Local Domain Size in Single-Chain Polymer Nanoparticles
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ABSTRACT: Single-chain polymer nanoparticles (SCNPs) obtained through chain collapse via intramolecular cross-linking are attracting significant interest for nanomedicine and biomimetic catalysis applications, among other fields. This interest arises from the possibility to bind active species (e.g., drugs and catalysts)—either temporally or permanently—to the SCNP local pockets formed upon chain collapse. However, direct quantification of the size and number of such local domains in solution—even if highly desirable—is currently highly demanding from an experimental point of view because of the small size involved (<5 nm). On the basis of a scaling analysis, we establish herein a connection between the global compaction degree (R/R₀) and the size (ξ) and number (n) of the “collapsed domains” generated upon SCNP formation at high dilution. Results from molecular dynamics simulations and experimental data are used to validate this scaling analysis and to estimate the size and number of local domains in polystyrene SCNPs synthesized through a “click” chemistry procedure, as a representative system, as well as for relevant catalytic SCNPs containing Cu, Pt, and Ni atoms. Remarkably, the present work is a first step toward tuning the local domain size of the next generation of SCNPs for nanomedicine and bioinspired catalysis applications.

1. INTRODUCTION
Intramolecular cross-linking of individual polymer chains in a good solvent at high dilution produces single-chain polymer nanoparticles (SCNPs) via intrachain collapse.1–5 The compaction of a single chain to a SCNP resembles—in some way—the conformational rearrangement needed by some biomacromolecules to reach its functional state.6–8 Depending on the specific nature of the intramolecular cross-links formed, dynamic or permanent SCNPs result by involving reversible or irreversible intrachain interactions, respectively.7,10 These soft nano-objects have attracted significant interest for a variety of applications, including nanomedicine and biomimetic catalysis uses.3 The possibility to bind active species (e.g., drugs and catalysts)—either temporally or permanently—to the SCNP local pockets formed upon intrachain chain collapse remains as a driving force toward bioinspired applications.5,8 To understand the possibilities that SCNPs offer for nanomedicine and biomimetic catalysis, the reader is referred to several illustrative works11–25 and a recent book.26

Significant theoretical effort27–32 has been recently devoted to understand how the nature of the intramolecular cross-links (both reversible and irreversible interactions), the amount of functional reactive groups, x, and the precursor molecular weight, M₀, determine the global collapse degree upon intramolecular cross-linking, R/R₀ where R₀ and R are the linear precursor polymer size and the SCNP size, respectively. However, to our best knowledge, no attempt has been yet carried out to establish a connection between the global compaction degree (R/R₀) and the size (ξ) and number (n) of local pockets (domains) generated upon SCNP formation at high dilution. It is worthy of mention that a direct visualization/quantification of such local domains in solution—even if highly desirable—is currently highly demanding from an experimental point of view.25

We use herein the analogy of chain confinement into a spherical cavity33 to the collapse of a linear chain to a SCNP to perform a scaling analysis,34,35 allowing to establish a connection between the global compaction degree (R/R₀) and the size (ξ) and number (n) of “collapsed domains” generated upon SCNP formation at high dilution. It is worthy of mention that the case of confinement of a linear semiflexible polymer chain into a cavity under good solvent conditions has recently attracted significant theoretical and computer simulations efforts.36–39 Remarkably, the present work provides a solid basis to understand the effect of (i) the strength of the intramolecular interactions, (ii) the amount of functional groups, (iii) the precursor molecular weight, and (iv) the precursor chain stiffness on the size and number of local domains of SCNPs in solution.

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The article is organized as follows. In Section 2, we first introduce two expressions for the change in free energy upon collapse based, respectively, on the analogy of SCNP formation to the case of chain confinement into a spherical cavity under good solvent conditions and on the number of new intramolecular bonds formed and the change in free energy per each new bond formed. Next, useful scaling expressions for the global compaction degree and the size and number of local domains are derived. Validation of the scaling analysis with results from molecular dynamics (MD) simulations and reliable experimental data, as well as an estimation of the size and number of local domains for relevant catalytic SCNPs in solution containing Cu, Pt, and Ni atoms, is provided in Section 3 and, finally, the conclusions of the work are given in Section 4.

2. SCALING ANALYSIS

2.1. Free Energy of Collapse. Let us assume that the change in free energy, $\Delta F$, upon collapse of a linear precursor polymer of size $R_0$ to a SCNP of size $R$ in a good solvent under high dilution conditions follows an expression similar to that corresponding to chain confinement into a spherical cavity under good solvent conditions:

$$\frac{\Delta F}{k_B T} \approx \left( \frac{R_0}{R} \right)^{3/3\alpha - 1}$$

where $k_B$ is the Boltzmann’s constant, $T$ the absolute temperature, and $\alpha$ is the scaling exponent of the resulting collapsed domains upon SCNP formation (see below). It is reasonable to assume that SCNP’s with different chain stiffness will show different values of the exponent in eq 1, as observed in computer simulations of semiflexible chains confined in a spherical cavity.

Because the free energy of collapse comes from all of the new intramolecular bonds formed, we can additionally write

$$\frac{\Delta F}{k_B T} \approx \frac{xN}{2} |\Delta f_c|$$

where $xN/2$ is the number of new intramolecular bonds formed, $x$ is the fraction of reactive groups in the linear precursor polymer of total number of monomers $N$, and $|\Delta f_c|$ is the absolute value of the change in free energy per each new bond formed. Implicit in eq 2 is the assumption that by means of dimerization of the corresponding reactive monomers the maximum number of intrachain bonds ($xN/2$) is obtained. Experimentally, this is expected to be the case for SCNP’s prepared through highly reactive cross-linking procedures (e.g., “click” chemistry reactions) but not for SCNP’s prepared by means of weak, dynamic interactions (e.g., hydrogen bonds).

For real systems, $\Delta f_c$ is expected to contain a favorable enthalpic contribution, $\Delta h_f < 0$, because of (exothermic) bond formation and an unfavorable entropic contribution, $\Delta s_f < 0$, because of severe configurational restriction upon chain collapse.

2.2. Global Compaction Degree. By combining eqs 1 and 2, we obtain an analytical expression for the compaction degree ($R/R_0$) as a function of $x$ and $N$ such as

$$R \approx R_0 \left( \frac{xN}{2} |\Delta f_c| \right)^{\beta}$$

$$\beta \equiv \frac{-3\alpha - 1}{3}$$

Taking into account that the size of a semiflexible linear chain in a good solvent is given (to a first approximation) by $R_0 \approx bC_\infty^{1/5}N^{\nu}$, where $b$ is the monomer size, $C_\infty$ is the characteristic ratio, and $\nu$ is the Flory exponent ($\nu \approx 3/5$), eq 3a can be rewritten as

$$R \approx bC_\infty^{1/5} \left( \frac{|\Delta f_c|}{2} \right)^{\beta} x^\beta N^{\nu}$$

$$\nu \equiv \nu_0 + \beta = \nu_0 - \frac{3\alpha - 1}{3}$$

Consequently, according to the present scaling analysis, the exponents of the dependence of SCNP size $R$ on $x$ and $N$ are actually connected through eq 4b.

2.3. Local Domain Size. Similar to the case of a linear chain confined in a spherical cavity, we introduce herein the concept of cross-linked blobs or collapsed domains upon SCNP formation via chain collapse. The average number of such domains ($n$) each one having associated a free energy around $k_BT$ and a size $\xi$ can be estimated from the free energy of collapse such as

$$\frac{\Delta F}{k_BT} \approx \frac{R^3}{\xi^5}$$

Therefore, by using eqs 1 and 2, we obtain the following expressions for the domain size

$$\xi \approx R \left( \frac{R}{R_0} \right)^{1/3\alpha - 1}$$

$$\xi \approx R \left( \frac{xN}{2} |\Delta f_c| \right)^{-1/3}$$

whereas the number of monomers in each collapsed blob ($g$) is just given by

$$g \approx \frac{N}{n}$$

It is worthy of mention that $\alpha$ in eq 6a is related to the scaling exponent of the cross-linked blobs, so its value gives an idea of compaction at local level (i.e., at domain size $\xi$). Conversely, the value of $\nu$ in eq 4a gives an indication of chain compaction at global scale (i.e., at SCNP size $R$). In general, one expects $1/3 \leq (\alpha, \nu) \leq 1$ where the lower value is expected for globule-like compaction, whereas the upper value corresponds to rod-like compaction.

It is instructive to rewrite eqs 5 and 7 by using eq 6b, such as

$$n \approx \frac{xN}{2} |\Delta f_c|$$

and

$$g \approx \frac{2}{x|\Delta f_c|}$$

Hence, according to the present scaling analysis $n$ depends linearly on $x$, $N$, and $|\Delta f_c|$, whereas $g$ depends inversely on $x$ and $|\Delta f_c|$ but it is independent on $N$. DOI: 10.1021/acsomega.8b01331

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As derived from the present scaling analysis, to determine the scaling exponent $\beta$ (and hence $\alpha$ from eq 3b) as well as the absolute value of the change in free energy per each new bond formed, $|\Delta f|$, Figure 1 shows such an analysis for SCNPs having different chain stiffness, as characterized by the value of the bending constant $k$ employed in the coarse-grained MD simulations.40 Note that $k$ is related to the well-known characteristic ratio, $C_\infty$, and it was previously reported that $C_\infty \approx 1.7, 5, 9,$ and $15$ for $k = 0$ (fully flexible case), $3, 5,$ and $8$, respectively.40 The dependences of $\beta$, the exponent of the free energy of collapse $3/(3 \alpha - 1)$, and $|\Delta f|$ on chain stiffness are illustrated in Figure 2 for semiflexible SCNPs. Upon increasing the SCNP characteristic ratio, the value of $\beta$ was found to decrease nearly linearly with $C_\infty$ (see Figure 2A). Concerning the exponent of the free energy of collapse, it decreases abruptly on increasing $C_\infty$ toward a plateau value for the stiffer SCNPs (Figure 2B). This behavior is in agreement with that reported by Cifra and Bleha36 in computer simulations of the confinement of a semiflexible linear chain in a closed spherical cavity reaching a limiting value of 2.6 upon increasing chain stiffness. Interestingly, $|\Delta f|$ also reaches a plateau value upon increasing SCNP stiffness (Figure 2C). As noted by Cifra and Bleha,40 for semiflexible linear chains, the free-energy penalty on chain compaction is maximum for the fully flexible case when compared with the case of stiffer systems. According to the data in Figure 2C, there is a difference in $|\Delta f|$ between the fully flexible and stiffer SCNP around 3.7 $k_B T$. An estimation of the free energy of collapse as a function of SCNP stiffness at identical compaction degree can be obtained from eq 1. As an example, at a compaction degree $R/R_0 = 0.65$, we obtain $C_\infty = 218.0$, 14.8, 7.1, and 4.4 for SCNPs with $C_\infty = 1.7, 5, 9,$ and $15$, respectively.

Table 1 shows a comparison of the values of $\nu = \nu_0 + \beta$ and $\alpha = \frac{1}{3} - \beta$, as derived from the present scaling analysis, to those previously reported for semiflexible SCNP with different $C_\infty$ values as estimated directly from MD simulations data.40

As stated previously in Section 2, $\nu$ gives an indication of chain compaction at global scale (i.e., at SCNP size $R$) whereas the value of $\alpha$ is indicative of chain compaction at local level (i.e., at domain size $\xi$). In general, a good agreement is observed between the values of $\nu$ from the present scaling analysis and MD simulations. Concerning the values of $\alpha$, the MD simulations provide values that are systematically larger than those derived from the scaling analysis, although both data sets follow the general trend of a higher value of $\alpha$ on increasing $C_\infty$.

Figure 3 shows the evolution of the collapsed domain size, $\xi$ (in $\sigma$ units, where $\sigma$ is the bead size) and the number of beads in a domain, $g$, as a function of SCNP stiffness, for SCNP with a fraction of reacting monomers $x = 0.2$ and $N = 400$, as calculated from eqs 4a–5 with data from Figure 1 and Table 1. Inspection of Figure 3 reveals that a minimum SCNP stiffness is required for the scaling analysis to provide consistent values of $\xi$ and $g$. As a matter of fact, the domain size of fully flexible SCNP in Figure 3A approaches the bead size which invalidates the scaling analysis for this case. Inasmuch $C_\infty \geq S$, consistent values of $\xi$, $n$, and $g$ are obtained showing a collapsed domain size around 3.7$\sigma$, about 33 collapsed beads per SCNP and ~12 beads per blob for semiflexible SCNP ($x = 0.2, N = 400$) with $C_\infty = 5, 9,$ and $15$ because of the similar values of $|\Delta f|$ (refer to eqs 6b, 8, and 9).

Figure 4 illustrates the dependence of $\xi$ and $g$ on the fraction of reacting monomers, $x$, for SCNP with $N = 400$ and $C_\infty = 9$. Chain collapse from a linear precursor with low amount of reacting monomers ($e.g., x = 0.05$) produces a few collapsed domains ($\sim 8$) of relatively large size ($\sim 8.4\sigma$) containing a large amount of beads per blob ($\sim 51$). Upon increasing $x$, both collapsed domain size and number of beads per blob reduce notably (refer to eqs 6bb and 9), whereas the number of blobs is found to increase linearly with $x$ (refer to eq 8).

3.2. Scaling Analysis Validation with Experimental Data. Complementary to the analysis based on MD simulations data of compaction degree ($R/R_0$) as a function of new intramolecular bonds formed ($xN/2$) for SCNPs having different chain stiffness:40 (A) $C_\infty = 1.7$, (B) $C_\infty = 5$, (C) $C_\infty = 9$, and (D) $C_\infty = 15$ (see text for details).

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**Figure 1.** MD simulations data of compaction degree ($R/R_0$) as a function of new intramolecular bonds formed ($xN/2$) for SCNPs having different chain stiffness:40 (A) $C_\infty = 1.7$, (B) $C_\infty = 5$, (C) $C_\infty = 9$, and (D) $C_\infty = 15$ (see text for details).
simulations data, we have also analyzed data for real SCNPs in terms of eq 3a. In this sense, compaction data from well-defined polystyrene (PS)-SCNPs synthesized via “click” chemistry, covering from $x = 0.025$ to $x = 0.3$ and three different values of weight-average molecular weight ($M_w \approx 44, 111, \text{ and } 232 \text{ kDa}$) were found to merge into a single master curve with $\beta \approx -0.20$ and $|\Delta f_c| \approx 0.16$, when plotted according to eq 3a (see Figure 5).

Apparently, the experimental data best follow the scaling behavior at large values of $N$. From $\nu = \nu_0 + \beta$ and $\alpha = \frac{1}{3} - \beta$, we obtain $\nu = 0.4$ and $\alpha = 0.53$ based on the value of $\beta \approx -0.20$. Note that the values of $\beta$ and $\nu$ for PS-SCNPs ($C_\infty \approx 9.5$ for PS) are in excellent agreement with those predicted by a model of elastic SCNPs recently developed by our group ($\beta = -1/5$, $\nu = 2/5$).

When compared with MD simulations of SCNPs prepared from a precursor polymer of $C_\infty = 9$, the value of $|\Delta f_c|$ was found to be about fivefold lower for real PS-SCNPs. However, it is worth stressing that similar values should not be expected even at a qualitative level. Thus, though one finds similar scaling properties for the molecular size and may expect similar entropy loss per monomer because of network formation in the coarse-grained and in the real SCNPs, this is not the case for the associated enthalpy change, $\Delta h_c$ because the bonded and nonbonded interactions in the simplified bead-spring model of the simulations are of different nature than that in the real polymers.

Figure 6 illustrates the dependence of $\xi$ and $g$ on the fraction of reacting monomers, $x$, for PS-SCNPs of $M_w \approx 44, 111, \text{ and } 232 \text{ kDa}$, as calculated from eqs 6bb and 9 with data from Figure 5. On increasing the amount of functional monomers from $x = 0.1$ to $x = 0.3$, a decrease in the domain size is observed from $\xi \approx 4 \text{ nm}$ to $\xi \approx 2 \text{ nm}$. According to the results

| $C_\infty$ | $\beta$ | $\nu$ | $\alpha$ | $\nu_{MD_{Dom}}$ | $\alpha_{MD_{Dom}}$ |
|-----------|--------|------|--------|-----------------|-----------------|
| 1.7       | -0.08  | 0.52 | 0.41   | 0.50            | 0.63            |
| 5         | -0.16  | 0.44 | 0.49   | 0.47            | 0.74            |
| 9         | -0.22  | 0.38 | 0.55   | 0.42            | 0.81            |
| 15        | -0.29  | 0.31 | 0.62   | 0.30            | 0.84            |

Figure 2. Dependence of (A) scaling exponent $\beta$, (B) scaling exponent $3/(3\alpha - 1)$, and (C) change in free energy per new bond formed, $|\Delta f_c|$, on chain stiffness for semiflexible SCNPs with different values of characteristic ratio, $C_\infty$, according to MD simulations (see eqs 1–3a and text for details).

Figure 3. Dependence of (A) collapsed domain size, $\xi$, (in $\sigma$ units, where $\sigma$ is the bead size) and (B) number of beads per collapsed domain, $g$, on chain stiffness for semiflexible SCNPs ($x = 0.2, N = 400$) as calculated from eqs 6bb and 9 with data from Figure 1 and Table 1.
displayed in Figure 6A, the domain size in PS-SCNPs shows a weak dependence on \( M_w \). Remarkably, on the basis of the present scaling analysis, the number of monomers in each local domain is expected to be independent of \( M_w \), as illustrated in Figure 6B. By taking into account that for real systems \( \sigma \approx 0.64 \) nm and each bead in the MD simulations comprises \( \approx 5 \) monomers, the results shown in Figure 6 are in good agreement with those displayed in Figure 4.

### 3.3. Estimation of Local Domain Size in Pt-, Cu- and Ni-Containing Catalytic SCNPs in Solution

Data about the local domain size, number of domains, and number of monomers per domain for relevant metal-containing catalytic SCNPs in solution are given in Table 2. The precursor polymers were based on either PS or poly(methyl methacrylate) (PMMA), both having a similar value of chain stiffness \( C_\infty \) \( (\text{PS}) = 9.5, C_\infty \text{(PMMA)} = 9.0 \). Estimations were carried out based on experimental \( R/R_0 \) data by assuming \( \alpha \approx 0.53 \) in eq 6aa, for Pt\( ^{II} \)-, Cu\( ^{II} \)-, and Ni\( ^{II} \)-containing SCNPs employed with success in amination of allyl alcohol, selective alkyne homo-coupling reactions, and photoreduction of carbon dioxide, respectively.

As stated previously, direct quantification of the size and number of SCNPs in solution is currently of great interest because of the possibilities that offer such local pockets to bind—either temporally or permanently—active species to them (e.g., drugs)

Figure 4. Dependence of (A) collapsed domain size, \( \xi \), and (B) number of beads in a collapsed domain, \( g \), on the fraction of reacting monomers \( x \) for SCNPs with \( N = 400 \) and \( C_\infty = 9 \), as calculated from eqs 6bb and 9 with data from Figure 1 and Table 1.

Figure 5. Compaction degree \( (R/R_0) \) as a function of new intramolecular bonds formed \( (xN/2) \) for PS-SCNPs \( (C_\infty \approx 9.5) \) of different molecular weight: \( M_w = 44 \) kDa (solid blue points), \( M_w = 111 \) kDa (solid red points), and \( M_w = 232 \) kDa (solid green points).

Figure 6. Dependence of (A) collapsed domain size, \( \xi \), and (B) number of monomers in a collapsed domain, \( g \), on the fraction of reacting monomers, \( x \), for PS-SCNPs \( (C_\infty \approx 9.5) \) of different molecular weight: \( M_w = 44 \) kDa (solid blue points), \( M_w = 111 \) kDa (solid red points) and \( M_w = 232 \) kDa (solid green points) as calculated from eqs 6bb and 9 with data from Figure 5.

4. CONCLUSIONS

Quantification of the size and number of local domains of SCNPs in solution is currently of great interest because of the possibilities that offer such local pockets to bind—either temporally or permanently—active species to them (e.g., drugs...
and catalysts) rendering the resulting SCNPs highly attractive for applications in nanomedicine and catalysis, among other fields. A scaling analysis was performed to establish a connection between the global compaction degree ($R/R_n$) and the size ($\xi$) and number ($n$) of collapsed domains generated upon SCNPs formation at high dilution from a linear semiflexible precursor polymer. The scaling analysis was validated with results from MD simulations and reliable experimental data. On the basis of the scaling equations here proposed, we have estimated—as an example of application—the size and number of local domains for relevant catalytic SCNPs in solution containing Cu, Pt, and Ni atoms. Remarkably, this work is a first step toward tuning the local domain size of the next generation of SCNPs for nanomedicine and bioinspired catalysis applications.

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**Notes**

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