Brownian dynamics simulations of complexes of hyperbranched polymers with linear polyelectrolytes: Effects of the strength of electrostatic interactions on static properties

G.K. Dalakoglou, K. Karatasos, S.V. Lyulin, A.V. Lyulin

1. Introduction

Hyperbranched molecules constitute a class of polymeric materials which have recently attracted strong scientific and industrial interest due to their unique characteristics [1]. These molecules are ideal when high functionality is desired within a very small volume (i.e. in nanoscale dimensions). Their capacity to be utilized as building blocks for several applications is mainly based on this attribute [2,3]. In cases where the surface groups are highly biologically active, their enhanced surface density may impart unwanted side effects like an increase in cytotoxicity. In such cases, “shielding” of the charged surface groups is usually an effective way to remedy this problem [4]. One of the most efficient and cost-effective routes to this end is complexation of hyperbranched molecules with oppositely charged linear polyelectrolytes (LPs). It has been experimentally verified that such a complexation mechanism can prolong cell viability and mediate for a successful gene-transfer inside the cell when hyperbranched molecules are utilized as gene-delivery vehicles [5,6], while it can also provide a stabilization mechanism against enzymatic degradation in targeted drug-delivery [7]. Owing to the potential of these systems for uses in a wide variety of applications in nanosciences [8], a deeper insight on the specific parameters which may affect their properties, is of particular importance.

Among the principal factors affecting the complexation mechanism, key role play the intrinsic characteristics of the hyperbranched molecule, like architecture and size, as well as external conditions like the ionic strength of the solution [9]. In terms of their structural details, hyperbranched molecules can be categorized to those who possess a “regular” dendritic topology, referred to as dendrimers, and to those with an “irregular” architecture usually termed simply as hyperbranched polymers (HP). HPs require simpler single-step synthesis procedures compared to the complicated multi-step synthetic strategies followed for the production of their regular dendritic counterparts [10]. Therefore, they are rightfully considered as cost-effective alternatives for dendrimers in a wide range of applications where high functionality and structural versatility is required [11].

On the accounts described above, we have studied by means of Brownian dynamics simulations static/structural features of complexes formed by terminally charged hyperbranched polymers and oppositely charged neutralizing linear polyelectrolytes, are examined by means of Brownian dynamics computer simulations. Excluded-volume, electrostatic and hydrodynamic interactions are taken into account in implicit solvent. Three pairs of complexes consisting of linear chains and hyperbranched molecules each bearing different molecular weight and distinctly diverse topologies are examined under conditions of varying electrostatic interactions. The findings from the present work demonstrate that through an appropriate modification of internal structure and external stimuli, key attributes of such complexes like size, shape and local density distribution, can be tuned at desired levels, rendering them promising candidates for a wide range of pertinent nanoscale applications.
Table 1

<table>
<thead>
<tr>
<th>Systems</th>
<th>HP (DB = 0.5)</th>
<th>LP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WI</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>G2_7MIN</td>
<td>990</td>
</tr>
<tr>
<td>2</td>
<td>G2_7MAX</td>
<td>1,327</td>
</tr>
<tr>
<td>3</td>
<td>G3_13MIN</td>
<td>6,384</td>
</tr>
<tr>
<td>4</td>
<td>G3_13MAX</td>
<td>9,710</td>
</tr>
<tr>
<td>5</td>
<td>G4_25MIN</td>
<td>37,670</td>
</tr>
<tr>
<td>6</td>
<td>G4_25MAX</td>
<td>60,351</td>
</tr>
</tbody>
</table>

Fig. 1. Schematics of the HP models invoked in the complexes. Charged terminal beads are shown in different tone.

2. Model and methodology

Bead-rod complex models, with rigid one-bond spacers of length $l$ (which is taken as the unit of length), forming complexes consisting by a terminally charged hyperbranched polymer and an oppositely charged linear polyelectrolyte were constructed. In addition, analogous systems formed by a single HP are generated to serve as reference systems for comparison purposes. HP molecules with tri-functional $AB_2$-type randomly branching groups are studied. Each HP terminal bead carries a positive unit charge, while each LP bead is oppositely charged.

Hyperbranched structures are characterized according to their number of monomers, $N$ and degree of branching, DB, which is defined as $DB = 2D/(2D+l)$, where $D$ is the number of fully branched monomers and $l$ the number of linear beads, respectively [12,13]. Apart from DB Wiener index ($WI$) is also used in order to describe topologically the different structures [14]. $WI$ is the cumulative distance between all pairs of beads measured in terms of the number of intervening bonds between them. Herein it is calculated according to the expression [15]:

$$WI = \sum_{i=1}^{N-1} (V_{L,i} \times V_{R,i})$$

where $V_{L,i}$ and $V_{R,i}$ are the number of beads in the left and in the right, respectively, of the centre of each bond, $s$. Therefore, $N$, DB and WI uniquely define the structure of the systems studied [15,16]. The number of monomers $N$ comprising each HP, corresponds to generations 2, 3, or 4, of perfect dendritic structures (Table 1). The DB is chosen to be 0.5, very close to the value for typical synthetic HPs [17]. For each HP molecular weight (number of beads), structures representing two topological extremes are generated; one with a relatively low WI, describing a compact structure, referred to as min and one with two topological extremes are generated; one with a relatively low WI, describing a compact structure, referred to as min and one with a relatively high WI corresponding to a less compact object which referred to as max (Fig. 1). In the formed complexes each LP bears a total number of charged monomers, $N_l$, equal to the number of the charged HP beads ($N_l$), preserving thus the overall electrical neutrality of the simulated systems.

Ermak–McCammon algorithm is utilized as the Brownian dynamics stochastic differential equation [18]. Solvent is considered implicitly as a viscous continuum by a random force (white noise), while the main physicochemical interactions of beads are taken into account explicitly by means of appropriate potentials. All the non-bonded beads interact via a Lennard–Jones potential (for charged beads only the repulsive part is taken into account), $U_j(r_{ij}) = 4\varepsilon_{ij}[(\sigma_{ij})^{12} - (\sigma_{ij})^6]$ with the cutoff distance $r_{cut} = 2.5\sigma$ and characteristic length and energy parameters $\varepsilon_{ij} = 0.3 k_B T$ ($k_b$ is the Boltzmann’s constant and $T$ is the temperature) and $\sigma = 0.8 l$, respectively, as in previous studies [9]. $r_{ij}$ is the distance between beads $i$ and $j$. Electrostatic interactions between charged beads (both of intra and inter pairs) are taken into account through the Debye–Hückel potential, $U_e$ defined as $U_e/k_B T = -e^2/(4\pi\epsilon \varepsilon_0 k_B T)$, where $\epsilon_0$ is the dielectric constant of the solvent and $k_B T$ is the thermal energy. $\varepsilon_0$ is calculated from Debye–Hückel approximation.

Hydrodynamic interactions are taken into account explicitly through the Rotne–Prager–Yamakawa tensor [20,21]. The hydrodynamic interactions strength is set by the dimensionless hydrodynamic parameter $h^*$, which is taken 0.25 as in past pertinent studies [22]. SHAKE algorithm is used to maintain a fixed bond length [23]. Dimensionless quantities used, such as bond length $l$, thermal energy $k_B T$, translational friction coefficient $\zeta$ and time $t^*$ are set to unity. The initial configuration of each system is equilibrated for several runs, and then production runs of $1.4 \times 10^7$ time steps are performed. Additional information about simulation algorithm and model can be found from authors’ previous relevant works [9,24].

3. Results and discussion

Response of conformational features like size and geometry upon modification of $\lambda_B$ for the examined systems, were monitored (i) by calculating the average radius of gyration defined as $<R_g^2> = 1/N \sum_{n=1}^{N} R_g^2$ where $N$ refers to the number of HP or linear–polymer beads, while $R_g$ denote the position vectors of the nth bead and that of the center of mass, respectively, and (ii) by probing the degree of anisotropy through the behavior of the Eigenvalues of the moment of inertia tensor of the HPs. Spatial arrangement of the hyperbranched and linear polymers’ beads was examined by calculating the bead number, $n(r)$ and density, $\rho(r)$, profiles with respect to the distance from the center of mass of the HP of each complex.

The response of geometrical characteristics of complexes to varying strength of electrostatic interactions was followed by examining the aspect ratios $a/b$, $a/c$, $b/c$, where $a > b > c$ correspond
Fig. 2. Root mean square $R_g$ as a function of Bjerrum length for the HP constituents of the studied complexes.

The lengths of the semi-axes of the ellipsoid of inertia, defined through the relations:

$$a = \sqrt{\frac{5}{2m} (I_x + I_y - I_z)}, \quad b = \sqrt{\frac{5}{2m} (I_x + I_z - I_y)}, \quad c = \sqrt{\frac{5}{2m} (I_y + I_z - I_x)}$$

where $I_x > I_y > I_z$ represent the eigenvalues of the moment of inertia tensor and $m$ denotes the total mass of the examined system.

Fig. 2 shows the dependence of the $<R_g^2>^{1/2}$ for the HP constituents of the complexes on Bjerrum length. For LPs (not shown here), no noticeable HP topology-effect is observed. Chains participating in min and max WI complexes behave in a similar fashion. Moreover, only for the longer LPs a trend towards lower size appears as $\lambda_B$ increases. In contrast, average dimensions of the HPs, exhibit a strong dependence on architectural details (max WI systems always appear larger in size), while reduction of their size as $\lambda_B$ increases, appears as a rather general tendency which is more prominent for max WI systems. Moreover, it appears that the relative change in the size of max WI models upon increase of $\lambda_B$ is higher for larger molecular-weight HPs.

To isolate the effect of complexation, the average dimensions of HP participating in complexes were compared to those of analogous non-charged and non-complexed hyperbranched models. The result of such comparison is presented in Fig. 3. For low $\lambda_B$ values and for both topologies the corresponding ratio of the radii of gyration is very close to unity. Augmentation of the strength of the electrostatic interactions results to significantly lower ratios. This reduction of average dimensions occurs “earlier” (i.e. at smaller $\lambda_B$ values) for max WI models, while it proceeds with a faster rate compared to the behavior of the min WI systems. In addition, while min WI HPs follow practically a common mastercurve, in max WI models a molecular-weight dependence is observed.

The influence of the variation of $\lambda_B$ to the shape of the examined models was followed by monitoring the relevant aspect ratios of the ellipsoid of inertia as discussed earlier. Fig. 4 depicts their behavior, for the lower and the higher molecular weight systems examined. As a general remark we note that in all systems the shape of HPs deviates from the spherical geometry, corresponding to elongated ellipsoidal objects. However, differences between systems belonging to the two extreme topologies can be discerned. While the shape of min WI models remains rather insensitive to $\lambda_B$ variation, max WI HPs tend to more isotropic shapes at higher intensities of electrostatic interactions. Comparison between the responses of the low and the high MW HPs bearing max WI, shows that while at G2 systems the “transition” to more isotropic shapes is manifested via a sigmoidal step-like manner close to $\lambda_B = 1$, for the larger size models this change assumes a more “continuous” character towards lower values of aspect ratios.

To probe the effects of $\lambda_B$ variation at shorter lengthscales as it is reflected to local bead arrangements, we have examined the bead and density profiles of the models with respect to the center of mass of the HP. Fig. 5 displays such bead distributions for the G3 models. The qualitative picture emerging from the observed behavior is representative for the G2 and the G4 systems as well. For the more compact min WI model, increase of $\lambda_B$ imparts a rather moderate narrowing of the distributions, while for the more “open” max WI system, the same effect becomes more pronounced at larger $\lambda_B$ values. This behavior is fully consistent with the reduction of dimensions observed upon increase of Bjerrum length. Such changes have a direct impact in local densities of the systems. Figs. 6 and 7 group together variations of the local densities imparted to min and max WI HPs participating in complexes, for low and high Coulombic strength conditions. Comparison between min and max WI systems of the same size and at constant $\lambda_B$ shows that HPs bearing the...
Fig. 5. Effect of Bjerrum length on HPs’ average radial bead distributions of (a) G3_13MIN and (b) G3_13MAX HPs in complexed systems. Distributions corresponding to single non-charged HPs are denoted by solid lines for comparison.

Fig. 6. Average radial density distributions of MIN WI HPs in complexes for Bjerrum lengths equal to 1 (points) and 8 (lines).

Fig. 7. Average radial density distributions of MAX WI HPs in complexes for Bjerrum lengths equal to 1 (points) and 8 (lines).

min topology assume higher densities close to the center of mass compared to their max analogues. This observation is compatible to the denser branching pattern characterizing min models. As for the effect of electrostatic interactions, increase of $\lambda_B$ results to less broad profiles for all the models studied. This effect is more prominent for max systems, for which at large Bjerrum lengths and at high molecular weight a plateau-like profile with a gradual monotonic decrease close to the HP periphery, is observed.

4. Summary/conclusions

The response of static/structural properties of the LP and HP constituents of non-covalent electrostatically maintained complexes was examined by means of Brownian dynamics simulations, as a function of the strength of Coulombic interactions, for systems bearing different topologies and sizes. In most cases it was required that $\lambda_B$ was increased above a threshold of $\lambda_B = 1$ for appreciable changes to be observed. At all cases, increase of $\lambda_B$ incurred smaller in size and more isotropic complexes, with more homogenized density profiles. The shape of the complexes at different $\lambda_B$s exhibited molecular weight dependence as far as it concerned the degree of elongation. Molecular weight dependence was also noted regarding changes in the internal mass/density distributions. The larger the models are the more effective the increase of electrostatic interactions towards homogenization of their profiles, since interpenetration between the HP and the linear chain increases.

The findings concerning the relative response of min and max WI models to changes of the intensity of electrostatic interactions can be understood in terms of the “openness” or “compactness” of the corresponding HP structures utilized. The more compact complexes formed by min WI HPs, possess a dense connectivity pattern close to the topological center, are not easily deformable and thus less prone to significant changes in size, shape and mass distributions as well as to penetration by the linear electrolyte. On the contrary, the more open structure characterizing complexes comprised by max WI HPs, allows a larger degree of deformation, leading to an increase of the average size and the anisotropy in shape, while permitting a larger degree of penetration of the linear chain as well. Therefore, increase of Coulombic interactions can incur more drastic changes to all the observed quantities (local density profiles, size and shape) in these models.

Recapitulating, it was demonstrated that several structural characteristics of such complexed systems can be manipulated by modification of topology, size and an external parameter like the intensity of Coulombic interactions. As changes in these factors are readily realizable in actual systems, the results presented may serve as a guide in cases were control of any of the above parameters is important for applications involving systems bearing similar structural attributes as the ones examined.

Acknowledgements

Funding from Hellenic General Secretariat for Research and Technology (PENED 2003, Grant No. 03E$\Delta$716) is acknowledged. S.V.L. also acknowledges funding from NWO Grant No. 047.019.001 and RFBR Grant No. 05-03-32450.

References