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Abstract

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A MODEL THERMODYNAMIC THEORY OF THE POLYCONDENSATION OF DEOXYRIBONUCLEIC ACID

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In previous communications ([1,2]) a theory was proposed for the reduplication synthesis of deoxyribonucleic acid (DNA), based on the concept of a cooperative process of nucleotide polymerization. This theory made it possible to elucidate the thermodynamic nature of reduplication, starting from a simple model. However, as was shown in Kornberg' s experiments ([3]), DNA synthesis proceeds not as a polymerization process, but as a polycondensation process. Nucleotide triphosphates (NTP) join into chains, and an equimolecular amount of inorganic diphosphate (pyrophosphate, PP) enters the solution. In considering such polycondensation we may use the same mathematical method as before ([1,2]). As was shown, reduplication takes place in a manner similar to a first-order phase transition. This proposition is also retained in the theory of polycondensation, but the transition point turns out to depend not on the absolute concentration of nucleotides, but on the ratio between the concentrations of NTP and PP.

The calculation gives the following value for the difference of the free energies of two double helices and the initial single double helix of DNA in solution

$$\Delta F \simeq -N(2\varepsilon_1 + \varepsilon_2) - 2NkT \ln\left(\frac{qq''}{q'}\frac{M}{4}a\right), \tag{1}$$

where N is the number of nucleotides in one DNA chain; M is the number of NTP in the solution surrounding the double helix; q, q', q'' are the statistical sums, respectively, of a nucleotide in the DNA chain, of one NTP molecule in solution, and of one PP molecule in solution; ε_1 is the energy released in the polycondensation of one NTP; ε_2 is the mean energy of the hydrogen bonds between two nucleotides in DNA. The value of the quantity a depends on the nature of the solution. If the initial solution contained no PP, then

$$a = \frac{e}{2N},$$

and if the initial number of PP molecules in the solution is $L \gg N$, then

$$a = \frac{1}{L}.$$

The condition for reduplication is

$$\Delta F \ll 0. \tag{2}$$

For $L \gg N$, the transition is determined by the relation

$$\frac{2\varepsilon_1 + \varepsilon_2}{2kT} \gg \ln\left(\frac{4L}{M}\frac{q'}{qq''}\right). \tag{3}$$

Let us take $\varepsilon_1 \simeq 4$ kcal/mol, $\varepsilon_2 \simeq 7$ kcal/mol. A rough estimate gives $qq''/q' \simeq 10^{-2}$, and consequently, if $L/M < 7 \cdot 10^2$, then reduplication pre-

decreases. Kornberg brought the maximum ratio of the quantities of PP and NTP up to 10^2. In this case DNA reduplication still proceeded, but at a reduced rate ([3]).

With successive reduplication of DNA in solution, the content of PP increases and the content of NTP decreases. Thus a kind of "feedback" is effected—the process ultimately ceases. Suppose that at some stage of the process there were s double helices of DNA, M molecules of NTP, and L molecules of PP. The maximum number of double helices obtained, $s + t$, is found from the condition of minimum free energy. We obtain

$$t = \frac{\frac{M}{4}\frac{qq''}{q'} - \exp\left(-\frac{2\varepsilon_1 + \varepsilon_2}{2kT}\right) \cdot L}{2N\left[\exp\left(-\frac{2\varepsilon_1 + \varepsilon_2}{2kT}\right) + \frac{qq''}{4q'}\right]}. \tag{4}$$

For the same values of the constants,

$$t \simeq \frac{M - 15 \cdot 10^{-4} L}{2N}.$$

The yield of DNA, characterized by the quantity t, must depend on the relative content of guanine–cytosine pairs ($\Gamma +$) and adenine–thymine (A + T), since $\Gamma +$ form three, while A + T form two hydrogen bonds. If ε_2^* is the energy of the hydrogen bonds of A + T, and $\varepsilon_2^* + \Delta\varepsilon_2$ is the energy of the hydrogen bonds of $\Gamma +$, then

$$\varepsilon_2 = \varepsilon_2^* + x\Delta\varepsilon_2, \tag{5}$$

where

$$x = \frac{[\Gamma + \ ]}{[\Gamma + \ ] + [\mathrm{A} + \mathrm{T}]}. \tag{6}$$

Substituting (5) into (4), we obtain

$$2Nt = M - \exp\left(-\frac{2\varepsilon_1 + \varepsilon_2^*}{2kT}\right) \frac{4L}{qq''} q' \exp\left(-x\frac{\Delta\varepsilon_2}{2kT}\right) \tag{7}$$

or

$$[\mathrm{DNA}] = [\mathrm{NTP}] - \alpha e^{-\beta x}.$$

The quantities

$$\beta = \frac{\Delta\varepsilon_2}{2kT} \simeq 1.7, \qquad \alpha \simeq [\mathrm{PP}]\, 2 \cdot 10^{-2}.$$

The condition for DNA denaturation has the same form as in the polymerization model ([2]).

Let us consider the probability of an incorrect attachment of a nucleotide to a DNA chain under the assumption that such an incorrect attachment does not allow the nucleotide to join with neighboring nucleotides of the given chain. Indeed, in such a case the regularity of the double helix is disturbed and steric factors will hinder the polycondensation of the incorrectly attached nucleotide. If there is no polycondensation, then the energy of two chemical bonds $2\varepsilon_1$ is lost and the entropy of the system decreases, since two molecules of PP are not released into solution. The probability of an incorrect attachment at a given site of the chain is characterized by the quantity

$$w = \exp\left(-\frac{\Delta E - T\Delta S}{kT}\right),$$

where $\Delta E = 2\varepsilon_1$; $\Delta S \simeq -k\ln[Q(n/L)^2]$; $Q \simeq q''^2/3$ is a statistical factor associated with a twofold decrease in the number of PP in solution; $(n/L)^2$ characterizes

corresponding change in the entropy of mixing (n is the number of solvent molecules). In view of the fact that $n/L \sim 10^6$ in Kornberg' s experiments, w, in any case, is less than 10^{-16}. At the same time $q'' \gg 1$. The probability w is vanishingly small. Consequently, the accuracy of specific reduplication synthesis is very high; in other words, the probability of spontaneous mutations modeled in the indicated way is small. Once they have occurred, however, mutations are reduplicated.

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CITED LITERATURE

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Note: Figure translations are in progress. See original paper for figures.