and $en_{tot}(\vec{x}) = e\Sigma_s s n_s(\vec{x}) \theta(r-R) + en_{st}(\vec{x}) - en_b(\vec{x})$ is the total charge distribution for a WS cell.

The correlation of ions condensed on two neighboring rods in the bundle leads to the formation of a "bond" of energy $E_{bond} = -\gamma k_B T L$ between the rods, so that $\beta F_{attr} = \beta E_{bond} B$, where B is the number of bonds in a bundle. It has been observed experimentally that the rods in the bundle are hexagonally packed [2,3,5,6]; in this case, it can be shown that $\beta F_{attr} \approx -\gamma L (3M - 3.6\sqrt{M})$ for all $M \geq 2$. The first term is the bulk attractive energy; the second term is an effective surface tension due to the fact that the rods on the bundle

surface have fewer neighbors than the bulk rods. Thus, each bundle in our model is equivalent to a homogeneously charged cylinder with an effective surface tension in the presence of counterions. This is very similar to the Rayleigh instability [27] of a charged water droplet in the presence of counterions [28], and to the aggregation of polyelectrolytes in poor solvent [28,29].

The number of ions inside each bundle and its surrounding Stern layer, as well as the ion distributions outside these regions, minimize the total free energy βF (subject to the constraint of overall charge neutrality). For the ion distributions $n_s(\vec{x})$, this minimization yields the expected Debye-Huckel (DH) distributions, $n_s(\vec{x}) = n_s[1 - s\psi(\vec{x})]$, where the dimensionless electrostatic potential

$$\psi(r) = \begin{cases} \dfrac{l_B \lambda}{a^2}(r^2 - R^2) - \dfrac{2l_B \lambda_{tot} K_0(\kappa R)}{\kappa R K_1(\kappa R)}, & r < R \\[3mm] -\dfrac{2l_B \lambda_{tot} K_0(\kappa r)}{\kappa R K_1(\kappa R)}, & r > R. \end{cases} \qquad (4)$$

Here, $-e\lambda_{tot} = -e\lambda M + e\lambda_{st}$ is the total linear charge density of the bundle and its Stern layer, $\kappa^2 = 4\pi l_B \Sigma_s s^2 n_s$, and $K_\nu(x)$ is the modified Bessel function of the second kind of order ν. Clearly, both γ and βF_{corr} should depend on λ_q. However, since the precise nature of the counterion correlations is not specified in our model, we ignore this dependence; that is, we calculate λ_q at the mean-field level. Discarding all constant terms, the free energy Eq. (1) can be written as $\beta F = N[a^2 \mathcal{F}_1/R^2 + \mathcal{F}_2 L]$ where $\mathcal{F}_1$ is given by the final three terms of Eq. (2) and

$$\mathcal{F}_2 = \frac{3.6\gamma a}{R} + \frac{l_B \lambda^2 R^2}{4a^2} + \frac{l_B a^2 \lambda_{tot}^2 K_0(\kappa R)}{\kappa R^3 K_1(\kappa R)}. \qquad (5)$$

Minimization of βF with respect to λ_q and λ_s^{st} gives

$$\ln\left(\frac{\lambda_q}{n_q \alpha_b} \right) - \frac{l_B q \lambda R^2}{2a^2} - \frac{2l_B q \lambda_{tot} K_0(\kappa R)}{\kappa R K_1(\kappa R)} = 0, \qquad (6)$$

$$\ln\left(\frac{\lambda_s^{st}}{n_s \alpha_{st}} \right) - \frac{2l_B s \lambda_{tot} K_0(\kappa R)}{\kappa R K_1(\kappa R)} = 0, \quad s = \pm 1, q. \qquad (7)$$

If we solve Eqs. (6) and (7), we can see that λ_{tot} approaches a constant at large R (see inset of Fig. 1). Indeed, in the limit $R \to \infty$, the second term in Eq. (6)—which is due to the electrostatic self-energy of the bundle—dominates, causing $\lambda \to (2a^2/l_B q R^2) \ln(\lambda_0/qn_q \alpha_b)$ and $\lambda_{tot} \to M\lambda/(1+\kappa w)$. Thus, as the bundle grows, additional counterions condense inside the bundle, so that the total charge of the bundle remains constant.

The equilibrium bundle radius R_{eq} is given by the value of R that minimizes the free energy. Figure 1 shows the free energy as a function of R for various values of n_q. We can see that as soon as the attractive energy is strong enough to induce bundle formation, $R_{eq} \to \infty$. This is due to the large amount of counterion condensation inside each bundle, which causes the entropic and electrostatic resistance to bundle growth to be weak: in the limit $R \to \infty$, $1/M(\beta F_{ES} + \beta F_{ent}) \sim -1/R^2$. This resistance is overwhelmed by the attractive energy $\beta F_{attr}/M \sim 1/R$, thus causing the equilibrium
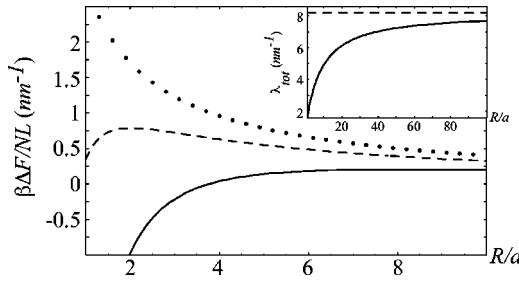
FIG. 1. Free energy difference $\Delta F(R) \equiv F(R) - F(100a)$ for $a_0 = 1$ nm, $a = 1.4$ nm, $w = 1$ nm, $\lambda_0^{-1} = 0.17$ nm, $n_1 = 10$ nM, $q = 3$, $\gamma = 1.4$ nm^{-1}, and $n_q = 0.1$ μM (solid line), 10 μM (dashed line), and 1 mM (dotted line). Inset: $\lambda_{tot}(R)$ for the above parameter values with $n_q = 10$ μM. The dashed line indicates the asymptotic value of λ_{tot} (see text).
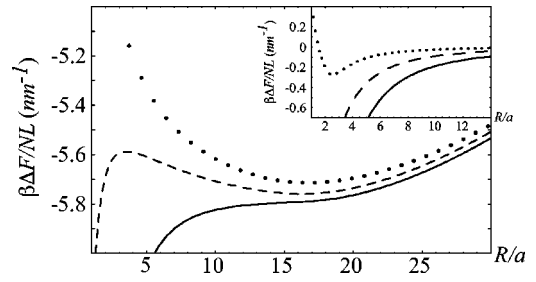

FIG. 2. Free energy difference $\Delta F(R) \equiv F(R) - F(100a)$ for finite size ions inside the bundle, with $\gamma = 1.7$ nm^{-1} and $\lambda^* = 0.01\lambda_0$ (the remaining parameter values are the same as in Fig. 1). Inset: $\Delta F(R)$ for frustrated attractive interactions, with $\xi = 0.1$, $\phi_{max} = 2$, and $\gamma = 1.7$ nm^{-1} (the remaining parameter values are the same as in Fig. 1).

bundle size to diverge. This result is consistent with earlier work on penetrable water droplets [28] and PEs in poor solvents [28,29]. It is important to note that finite-size aggregates can be obtained in these systems when the charge of the aggregates is small enough to avoid significant counterion condensation. This region is not accessible in our system, however, because like-charge attraction only occurs when there is significant counterion condensation.

As stated above, these results do not take into account the dependence of γ and βF_{corr} on λ_q. It is important to note, however, that the asymptotic results $|\lambda| \sim 1/R^2$ and $\beta F \sim 1/R - 1/R^2$ hold for *any* such dependence (even those that cause overcharging): When the bundle is large, the long-range mean-field self-energy of the bundle dominates over the short-range correlation energy, causing the renormalized charge density of the bundle to be small and the resistance to bundle growth to be weak.

In the model discussed above, the density of ions inside the bundle can, in principle, be arbitrarily high. In reality, however, steric interactions prevent the ion density inside the bundle from exceeding the close packing density. Furthermore, when the density of ions in the bundle is high, the mean-field electrostatic repulsion between the ions confined to the small volume available inside the bundle is severely underestimated by our model (which smears out the charge of these ions throughout the entire bundle). This additional short-range electrostatic repulsion effectively increases the size of the ions in the bundle (i.e., it prevents the ion-ion separation from becoming too small). If we treat the ions inside the bundle as finite-size particles with an effective volume v_{eff}, then $\beta F_{ent} \rightarrow \beta F_{ent} + ML[(\Lambda - \lambda_q)\ln(1 - \lambda_q/\Lambda) + \lambda_q]$, where $\Lambda \approx \alpha_b/v_{eff}$ is the maximum number of ions per unit length that can condense on a single rod. This adds a term $-\ln(1 - \lambda_q/\Lambda)$ to the right-hand side of Eq. (6), which diverges as $\lambda_q \rightarrow \Lambda$, thus forcing $\lambda_q < \Lambda$ for any bundle size R. If $\lambda^* \equiv \lambda_0 - q\Lambda > 0$, then the asymptotic result $\lambda \sim 1/R^2$ no longer holds; rather, $\lambda \rightarrow \lambda^*$ for large R. As a result, the self-energy of the bundle—in particular, the second term in Eq. (5)—diverges at large R, leading to the formation of finite-size bundles at equilibrium, as shown in Fig. 2. Note that for DNA, where $1/\lambda_0 = 1.7$ Å, $a_0 = 10$ Å, and $a \approx 14$ Å in the presence of trivalent cobalt hexammine [2,3], $\lambda^* > 0$ when the effective radius of the ions $\delta_{eff} \gtrsim 7$ Å.

We can use this model to predict the equilibrium behavior of the system for different multivalent salt concentrations (see Fig. 2). At small n_q, the total attraction is not large enough to overcome the electrostatic repulsion between rods, and no minimum in $\beta F(R)$ is obtained. As n_q increases, however, more ions enter inside the bundle and reduce the electrostatic repulsion for small bundles, thus creating a local minimum in $\beta F(R)$ that is primarily determined by the balance of the first two terms in Eq. (5), $R_{eq} \approx a(7.2\gamma/l_B\lambda^{*2})^{1/3}$. Notice that the bundling transitions is discontinuous, and that the bundle size is invariant upon further increases in n_q, as has been recently observed for microtubule bundles [30].

The above model implicitly assumes that the rod-rod spacing (i.e., α_b) is independent of R. If this spacing increases as the bundle grows, more counterions can enter the bundle, thus decreasing the electrostatic resistance to bundle growth. However, the correlation energy will also decrease as the spacing increases. Therefore, in order for our assumption to be valid, the rod-rod attractive interaction must have a sharp minimum that prevents the spacing from increasing as the bundle grows.

Up to this point, we have assumed that the attraction between neighboring rods is independent of the bundle size. There are several mechanisms, however, that can frustrate the bonds between rods as the bundle grows. For short-ranged, pairwise additive interactions, only a fraction of ions in a narrow "contact stripe" between the two rods become correlated with one another [17]. When rod-rod dimers form, the size of the contact stripe is maximized. However, each rod has one contact stripe per bond, and these stripes cannot overlap if the interactions are pairwise additive. Therefore, if the contact stripe for dimers is wide enough, the stripes will have to shrink for a rod with many neighbors, causing the bond energy to decrease. Alternatively, a nonuniform PE charge distribution results in a relative orientation that minimizes the electrostatic repulsion between two neighboring rods. Achieving the optimum orientation between a rod and every one of its neighbors may cost energy or be physically impossible; in either case, the bond energy effectively decreases as the bundle grows. Indeed, it has been experimentally observed that F-actin filaments undergo twist distortions when forming bundles to reduce the electrostatic repulsion between neighboring rods [5]. If we write βF_{attr}

$=-\gamma LM\phi(B/M)$, where $B/M \equiv b$ is the average number of bonds per rod ($b < 3$ for hexagonally ordered bundles), then $\phi(b)=b$ for unfrustrated interactions. To encapsulate the effects of bond frustration, we chose $\phi(b)$ to be a hyperbola that approaches the asymptote $\phi=b$ for small b and $\phi=\phi_{max}$ for large b, $\phi(b)=\frac{1}{2}(b+\phi_{max})-\frac{1}{2}|\phi_{max}-b|\sqrt{1+\xi/(b-\phi_{max})^2}$. In other words, the total attractive energy gained for each rod in the bundle saturates as b increases; by adjusting ϕ_{max} and ξ, we can control the saturating value and rate of saturation, respectively. As shown in the inset of Fig. 2, a local minimum in $\beta F(R)$ can be obtained for certain values of ϕ_{max} and ξ. Unlike the minimum obtained with finite-size ions, this effect cannot lead to arbitrarily large bundles; rather, the onset of frustration must occur at a sufficiently small bundle size, or the resistance to bundle growth will be too weak to prevent infinite bundles.

In summary, we have presented a simple model to calculate the equilibrium bundle size of highly charged, rodlike polyelectrolytes in the presence of multivalent counterions. For pointlike counterions and unfrustrated attractive interactions, the equilibrium bundle size diverges. Finite bundles can be obtained at equilibrium if the short-range interactions between the ions inside the bundle prevent the ions from neutralizing the charge of the bundles, or if the interactions between rods in the bundle become frustrated as the bundle grows.

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