On aggregation in binary biopolymer systems

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Abstract: The main structural protein of the human eye, which accounts for about 50 % of the mass of all water-soluble proteins comprising the lens, is α-crystallin. Alpha-crystallin functions as a molecular chaperone, preventing other lens crystallins from interfering in the vital activity. Alpha-crystallins partially or fully stabilise unfolded proteins, preventing the formation of deposits, helping to preserve the lens transparency and reducing the risk of a number of diseases, including cataracts. This biological phenomenon can be considered in the framework of materials science when considering the problem of slowing down the aging processes of polymers. In the present study, methods for slowing down the process of aggregation of α-lactalbumin in solution are considered, using the binary system α-lactalbumin–α-crystallin as an example. To this end, experimental data on the rate of change of the aggregation process were formalised, i.e. expressed in terms of transition temperatures and plasticisation functions of the components. The proposed expressions make it possible to clarify the concentration dependence of the initial aggregation rate, its order, and also to quantify the effect of the dose of UV irradiation on the aging process of the system. The experimentally obtained result means that an increase in the content of α-crystallin leads to an additional blocking of hydrogen bonds in the surface layers of α-lactalbumin and, accordingly, to an increase in the plasticising effect. In addition, the obtained expression of the activation energy of polymer chain rearrangement helps to account for the influence of infrared radiation on the development of so-called thermal cataracts (usually occurring in glassblowers, steelmakers, blacksmiths, welders, etc.), when the etiological factor consist in infrared rays having wavelengths from 0.74 to 2.50 microns, which freely pass through the cornea and iris without damaging them, and are largely adsorbed by the lens, causing its overheating.

Keywords: α-lactalbumin, crystallin, binary system, aggregation order, plasticisation functions, transition temperatures

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INTRODUCTION

Binary biopolymer systems, such as protein-protein and protein-polysaccharide formations, are widespread in nature. Moreover, processes occurring in such systems under the influence of various external factors are of practical interest not only for the biological systems themselves as an example of self-regulation, but also for binary systems based on synthetic polymers.

An analytical description of such processes is of significant interest both in the case of medicine (for example, in the development of drugs to slow the development of cataracts), and in the case of polymer materials science when attempting to slow down processes leading to degradation of materials.

Typically, the development of aging processes is influenced by many factors (heat, light, penetrating radiation, oxygen, moisture, aggressive chemicals, mechanical stresses) that cause two types of irreversible chemical reactions in polymers: destruction, when bonds in the main chain of macromolecules break, and structuring when chain stitching occurs. A change in the molecular structure leads to changes in the properties of the polymeric material: elasticity is lost, rigidity increases, dielectric parameters deteriorate, etc. [1].

Here we will focus on the action of only one factor, namely light (photochemical destruction), when the destruction of macromolecules occurs under the influence of ultraviolet (UV) rays having a wavelength $\lambda < 400 \text{ nm}$. Polymers containing atomic groups or individual polar groups capable of absorbing light are particularly intensively degrade. In the case of proteins, these are amino acids tryptophan ($W$) and tyrosine ($Y$) [2]. The choice of the protein-protein system of the eye lens as an example was motivated by the significant accumulation of experimental material obtained during studies of the aging of this system (development of cataracts) [3, 4], which can be formalised in the framework of polymer physics.

One of the natural mechanisms of inhibition of cataract development in the human eye is associated with the presence of the $\alpha$-crystallin protein in the lens, which performs a molecular chaperone role — in this case, preventing the aggregation of $\beta$-crystallin and thereby preventing the development of cataracts [4]. In this case, the $\alpha$-crystallin molecules permeate into a $\beta$-crystallin structure that has denatured under the influence of UV radiation, permeating it and reducing the $\beta$-crystallin thermal aggregation rate.

The influence of infrared radiation can be seen in the development of so-called thermal cataracts typically occurring in glassblowers, steelmakers, blacksmiths, welders, etc. Here, the etiological factor consists in infrared rays having wavelengths from 0.74 to 2.50 microns, which freely pass through the cornea and iris without causing damage to them, but are then largely adsorbed by the lens, leading to overheating. An increase in the temperature of the lens in turn leads to an increase in the rate of thermal aggregation of $\beta$-crystallin.

EXPERIMENTAL PART

An analytical description of the effect of $\alpha$A-crystallin on aggregation of $\beta$-crystallin and the effect of UV irradiation on initial adsorption ability of $\alpha$-crystallin were examined in detail on the example of the $\alpha$-lactalbumin–$\alpha$A-crystallin model system. The results of experimental studies given in [5, 6] were used as the initial data together with information on the amino acid composition of the proteins of the system under consideration. $\alpha$-Lactalbumin has a molecular weight of about 14 000 g/mol; its molecule is comprised of a sin-
gle polypeptide chain consisting of 123 amino acid residues and containing four disulphide bonds. The predominant amino acids of α-lactalbumin are, mg / g: aspartic acid – 18.7; glutamic acid – 12.9; leucine – 11.5; lysine – 11.5; tryptophan – 7.0; isoleucine – 6.8; cystine – 6.4 etc. The eye lens protein αA-crystallin, consisting of 173 amino acid residues (AAR), belongs to the family of small heat shock proteins (sHSPs), having a molecular weight of about 20 000 g/mol.

RESULTS AND DISCUSSION
Refinement of the concentration dependence of the initial aggregation rate and the physical meaning of the parameters included therein

An empirical expression for determining the initial aggregation rate of v as a function of x (phase concentration ratios of α-crystallin and α-lactalbumin) was proposed in [5]:

\[ \frac{v}{v_0} = 1 - AC_\alpha x, \]

where \( v_0 \) – is the initial aggregation rate when \( x = 0 \); \( n \) – the aggregation order, which according to [7] is equal to 5.3±0.3; \( AC_\alpha \) – initial chaperone adsorption capacity; \( x = [\alpha\text{-crystallin}]/[\alpha\text{-lactalbumin}], \) [α-crystallin] and [α-lactalbumin] – molar concentrations of αA-crystallin and α-lactalbumin in a solution. In the study of anti-aggregation activity of αA-crystallin the authors of [6] obtained the value \( AC_\alpha = 1.18 \) with [α-lactalbumin] = 0.5 mg/ml.

In order to establish the dependence of the coefficient \( AC_\alpha \) on the characteristic temperatures of the polypeptides of the system αA-crystallin and α-lactalbumin, we use the theory of absolute reaction rates [8] in calculating v:

\[ v = \frac{kT}{2\pi\hbar} \exp \left( \frac{\Delta S^*}{k} \right) \exp \left( \frac{-\Delta H^*}{kT} \right). \]

The values of \( \Delta S^* \) and \( \Delta H^* \) represent changes in the system’s entropy and enthalpy during the transition of the rotational polymer isomers (α-lactalbumin and αA-crystallin) into an activated state.

Let us determine the relative concentration of α-crystallin \( C_{\alpha\text{-cryst}} \) in the original system as

\[ C_{\alpha\text{-cryst}} = \frac{[\alpha\text{-cryst}]}{[\alpha\text{-cryst}]+[\alpha\text{-lact}]}, \]

and \( C_{\alpha\text{-lact}} \) like

\[ C_{\alpha\text{-lact}} = \frac{1}{1+x}. \]

Then the activation enthalpy of the complex α-crystallin and α-lactalbumin \( \Delta H^\#_{\text{cpl}} \) can be represented as

\[ \Delta H^\#_{\text{cpl}} = \frac{1}{1+x} \Delta H^\#_{\alpha\text{-lact}} + \frac{x}{1+x} \Delta H^\#_{\alpha\text{-cryst}}. \]

Equal assumption that the changes in the activation entropy of α-crystallin and α-lactalbumin are the same and using expression (2), equation (1) in general form can be written as follows:

\[ \frac{\exp \left( -\frac{\Delta H^\#_{\text{cpl}}}{nkT} \right)}{\exp \left( y \frac{x}{1+x} (1-y) \right)} = \frac{\exp \left( -\frac{\Delta H^\#_{\alpha\text{-lact}}}{nkT} \right)}{\exp \left( -\frac{\Delta H^\#_{\alpha\text{-cryst}}}{nkT} \right)}, \]

where \( y = \frac{\Delta H^\#_{\alpha\text{-lact}}}{\Delta H^\#_{\alpha\text{-cryst}}}. \)

Given that \( 1-y \ll 1 \), the dependence of \( (v/v_0)^{1/n} \) from x will be non-linear:

\[ \frac{v}{v_0} = 1 - AC_\alpha \frac{x}{1+x}, \]

where

\[ AC_\alpha = y (1-y). \]

From expression (9) it follows that for \( x_{\text{max}} \sim 5.5 \ AC_\alpha = 1.18 \), \( (v/v_0)^{1/n} \sim 0 \), i.e. the aggregation process is completely stopped. Accordingly, the dependence \( (v/v_0)^{1/n} = f(x) \) will differ from the linear (1) already for \( x = 0.35 \) and 0.5 (see. Fig. 6 in [5]). Dependence (1) can be obtained from expression (9) when \( x << 1 \).

Unfortunately, in [5], measurements for \( x = 0.5 \) and \( x = 0.6 \) were not performed; however, measurements for \( x = 0.7 \) show that in this case \( (v/v_0)^{1/n} = f(x) \) at three points for \( x = 0.14, x = 0.35 \) and \( x = 0.7 \), estimate its values at the points \( x = 0.5 \) and \( x = 0.6 \). The obtained values are given in Table 1. The experimental values are shown in bold type and the corrected corresponding values are indicated in brackets (for \( x = 0.6 \)) when approximating the \( P(l(W, x)) \) quadratic parabola.

To identify the causes of the discrepancy of function (9) with constant \( AC_\alpha \) from the experimental dependence, we will dwell in more detail on expression (8). It was shown in the work [9] that the activation energy of the rearrangement of the polymer chain can be expressed in terms of its glass transition temperature. In this case,
Values of the plasticisation function \( P(W, x) \) for \( 0.35 < x \leq 0.7 \)

| \( x \) | 0.140 | 0.349 | 0.500 | 0.600 | 0.701 |
|---|---|---|---|---|---|
| \( (\sqrt[1/n]{\nu})^{1/n} \) | 0.840 | 0.661 | 0.520 | 0.400 (0.467) | 0.002 |
| \( P(W, x) \) | 1.000 | 1.000 | 0.989 | 0.982 (0.971) | 0.947 |

It follows from expression (10) that, in the case of the model system under consideration, \( y \sim const \). However, \( y \) may change when switching from a model system to a real one. If in the model system a decrease \( (T_{ch})_{\text{a-lact}} \) is achieved due to the plasticising effect of dithiothreitol (DTT) [6], then with UV irradiation of \( \beta_L \)-crystallin, plasticising effect is driven by the destruction of tyrosine and tryptophan due to photoionisation and subsequent formation of radicals and solvated electron. Therefore, in the case of a model system

\[
y = \frac{const \cdot (T_{g})_{\text{a-crist}}}{nT}, \quad \text{and} \quad y = \frac{(T_{g})_{\text{a-lact}} / (T_{g})_{\text{a-crist}}}{(T_{g})_{\text{a-lact}}},
\]

and the expression (8) takes the following form:

\[
AC_o = \frac{const \cdot (T_{g})_{\text{a-crist}}}{nT} \left(1 - \frac{(T_{g})_{\text{a-lact}} / (T_{g})_{\text{a-crist}}}{(T_{g})_{\text{a-lact}}}ight) (10)
\]

Using expression (11) and the values \( (\sqrt[1/n]{\nu})^{1/n} \) and \( x \) given in the table 1, we obtain the values of the plasticisation function \( P(W, x) \) with the corresponding values of \( x \) (see Table 1). The function \( P(W, x) \) will be approximated by a quadratic parabola: \( P(W, x) = 1 - ax - bx^2 \). The coefficients \( a \) and \( b \) can be found from the values of \( P(W, x) \) for \( x = 0.5 \) and \( x = 0.7 \). As a result, the dependence \( P(W, x) \) will take the following form:

\[
P(W, x) = 1 + 0.113x - 0.27x^2.
\]

Correction \( P(W, x) \) for \( x = 0.6 \) gives \( P(W, x) = 0.971 \).

The empirically-obtained result means that an increase in the content of \( \alpha \)-crystallin leads to an additional blocking of hydrogen bonds in the surface layers of \( \alpha \)-lactalbumin and, accordingly, to an increase in the plasticising effect. In this case, plasticisation occurs in the area of action of the Zhurkov mechanism [12], i.e. due to blocking of hydrogen bonds.

Similarly, if the dependence \( (\sqrt[1/n]{\nu})^{1/n} = f(x) \) it is possible to perform estimates for the system \( \alpha \)- and \( \beta_L \)-crystallins irradiated with UV. It should be noted that \( x = 0.7 \) is the limit value \( x_{\text{lim}} \) which does not depend on the model substance, since all measurements are carried out at physiological temperature, the molecular chaperone properties of \( \alpha \)-crystallin are studied.

On the reason of the temperature decrease of \( \beta \)-crystallin denaturation and the initial adsorption ability of the chaperone \( AC_o \), under UV irradiation. Under UV irradiation of \( \beta \)-crystallin, two amino acids (tryptophan and tyrosine) are exposed, which \( \beta \)-crystallin contains significantly more than \( \alpha \)-crystallin. The resulting amino acid radical interacts with neighbouring peptide chains of the
Матвеев Ю.И., Аверьянова Е.В. Об агрегации в бинарных биополимерных системах ...
protein molecule\(^1\). As a result, it is possible to form ring structures along the macromolecule chain, which will be a mixture of ring and linear sections with a significantly lower degree of polymerisation (the number of amino acid residues) than the initial chain. The latter will lead to the temperature denaturation of such a chain decreasing. Therefore, by selecting a dose of radiation, it is possible to achieve the transition of \(\beta\)-crystallin to a disordered state at physiological temperature. This is the difference in the conversion of \(\alpha\)-lactalbumin to a disordered state (this occurs due to plasticisation of DTT) from \(\beta\)-crystallin.

Moreover, since \(\alpha\)-crystallin also contains tryptophan and tyrosine, although in smaller quantities than \(\beta\)-crystallin, UV radiation can affect \((T_g)_{\alpha\text{-crist}}\) through its decline on the basis of the mechanism mentioned above. The latter is confirmed by the data given in [5]. The dependence found in [5] is well-described using equation (10) if instead of \((T_g)_{\alpha\text{-crist}}\) write \((T_g)_{\alpha\text{-crist}}P_l(D)\) (hereinafter the meaning of \(P_l(D)\) will be clarified).

The value of \(AC_\alpha/AC_{\alpha,\text{inact}} = 0\) corresponds to the condition \((T_g)_{\alpha\text{-lact}} = (T_g)_{\alpha\text{-crist}} = 1\). From this the glass transition temperature of irradiated \(\alpha\)-crystallin can be determined, which helps to calculate the change in its effective degree of polymerisation upon the formation of ring structures [11].

Since, upon irradiation, there is a decrease in \((T_g)_{\alpha\text{-crist}}\), then introducing the plasticisation function \(P_l(D) = (T_g)_{\alpha\text{-crist}}/T_g\), \(\alpha\text{-crist, inact}\), where \(D\) is the dose of UV irradiation; \(P_l(D) \leq 1\), and using expression (10), \(AC_\alpha/AC_{\alpha,\text{inact}}\) can be written as follows:

\[
AC_\alpha/AC_{\alpha,\text{inact}} = P_l(D) \left(1 - 0.9525P_l(W, x) / P_l(D)\right).
\]

From expression (11a), the dependence \(P_l(D)\) can be determined from the experimental values of \(AC_\alpha/AC_{\alpha,\text{inact}}\) given in [4]. In Table 4 the calculated values of \(P_l(D)\) are given. For \(P_l(D) = 0.9525\), where \(D^* = 32.5\) J/cm\(^2\), \(P_l(W, x) = 1\), the value \(AC_\alpha/AC_{\alpha,\text{inact}} = 0\), a change in the effective degree of polymerisation of the chain of \(\alpha\)-crystallin \(\Delta N\) under UV irradiation will be \(\approx 4\) units (per 4 amino acid residues). When evaluating \(\Delta N\), the Fox – Flory equation was used, which is usually used to calculate \(T_g\) polymers with a degree of polymerisation below critical. Most of the proteins are polymers of this kind, including \(\alpha\) – and \(\beta\)-crystallin.

Approximation of the data presented in Table 4 gives the following dependency:

\[
P_l(D) = 1 - 0.244D + 0.169D^2.
\]

It should be noted that while an increase in the content of \(\alpha\)-crystallin leads to a decrease in the rate of aggregation, then UV irradiation leads to inhibition of this process (an increase in the aggregation rate). Thus, considering the effect of irradiation, equation (11) can be written as follows:

\[
\left(\frac{V}{V_0}\right)_{\text{inact}} = 1 - 24.85P_l(D)(1 - 0.9525P_l(W, x) / P_l(D))^{1/x}.
\]

**Determination of the aggregation order by calculation**

Equation (11) includes the aggregation order parameter \(n\), which, according to [7], is equal to \(n = 5.3 \pm 0.3\). Show that the found value \(n\) can be estimated using the data of A.N. Kolmogorov cited in [13], where first proposed the equation that describes the kinetics of crystallisation of metals, which later became widely used in the description

| Parameter     | Value     |
|---------------|-----------|
| \(\bar{D}\)   | 0.038 0.077 0.154 0.231 0.308 0.407 |
| \(AC_\alpha/AC_{\alpha,\text{inact}}\) | 0.83 0.70 0.35 0.40 0.20 0.06 |
| \(P_l(D)\)    | 0.987 0.977 0.951 0.955 0.940 0.929 |

Note in the considered range of \(x\), the function \(P_l(W, x) = 1\), \(\bar{D} = D/D^*\).

Примечание. В рассматриваемом диапазоне изменения \(x\) функция \(P_l(W, x) = 1\), \(\bar{D} = D/D^*\).

\(^1\)Владимиров Ю.А., Потапенко А.Я. Физико-химические основы фото-биологических процессов: учеб. пособие для мед. и биол. спец. вузов. М.: Высш. шк., 1989. 199 с.
of nucleation processes of various structures in food, biological and pharmaceutical materials [14]. Usually in the modern notation [14] the equation of A.N. Kolmogorov, which abroad is called the Avrami equation, has the following form:

\[ 1 - \alpha = \exp(-K_c t^n), \quad (12) \]

where \( \alpha \) is the degree of structural order (crystallinity) of the solution; \( K_c \) is speed constant; \( n \) is a parameter characterising nucleation (in our case, the aggregation parameter).

A.N. Kolmogorov wrote the right side of equation (12) as \( \exp \left( -\frac{4\pi}{3} \cdot t^3 \cdot \Omega \right) \), while

\[ \Omega = \int \alpha(t') \int k(x) dx \cdot dt', \quad (13) \]

where \( k(t) \) is the rate of increase of the crystallised mass; \( \alpha(t) \) is the probability of formation per unit volume unit time interval of one crystallisation centre [13].

A.N. Kolmogorov showed that, given the various functions \( \alpha(t) \) and \( k(t) \), one can obtain \( \Omega = \text{const} \cdot t^3 \). Two cases were considered:

– when \( \alpha(t) \) and \( k(t) \) do not depend on time, i.e. \( \alpha(t)=\alpha=\) const, and \( k(t)=1 \), and then \( t^3 \sim t^3 \);

– when all crystallisation centres are formed at the beginning, and then \( t^3 \sim t^3 \).

In our case, the decrease in the rate of aggregation of \( \alpha \)-lactalbumin occurs due to the capture of molecules of \( \alpha \)-lactalbumin by molecules of \( \alpha \)-crystallin when they converge and mutually penetrate each other. In this case, \( k(t) \) will be proportional to the size of the diffusion zone of their mixing, i.e. \( t^{\frac{3}{2}} \) [15].

For \( \alpha(t)=\alpha=\) const, and \( k(t)\sim t^{\frac{4}{3}} \) from equation (13) we obtain \( t^{\frac{4}{3}} \sim t^{\frac{5}{3}} \), i.e. in equation (1) \( n \approx 5.5 \), which, within the limits of measurement accuracy, corresponds to the data [7].

CONCLUSIONS

Thus, as a result of the transformations of the equation for calculating the initial aggregation rate of \( \alpha \)-crystallin, the physical meaning of the coefficients included in it was revealed, which allows us to determine ways to slow down the aggregation process in the binary system \( \alpha \)-lactalbumin-\( \alpha \)-crystallin.

Due to the fact that \( \alpha \)-crystallin has a high degree of polydispersity, both aggregates of various sizes and individual molecules of \( \alpha \)-crystallin will be present in its solution. It was shown that the enhancement of the chaperone-like action of \( \alpha \)-crystallin is achieved either by increasing the concentration of individual molecules with an increase in its total content in the system, or by external action on aggregates of \( \alpha \)-crystallin, causing them to decompose into individual molecules. This property can be used in the development of drugs that slow cataract development, either by selecting substances that contribute to the decomposition of \( \alpha \)-crystallin aggregates, or by causing plasticisation of \( \beta \)-crystallin and increasing initial adsorption capacity of chaperone.

The calculation equation of the initial molecular chaperone adsorption capacity (10) also allows us to consider the influence of infrared radiation on the development of the so-called thermal cataract typically occurring in glassblowers, steelmakers, blacksmiths, welders, etc.

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Contribution

Yuri I. Matveev, Elena V. Averyanova carried out the experimental work, analyzed the experimental results and prepared the text of the manuscript. Yuri I. Matveev, Elena V. Averyanova have equal author’s rights and bear equal responsibility for plagiarism.

Conflict of interests

The authors declare no conflict of interests regarding the publication of this article.

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