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Structure and dynamics of single-chain nano-particles in solution

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ABSTRACT

By means of intramolecular folding/collapse of individual polymer chains (precursors), ultra-small soft nano-objects called single-chain nano-particles (SCNPs) can be synthesized. Here we present a combination of scattering techniques [small angle X-Ray and neutron scattering (SAXS and SANS), neutron spin echo (NSE) and dynamic light scattering (DLS)] to investigate the structure and dynamics of SCNPs in solution and their linear precursors as reference. Coarse-grained molecular dynamics (MD) simulations have also been carried out to complement this study. The application of SANS and SAXS has proved the compaction of the macromolecules upon creation of internal cross-links. However, the SCNPs obtained by different routes exhibit a far from globular topology in good solvent. Regarding the dynamics, we report on the first experimental investigation of the dynamic structure factor of SCNPs in solution. It reveals a clear impact of internal cross-links through (i) a reduction of the translational diffusion coefficient and (ii) an important slowing down of the internal modes. The data have been analyzed in terms of theoretical approximations based on the Zimm model. Both, structurally and dynamically, SCNPs show striking resemblances with intrinsically disordered proteins: similar scaling properties reflecting sparse morphologies and an extremely high internal friction.

1. Introduction

Single-Chain Nano-Particles (SCNPs) are ultra-small soft nano-objects (5–20 nm) synthesized by means of intramolecular folding/collapse of individual polymer chains via covalent or non-covalent bonds [1–10]. Research in SCNPs is currently at the boundary between polymer science, nanotechnology and biology. In this sense, the folding/collapse of single chains to SCNPs is reminiscent of protein folding to its functional, native state although it is still very far from the extreme precision found in these natural biomacromolecules. Recently, the potential prospects of SCNPs have been expanded significantly by taking inspiration from the different morphologies displayed by native, globular proteins (e.g., enzymes) and intrinsically disordered proteins (IDPs) [11–13].

SCNPs prepared through covalent bonds give rise to permanent SCNPs [8], whereas SCNPs constructed by means of non-covalent interactions (e. g., multiple hydrogen bonding, metal complexation, host-guest interactions) provide with valuable stimuli-responsive SCNPs [6]. On one hand, permanent SCNPs could find their place in applications requiring high structural and thermal stability (e. g., additives for all polymer nano-composites, catalytic systems). On the other hand, responsive SCNPs are more appropriate for nano-medicine, sensing and self-healing applications where different physical and chemical stimuli can be employed, such as light, heat, pressure and pH, ionic strength or redox potential. Even if successful proof-of-concept experiments have been carried out with SCNPs in drug delivery, sensing and catalysis applications, significant work is still necessary for unraveling the actual structure and dynamics of functional SCNPs and, hence, to establish reliable structure-properties relationships.

In this context, scattering techniques are specially well suited to realize a significant advance in this novel field. Scattering

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experiments provide spatial resolution through the wave-vector (Q) dependence of the measured magnitudes. For instance, the use of dynamic light scattering (DLS) is widely spread, being a powerful tool to get quick information about the dimensions of particles in solution through the determination of the diffusion coefficient. However, finer structural details on the macromolecular conformations cannot be resolved by photons in the visible spectrum. Thanks to the range of their typical wavelengths, X-Ray (XR) and neutrons constitute ideal probes to decipher the structural features at intra- and inter-molecular length scales (atomic/monomeric level) by wide angle experiments, as well as to determine the macromolecular conformation from the analysis of the intensity scattered at small angles. In addition, the energies of neutrons also match the typical excitations range in condensed matter, providing a unique tool for the investigation of the molecular dynamics at the proper length/time scales. Creation of an additional contrast –i. e., by increasing the difference in scattering length density– allows labeling given molecular groups or whole macromolecules in the system. In particular, the big difference in the neutron scattering length of H and D nuclei facilitates selective studies of particular components in complex systems by isotopic substitution.

Up to date, not many investigations have been reported on SCNPs by XR and/or neutron scattering experiments. In particular, to our knowledge the characterization of the internal dynamics of SCNPs in solution has not been addressed up to now. One of the main problems for this kind of studies is the lack of a theoretical framework to interpret the results. In this direction, the aid of molecular dynamics (MD) simulations could be of great importance. The combination of scattering and simulation techniques has proved to be a powerful tool to investigate the structural and dynamical features of linear polymers [14]. Most of such synergetic studies have been performed by using fully atomistic MD-simulations that mainly address questions related to bulk properties at relatively small length scales (inter- and intra-molecular levels). However, if the focus of the study is on the large-scale properties (e. g., the macromolecular conformation and dynamics) the use of fully atomistic models is severely limited by state-of-the-art computational resources. At a lower computational expense coarse-grained models provide, by retaining the basic ingredients of the interactions (excluded volume, connectivity…), an useful tool to explore large scales and to elucidate the microscopic origin of general properties that are common to systems of different chemical nature.

In this work we intend to demonstrate the potential of scattering techniques to determine the structural and dynamical features of SCNPs in solution. We present new results – in particular, we report for the first time on the chain dynamics of these systems – and also give a flavor of the outcome of previous studies regarding the structural properties of these novel nano-objects in solution. In more detail, in a first part we deal with the structural aspects and show how the chain dimensions and conformation (full form factor) of the macromolecules in solution can be determined. We illustrate this with new SANS results on solutions of SCNPs obtained through two different synthesis routes, leading to either covalent or non-covalent (metal complexation) intra-molecular bonds. In addition, we present a kinetic small angle X-Ray scattering (SAXS) study on the macromolecular conformation of SCNPs during the synthesis procedure by intra-molecular bond creation via enamine reaction. In all cases, the obtained SCNPs show a degree of compaction far from that in globular coils. We review the state–of–the–art regarding such an observation and its possible generalization (through results by more conventional techniques like size exclusion chromatography (SEC) or DLS). Also, we discuss the similarities with other nano-objects of utmost importance in biology, namely intrinsically disordered proteins. The crucial role of MD-simulations for the interpretation of the scattering results is highlighted. To finish with the structural study, we present the effect of increasing concentration, leading to the emergence of interactions between SCNPs, which is reflected in the structure factor. In a second part of the paper we face the dynamical aspects. First neutron spin echo (NSE) experiments on the single chain dynamic structure factor of SCNPs in dilute solution are presented. The NSE data are compared with the results on precursor solutions as reference and complemented with a DLS study. After a phenomenological analysis, three versions of the Zimm model (the original one, a modified version considering a limited number of contributing modes and one, which takes into account the internal friction) are considered as possible simplified theoretical frameworks. A study of the dynamical features from MD-simulations results is also presented. This study justifies the mapping of the large-scale dynamics of the topologically complex SCNPs to the Zimm dynamics of an effective linear chain and supports the role of intramolecular barriers in the deviations from Zimm dynamics at the local scales.

2. Experiments and simulations

2.1. Samples

We investigated SCNPs obtained through three different cross-linking mechanisms, starting from the same kind of linear precursors. Precursors were always random copolymers of methyl methacrylate (MMA) and (2-acetoacetoxy)ethyl methacrylate (AEMA), namely P($MMA_{0.63}$-co-$AEMA_{0.37}$). The three routes explored are illustrated in Fig. 1:

(i) Michael addition-mediated multidirectional self-assembly. This protocol was conducted at room temperature in tetrahydrofuran (THF, Scharlab) at 1 mg/mL during 72 h, by following the procedure reported in Ref. [15]. We will refer to the such obtained SCNPs as 'Mi-SCNPs'. Trimethylolpropane triacrylate (Sigma-Aldrich, technical grade) acted as intra-chain cross-linking agent.

(ii) Intrachain Cu(II) complexation of AEMA units, exploiting the β-ketoester functional groups in the copolymer precursors. Reaction times were of 24 h, at a concentration of 1 mg/mL in THF (Scharlab). The SCNPs synthesized by this method (described in detail in Ref. [16]) will be called 'Cu-SCNPs' throughout the manuscript.

(iii) Intrachain formation of dynamic covalent enamine bonds, by reacting the β-ketoester functional groups in the copolymer precursors with ethylenediamine (99.5%, Sigma-Aldrich) as described in detail in Ref. [17]. The typical conditions for this synthesis reaction consist of reaction times of 24 h, at a concentration of 1 mg/mL in THF (Scharlab) using equimolar concentrations of β-ketoester and amine functional groups. The such obtained SCNPs will be denoted as 'e-SCNPs'.

The comparative structural characterization of SCNPs obtained by the two first methods was realized by SANS on samples synthetized starting from a high-molecular weight precursor with $M_w^{Prec} = 272.1$ kg/mol. SCNPs used for the dynamical (NSE) investigation were obtained through Cu-complexation from a lower molecular weight precursor (52.5 kg/mol). In all cases, deuterated *N*,*N*-dimethyl formamide (dDMF, 99.5 atom% D, from Acros Organics) was used as solvent to achieve a high contrast for neutron scattering (see below). The SAXS investigation on the SCNPs obtained through the enamine reaction was conducted on solutions of precursors with $M_w^{Prec} = 209$ kg/mol in THF.

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