



## Nanoclusteration of DNA with Dendronized Polymer in Terms of Free Energy

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A thermodynamic cycle for the nanoclusteration between DNA and dendronized polymer is proposed and electrostatic free energies of a series of DNA- dendronized polymer nanoclusteration processes are calculated. The free energies for assembling fixed charges and mobile ions, and the bending energies of the DNA chain wrapped around the dendronized polymer are taken into consideration. The free energies of nanoclusteration are calculated for a number of nanoclusters with different conformations at constant temperature and constant ionic strength. The effects of temperature and ionic strength on the free energy of nanoclusteration and stability of their conformations are also investigated.

**Keywords:** Nanoclusteration, Dendronized polymer, DNA, Free energy, Nano-cylinder, Gene therapy

### INTRODUCTION

The investigation of nanoclusteration between flexible chain DNA with surface negative charges and macro-ions with opposite charges is an important subject in nanobiotechnology and genetic science [1]. There has been great interest in the aggregation of oppositely charged macro-ions in solution, experimentally [2]. For example, the nanoclusteration of DNA with oppositely charged liposomes has been intensely studied in the context of gene therapy [1-3]. DNA delivery has also been pivotal in developing new approaches (*e.g.*, gene therapy and DNA vaccination) for treating and controlling diseases that are likely to impact clinical medicine and nanobiotechnology over the next few years.

The main problem is to introduce DNA with negative

surface charges into the living cell which has a negatively charged membrane of lipoprotein. One approach pioneered by Felgner and Ringold [4] relies on associating anionic nucleic acids and cationic lipid liposomes, at which point the neutralized DNA-lipid complex can approach the negatively charged phospholipid membrane. In addition, there are a number of synthetic vectors, including polylysins, cationic polymers and, recently, dendrimers, which have been used for this purpose [5-7].

Dendrimers are a new class of synthetic, highly branched polymers, which have a structural advantage for gene transfer. These molecules are uniform in size with a high density of charged primary amino groups restricted to the surface and are highly soluble and stable in aqueous solution. Recent studies have shown that starburst dendrimers are non-immunogenic and can mediate the enhanced delivery of diverse nucleic acids, including single-stranded, double-stranded, natural, or synthetic DNA or RNA [8,9].

Despite of extensive theoretical and experimental research

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on the polyelectrolyte (PE) solutions [10], DNA solutions are relatively poorly understood compared to their importance. To simulate DNA-dendrimer nanoclusters, which are flexible polyelectrolyte chain systems, the effects of bending, twisting and the electrostatic potential of DNA in solution have to be considered. The aspects of bending, twisting and stretching under different ranges of forces (*i.e.* elastic DNA conformation) [11,12] have been analyzed for both closed circular and open linear configurations by using Lagrangian mechanics [13-16], numerical molecular dynamics [17] and statistical mechanics [18,19].

The electrostatic potential models are mainly based on the Poisson-Boltzmann (PB) equation [10]. The density of charges is applied and electrostatic potentials are calculated by solving the linear or nonlinear differential PB equation [20].

In our previous works [21-26], the electrostatic potential and then electrostatic free energies, entropic free energies and distribution of counter ions were determined for a series of DNA-dendronized polymer nanoclusters with different DNA pitches by application of the finite difference numerical method and solving the nonlinear PB equation at various ionic strengths and different temperatures. It was shown that in a series of conformations at constant ionic strength, the electrostatic free energies and entropic free energies primarily decrease sharply and then smoothly increase with the increase in DNA pitch size. It was also shown that, with the decrease in the ionic strength, electrostatic free energies and entropic free energies will decrease and the conformation with the least electrostatic free energy corresponds to the smallest DNA pitch. The effect of temperature on the most stable conformation of DNA-dendronized polymer nanocluster was also investigated.

In the present work we propose a thermodynamic cycle for the calculation of electrostatic free energies for the process of nanoclusteration between DNA and dendronized polymer at five different ionic strengths, 0.005, 0.05, 0.1, 0.15, and 0.2 M, at 298.15 K. The electrostatic effects of DNA, dendronized polymer and DNA-dendronized polymer nanocluster are modeled and the elastic effects were investigated by considering the bending and twisting aspects of DNA.

## Theory and Method

The free energy of nanoclusteration,  $\Delta G_{NC}$ , is produced by

two major effects, known as electrostatic and elastic effects, which have to be modeled and used in the nanoclusteration process.

**Electrostatic model.** The electrostatic potential of the nanocluster system can be modeled by the nonlinear PB equation, which is derived from the Poisson equation [10].

$$\nabla \cdot \epsilon(\bar{r}) \nabla \phi(\bar{r}) = \frac{-e}{kT} \left\{ \sum_j q_j^{f-} \delta(\bar{r} - \bar{r}_j) + \sum_i q_i^{f+} \delta(\bar{r} - \bar{r}_i) \right\} + \epsilon \kappa^2 \sinh \phi(\bar{r}) \quad (1)$$

where  $\epsilon$  is the dielectric constant ( $= \epsilon_r \epsilon_0 = 78 \times 8.854 \times 10^{-12} \text{ C}^2 \text{ m}^{-2} \text{ N}^{-1}$  (in water) and  $\Psi$  (volt) and  $\phi = \Psi e/kT$  are the electrostatic potential and dimensionless electrostatic potential, respectively. At any point in the system,  $q_i^{f+}$  and  $q_j^{f-}$  are positive and negative fixed charges, respectively.  $\kappa$  is the modified Debye-Hückel parameter,  $\kappa^2 = 1/\lambda^2 = 2e^2 I/\epsilon kT$ ,  $\lambda$  is the Debye length,  $I$  is the ionic strength of the bulk solution and  $\bar{r}$  (m) is the position vector of the charges. The analytical solution of this equation is only possible for simple and symmetrical systems. Since the DNA-dendronized polymer nanocluster is a complicated system and the analytical solution of the PB equation is impossible, the finite difference method is used to obtain the electrostatic potential of system [21].

Electrostatic free energies, which are produced in the process of nanoclusteration, result from the electrostatic potential [27-28] of the DNA, dendronized polymer and DNA-dendronized polymer nanoclusters.

**Elastic model.** The first elastic model for DNA supposes that the molecule is a slender cylindrical elastic rod [29] that is parameterized by arc length, denoted by  $s$ . We describe the rod by relating its local coordinate frame  $L$  to its frame  $L_0$  rigidly embedded in the curve in its relaxed configuration at each point of the arc length. The configurations are specified by each cross-section, described by a frame of three orthonormal unit vectors  $\{\mathbf{u}(s), \mathbf{n}(s), \mathbf{t}(s)\}$  along the chain, where  $\mathbf{t}(s)$  is the unit tangent vector determining the shape of the backbone,  $\mathbf{u}(s)$  is a perpendicular vector of  $\mathbf{t}(s)$  related to the bending of the chain, and  $\mathbf{n}(s) = \mathbf{t}(s) \times \mathbf{u}(s)$  is a unit vector that keeps track of the twist. The relationship between local frames is specified by the Euler angles  $\alpha(s)$ ,  $\beta(s)$  and  $\gamma(s)$ , which are needed to rotate  $L_0$  into  $L$  [30].









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*J. Iranian Chem. Soc. 3(2): 161-167, 2006*

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### SYMBOLS

$\epsilon$	Dielectric constant
$(= \epsilon_r \epsilon_0 = 78 \times 8.854 \times 10^{-12} \text{ C}^2 \text{ m}^{-2} \text{ N}^{-1} \text{ (in water)})$	
$\Psi$	Electrostatic potential [volt]
$\vec{r}$	Position vector
$q_i^{f+}$	Positive fixed charge
$q_j^{f-}$	Negative fixed charge
$e$	Charge of electron
$k$	Boltzmann constant
$T$	Absolute temperature
$\phi = \Psi e / kT$	Dimensionless electrostatic potential
$\kappa$	Modified Debye-Hückel parameter
$\delta(\mathbf{r} - \mathbf{r}_i)$	Kronecker Delta
$\lambda$	Debye length
$I$	Ionic strength of the bulk solution
$\Delta G_{el}$	Electrostatic free energy
$\Delta G_{elas}$	Elastic free energy of DNA
$\Delta G_{bend}$	Bending free energy of DNA
$\Delta G_{twist}$	Twisting free energy of DNA
$\alpha(s), \beta(s), \gamma(s)$	Euler angles
$l$	Length of DNA
$L$	Local coordinate frame
$L_0$	Rigidly local coordinate frame
$A$	Elastic constant of bending
$C$	Elastic constant of twisting
$s$	Arc length
$\eta$	Length of DNA per unit length of dendrimer
$\sigma$	Height per turn
$R$	Radius of wrapping