Molecular Biology, Vol. 35, No. 1, 2001, pp. 106–107. Translated from Molekulyarnaya Biologiya, Vol. 35, No. 1, 2001, pp. 117–119.

BIOPOLYMER PHYSICS AND PHYSICAL CHEMISTRY

UDC 577.323.722

Calculations of DNA Condensation Caused by Ligand Adsorption

V. B. Teif and D. Yu. Lando

Institute of Bioorganic Chemistry, Belarussian Academy of Sciences, Minsk, 220141 Belarus;
E-mail: lando@ns.iboch.ac.by

Received June 21, 2000

Abstract—A method for calculating the curves of DNA transition from linear to condensed state upon binding of condensing ligands has been developed. The character of the transition and ligand concentration necessary for condensation have been shown to be governed by the length of DNA molecule, energy and stoichiometry parameters of the DNA–ligand complex (equilibrium constant between linear and condensed form in the absence of ligands, constants for ligand binding to linear and condensed forms, the number of base pairs covered by one ligand, etc.). The results of the calculations indicate that a slight difference in the free energies of these DNA states (less than 6 cal/mol(bp) for a DNA of 500 bp) is sufficient for the existence of a stable linear state in the absence of ligands (in free DNA) and the formation of stable condensed state upon complexation.

Key words: DNA condensation, ligand adsorption on DNA

DNA condensation is a transformation of linear DNA chains into compact ordered species containing only one or several molecules. DNA in the condensed state exists in phages and chromosomes, where its dense packing is accomplished by special mechanisms elaborated by Nature.

Condensation can be achieved *in vitro* by adding ligands, e.g., polyamines or trivalent metal ions, to a DNA solution [1]. At a certain critical ligand concentration in solution, an abrupt transition of linear or circular DNA into a globular (condensed) form is observed [1–6]. Different forms of condensed DNA can be obtained, depending on DNA topology, condensing agent structure, etc. [5].

Earlier we modeled one of the mechanisms of DNA condensation caused by ligand adsorption [7]. Strong long-range order interaction between all adsorbed ligands is necessary to accomplish this mechanism. This paper reports an alternative approach, which does not require long-range interaction for the condensation.

Let us consider an ensemble of n DNA molecules, each of which consists of L base pairs (units). Each molecule can be linear (i = 1) or condensed (i = 2). The intermediate states for each separate molecule are forbidden, as often observed in experiment [2]. All DNA molecules in state i bind k_i ligands. The ligands can be also in a free (dissociated) state at a molar concentration c_o. Let N_i be the total number of units in n_i DNA molecules in state i ($N_i = n_i L$), while $c_i = k_i/N_i$ is the relative concentration of the ligands bound to form i. The binding is supposed to be reversible, i.e., each ligand can change its location at the DNA chain, dissociate, and bind again to other DNA molecules.

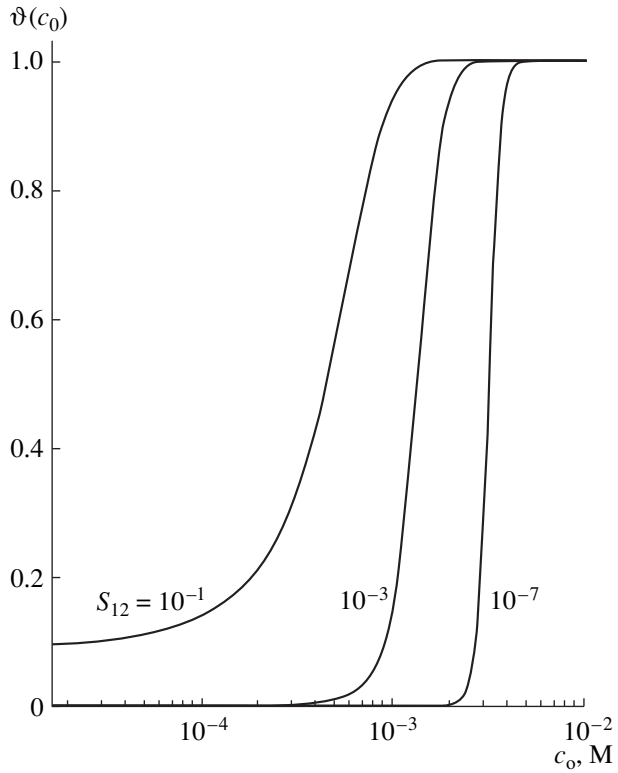
Ligand complex with the i form of DNA has the following parameters: K_i is the constant for ligand binding to DNA in state i; m_i is the number of bp covered by one ligand molecule on DNA upon binding; r_i is the number of bp per one center of ligand binding (see details in [7–9]).

Let k ligands, which bind to linear (k_1 ligands) and condensed (k_2 ligands) forms of DNA ($k = k_1 + k_2$), be removed from a solution of molar concentration c_o. The change in free energy [$\Delta F(k_1, k_2, c_o)$] resulting from the binding of k_1 ligands to n_1 linear DNA molecules and k_2 ligands to n_2 condensed molecules is determined by the expression

$$\Delta F(k_1, k_2, c_o) = \sum_{i=1}^{2} (n_i F_i + k_i \Psi_i - k_i \mu) - RT \ln(W), \quad (1)$$

where F_i is the free energy of DNA molecule in the i state in the absence of adsorbed ligands; Ψ_i is the free energy corresponding to ligand binding to DNA molecule in state i; R is the gas constant; T is the temperature (K); $\mu = \mu_o + RT\ln(c_o)$ is the chemical potential of free ligands, W is the number of different states of the system at a constant energy of DNA and bound ligand molecules. Earlier works [10–12] show that W is determined by expression (2) with sufficiently high accuracy at $L \gg m_1, m_2$:

0026-8933/01/3501-0106$25.00



Dependences of DNA condensation degree (ϑ) on free ligand concentration in solution (c_o) calculated for different values of S_{12}. L = 500 bp, $K_1 = 0$, $K_2 = 10$ M^{-1}, $m_1 = m_2 = r_1 = r_2 = 1$, $S_{12} = 10^{-1}$, 10^{-3}, 10^{-7} (no binding to linear DNA).

$$W = \prod_{i=1}^{2} \frac{[N_i/r_i - (m_i - 1)k_i]!}{k_i!(N_i/r_i - m_i k_i)!} \frac{n!}{n_1! n_2!}. \quad (2)$$

The equilibrium values of n_i and k_i correspond to the minimum of ΔF at $n_1, n_2, k_1, k_2 \longrightarrow \infty$. From the condition of free energy minimum $\partial(\Delta F)/\partial k_i = 0$, $\partial(\Delta F)/\partial n_i = 0$ and the Stirling formula, we obtain the mass action law (3) for the system under consideration and expression (4) for the condensation of DNA molecules [$\vartheta = N_2/(N_1 + N_2) = n_2/(n_1 + n_2)$]:

$$K_i = \frac{r_i c_i [1 - r_i(m_i - 1)c_i]^{m_i - 1}}{c_o (1 - r_i m_i c_i)^{m_i}}, \quad (3)$$

$$\vartheta = US_{12}/(1 + US_{12}), \quad (4)$$

where $K_i = \exp[(\mu_o - \Psi_i)/(RT)]$ is the binding constant for ligands to form i; $S_{12} = \exp[(F_1 - F_2)/RT]$ is the equilibrium constant for the linear and condensed states in the absence of ligands; U is determined by equation (5):

$$U = \prod_{i=1,2} \{[1 - r_i(m_i - 1)c_i]/(1 - r_i m_i c_i)\}^{(-1)^i (L/r_i)}. \quad (5)$$

The figure shows condensation curves (dependences $\vartheta(c_o)$) calculated from equations (3)–(5) for the case when the molar concentration of free ligands (c_o) is independent of the number of ligands bound to DNA, i.e. $c_o \gg M$, where M is the molar concentration of base pairs. At sufficiently low values of S_{12}, virtually all DNA molecules are in the linear state in the absence of ligands. DNA condensation takes place when c_o increases within a certain range if $K_2 > K_1$. The position and width of the transition range depend on the equilibrium constant S_{12}. The calculations indicate that the parameters of the transition into condensed state also depend on the DNA length (L), energy (S_{12}, K_i) and stoichiometric (r_i, m_i) parameters of the complex. It is seen from the figure that just a slight difference in the free energies of these states in free DNA (less than $0.01RT$, i.e., 6 cal/mol(bp) for a DNA of 500 bp) is sufficient for the existence of a stable linear state in the absence of ligands and for the formation of a stable condensed state upon complexation.

ACKNOWLEDGMENT

This work was supported by the Belarussian Foundation for Basic Research (project no. X99P–099), the International Science and Technology Center (ISTC, project A-301), and the Civilian Research and Development Foundation (CRDF Award AB2-2006).

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