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THE ESTIMATION OF HARD-TO-MEASURE PHYSICAL PARAMETERS OF THERMAL DISSOCIATION OF BIOMOLECULES FROM RESULTS OF INDIRECT MEASUREMENTS

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Abstract. The present paper is devoted to finding the necessary minimum of experimental information on biomolecules for quantitative evaluation of such physical parameters which cannot be directly measured for some reason, but are connected by known mathematical relations to any measureable quantities. For the case when thermal dissociation of a complex molecule is possible through several channels due to breaking of various intramolecular bonds, an original analytic expression relating the association degree of biomolecules to its physical parameters and the environment temperature has been deduced. It was exemplified the possibility to evaluate (with satisfactory accuracy) some physical parameters of thermal dissociation protease SARS-CoV-2 dimer and the temperature dependence of the association degree of this dimer as well.

Keywords: thermal dissociation, biomolecule, association degree, hard-to-measure parameter, protease SARS-CoV-2 dimer

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ОЦЕНКА ТРУДНОИЗМЕРЯЕМЫХ ФИЗИЧЕСКИХ ПАРАМЕТРОВ ТЕРМОДИССОЦИАЦИИ БИОМОЛЕКУЛ ПО РЕЗУЛЬТАТАМ НЕПРЯМЫХ ИЗМЕРЕНИЙ

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Аннотация. Работа посвящена нахождению минимума экспериментальной информации о биомолекулах, необходимого для количественной оценки значений таких их физических параметров, которые по каким-либо причинам невозможно измерить непосредственно, но которые связаны известными математическими соотношениями с величинами, поддающимися измерению. Для случая, когда термодиссоциация сложной молекулы возможна по нескольким каналам вследствие разрыва различных внутримолекулярных связей, получено оригинальное аналитическое выражение, связывающее степень ассоциации биомолекул с температурой окружающей среды и с физическими параметрами исследуемой молекулы. В качестве примера показана возможность оценки с удовлетворительной точностью некоторых физических параметров термодиссоциации димера протеазы SARS-CoV-2, а также температурной зависимости степени ассоциации этого димера.

Ключевые слова: термическая диссоциация, биомолекула, степень ассоциации, трудноизмеряемый параметр, димер протеазы SARS-CoV-2

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Introduction

Temperature is one of the crucial factors affecting the survival and growth of living organisms on Earth. The temperatures of the environments containing biomolecules of living organisms typically vary within the so-called thermal limits. The core temperatures in birds and mammals generally vary within 25–42 °C (298–315 K); they can vary within the ambient temperature range from −50 to +50 °C (223–323 K) in other animals and plants.

The energies of intramolecular bonds in biomolecules are relatively small and amount to several tenths of electron volts [1, 2]. The composition of the organism's biomolecules may change with these variations in temperature T due to thermal dissociation. The degree of dissociation, the concentration of dissociation products, as well as the rates of biochemical reactions may also vary along with the temperature.

Since biological reactions and the compositions of reagents and products are very diverse, it would be extremely difficult and time-consuming to run a full cycle of experimental studies to determine these values over the entire range of thermal limits. On the other hand, a purely theoretical *ab initio* calculation of the internal parameters of the biological environment and their dependences on temperature also appears complicated, both because the problem itself is complex and the data required are incomplete.

The goal of this study consisted in verifying the procedure for quantifying the parameters of the biological environment and their temperature dependences, whose values are extremely difficult or impossible to measure directly but can be found by analysis of some (a priori unknown) minimum of technically available experimental data.

In other words, the decision to be made is which parameters of the biological environment can be determined (calculated by a particular model) from the data for other parameters that can be measured directly.

Thermal dissociation and a simultaneous reverse process that is the recombination of fragments of a quasi-two-atom molecule (dimer) P corresponds to the reaction

$$\mathrm{P} + \mathrm{M} \leftrightarrow \mathrm{P}_1 + \mathrm{P}_2 + \mathrm{M}, \tag{1}$$

where M is the third body necessary for the reaction to proceed; P_1, P_2 are the macrofragments formed through dissociation of the molecule P. The relationship between the rate constants of the forward (K_d) and reverse (K_r) reactions (1), i.e., the dissociation of the dimer into monomers and the three-body recombination of monomers back into the dimer, is called the equilibrium constant K_c:

$$K_c = K_d / K_r. \tag{2}$$

Numerically, K_c is determined in terms of concentrations of reagents and products:

$$K_c = C_{P_1}^2 \big/ C_P, \tag{3}$$

since $C_{P_1} = C_{P_2}$ for reaction (1).

Rate constants of the given reactions

Recombination rate. Calculations by Bodenstein, Tolman, Steiner, and others [3] demonstrated that the reaction of three-body recombination of the type $\mathrm{P}_1 + \mathrm{P}_2 + \mathrm{M} \rightarrow \mathrm{P} + \mathrm{M}$ can only be described quantitatively assuming that triple collision proceeds in two phases: first, a close pair, that is, a doublet, is formed, followed by a triplet due to convergence with a third particle. The bimolecular mechanism of particle collision $\mathrm{P}_1 + \mathrm{P}_2$ does not correspond to the entire process of this reaction, since relaxation of the energy released during the collision is required to complete the process $\mathrm{P}_1 + \mathrm{P}_2$. The relaxation process can occur when a quasi-molecule collides with some third particle M, which removes the excess energy and brings the molecule P to a steady state [4]. A number of rather complex analytical expressions for K_r were obtained based on this mechanism (formulated by Tolman, Kassel, etc. [3, 5–7]). Unfortunately, the values of the parameters entering these expressions are either 'poorly known' (molecular masses of biomolecules, fragment diameters), or known only qualitatively for general reasons (the potential energy of a quasi-molecule at a distance r or the distance between the center of gravity of the doublet and the third particle), or completely unknown (as the parameter δ in Tolman's formula). For this reason, theoretical formulas cannot be applied to practical calculations of $K_r(T)$.

It follows from scarce experimental results that

$$K_r(T) \approx BT^{-b},$$

where B is a constant, and the value of parameter b according to [8] varies for different molecules within $0.4 \le b < 3.0$, but takes the value $b \approx 1.5$ [9] in most cases (data are available only for not very large molecules). The value of the constant B is usually determined empirically.

Dissociation constant. By definition,

$$K_d(T) = \left(\frac{8kT}{\pi\mu}\right)^{1/2} (kT)^{-3/2} \int_{W_d}^{\infty} \sigma_d(W) W \exp\left(-\frac{W}{kT}\right) dW,$$

where W, eV, is the kinetic energy of the relative motion of the collision partners; W_d, eV, is the dissociation energy; T, K, is the temperature; k, eV/K, is the Boltzmann constant; μ, g, is the reduced mass; σ_d, cm^2, is the cross section of collisional dissociation. The energy distribution of molecules is assumed to be Maxwellian.

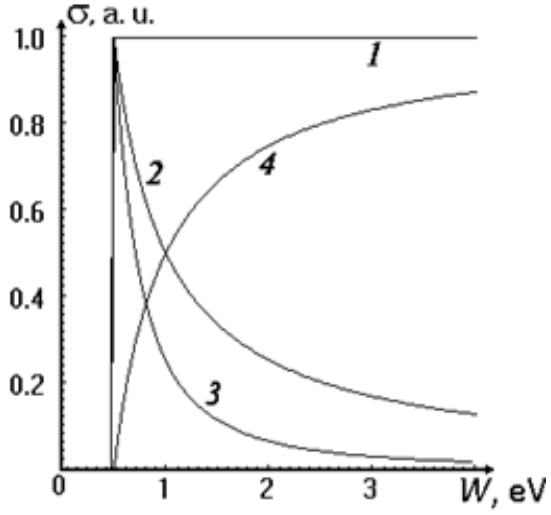

Fig. 1. Model energy dependences of dissociation cross sections for molecules in collisions with other molecules at $W_d = 0.5$ eV The curve numbers correspond to the numbers of the cases considered (see explanations in the text)

Theoretical expressions for collisional dissociation cross sections are $\sigma_d(W)$ available only for diatomic molecules [10]; there are no data for complex polyatomic molecules, and various cross-sectional shapes obtained based on 'reasonable considerations' are proposed for estimates.

Considering the effect that the cross-sectional shape of dissociation $\sigma_d(W)$ has on the dependence $K_d(T)$, we calculate this coefficient by Eq. (4) for some hypothetical cases of $\sigma_d(W)$ shapes found in the literature; we accept that the inequality $W_d >> kT$ holds true for biomolecules in the thermal range.

Case 1. The dissociation cross section takes the following form for the widespread model of solid spheres, (see Curve *1* in Fig. 1):

$$\sigma_d(W) = \begin{cases} \sigma_0 \text{ with } W \geq W_d; \\ 0 \text{ with } W < W_d. \end{cases}$$

Then the integral in Eq. (4) takes the form:

$$\int_{W_d}^{\infty} \sigma_d(W) W \exp\left(-\frac{W}{kT}\right) dW = \sigma_0 kT(W_d + kT)\exp\left(-\frac{W_d}{kT}\right) \approx \sigma_0 kT W_d \exp\left(-\frac{W_d}{kT}\right), \quad (5)$$

$$K_d(T) \approx 2\sigma_0 \sqrt{\frac{2}{\pi\mu}} \frac{W_d}{\sqrt{kT}} \exp\left(-\frac{W_d}{kT}\right). \quad (6)$$

Case 2. Provided that

$$\sigma_d(W) = \begin{cases} \sigma_0 \left(W_d / W\right) \text{ with } W \geq W_d; \\ 0 \text{ with } W < W_d \end{cases}$$

in the model (see Curve *2* in Fig. 1), then we obtain

$$\int_{W_d}^{\infty} \sigma_d(W) W \exp\left(-\frac{W}{kT}\right) dW = \sigma_0 kT W_d \exp\left(-\frac{W_d}{kT}\right),$$

and this coincides with Eq. (5), ultimately yielding the same result for $K_d(T)$, which gives expression (6).

Case 3. Provided that

$$\sigma_d(W) = \begin{cases} \sigma_0 \left(W_d / W\right)^2 \text{ with } W \geq W_d; \\ 0 \text{ with } W < W_d \end{cases}$$

in the model (see Curve *3* in Fig. 1), the following equality is satisfied:

$$\int_{W_d}^{\infty} \sigma_d(W) W \exp\left(-\frac{W}{kT}\right) dW = \sigma_0 W_d^2 \cdot \gamma\left(0, \frac{W_d}{kT}\right),$$

where $\gamma(x,y)$ is an incomplete gamma function.

If $W_d >> kT$, it is sufficient to consider the principal term of its asymptotic expansion:

$$\gamma\left(0, \frac{W_d}{kT}\right) \approx \frac{kT}{W_d} \exp\left(-\frac{W_d}{kT}\right),$$

and then

$$\int_{W_d}^{\infty} \sigma_d(W) W \exp\left(-\frac{W}{kT}\right) dW \approx \sigma_0 kT W_d \exp\left(-\frac{W_d}{kT}\right).$$

Comparing this approximate equality with Eq. (5), we again obtain the same result for $K_d(T)$ as expression (6).

Case 4. The following holds true for the model from [11] (see curve *4* in Fig. 1):

$$\sigma_d(W) = \begin{cases} \sigma_0 \left(1 - W_d / W\right) \text{ with } W \geq W_d; \\ 0 \text{ with } W < W_d, \end{cases}$$

$$\int_{W_d}^{\infty} \sigma_d(W) W \exp\left(-\frac{W}{kT}\right) dW \approx \sigma_0 (kT)^2 \exp\left(-\frac{W_d}{kT}\right)$$

and, accordingly,

$$K_d(T) \approx 2\sigma_0 \sqrt{\frac{2}{\pi\mu}} \sqrt{kT} \exp\left(-\frac{W_d}{kT}\right). \tag{7}$$

Thus, virtually identical results are obtained for $K_d(T)$ for the first three model cases with significantly different cross-sectional shapes of dissociation energy dependence (see Fig. 2). The exponent kT in the pre-exponential factor is different in the Case 4 from the first three cases. As we intend to prove below, such a difference has little effect on the magnitude of the discrepancy between the experimental and analytical dependences $K_d(T)$ in the thermal range. There is, however, no information about the specific value of σ_0 for biomolecules, making it problematic to use expressions (6) and (7) in practice.

Unfortunately, there are no reliable data on either the form of $\sigma_0(W)$ or the magnitude of σ_0, so estimates of the $\sigma_0(W)$ shape are generally limited to simple reasonable assumptions (see, for example, work [9]).

Equilibrium constant for thermal dissociation

It follows from the above analysis of theoretical and experimental studies that the dependence $K_c = K_d / K_r$ can be represented as a simple expression:

$$K_c(T) \approx \frac{A}{T^m} \exp\left(-\frac{W_d}{kT}\right), \tag{8}$$

where A is a constant depending on the type of molecules; m is a parameter whose values range from -0.5 to 2.0 (according to different sources).

Good approximations of experimental data for K_c are available in the literature, including for protein molecules, confirming that expression (8) is valid. For example, we were able to approximate the data from [1] with the following expression of type (8):

$$K_c \approx \frac{7.23 \cdot 10^8}{\sqrt{T}} \exp\left(-\frac{6342.8}{T}\right) \text{ μmol/l} \tag{9}$$

with an error $\rho = 3.3\%$ (see Fig. 2,*a*).

Expression (9) (as well as (10) and the data from the table below) was obtained by quasi-linear exponential approximation with weight iteration [12].

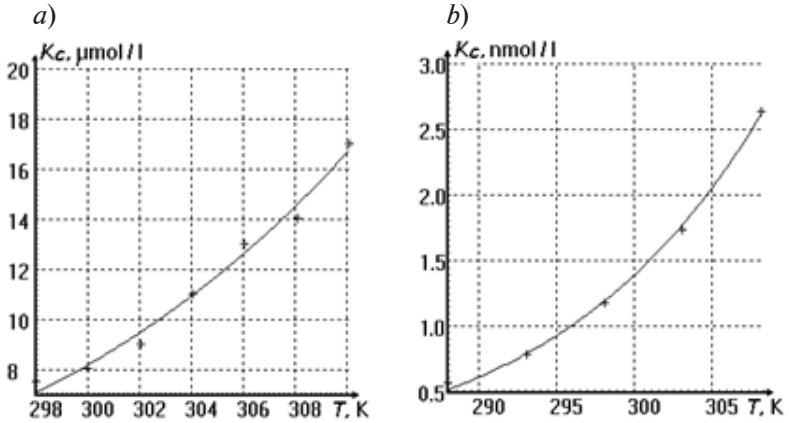

Fig. 2. Our approximations of experimental temperature dependences [1, 2] for the equilibrium constants of two thermal dissociation reactions of associated molecules: *a* is the dimer monomer of SARS-CoV-2 protease [1], *b* is the wild-type mutated hIL15 and its hIL15Ra receptor [2] in aqueous solutions

We also managed to approximate the data on the constant K_c from [2] by the following expression:

$$K_c \approx \frac{6.8 \cdot 10^5}{\sqrt{T}} \exp\left(-\frac{6851}{T}\right) \text{ μmol/l} \tag{10}$$

(see Fig. 2,*b*) with an error $\rho \approx 2.5\%$. It was additionally reported in [2] that the quantity

$$W_d \approx 0.580 \pm 0.026 \text{ eV};$$

it follows from approximation (10) that $W_d \approx 0.591$ eV (the discrepancy $\rho = 1.9$ %). In other words, if the quantity W_d is known a priori, the approximation accuracy can be controlled.

Let us try to refine the value of m in expression (8) using the results from [1, 2]: we are going to approximate the experimental data from these studies by expression (8) at different m (from −1 to +2) with T varying within 300 ± 15 K. The required parameters to be tailored were A and W_d. The results are summarized in Table.

Analyzing the approximations carried out, we can conclude the following:

the approximation error ρ is virtually independent of m with m varying in the range from −1 to +2;

the obtained values of W_d vary insignificantly (by no more than ± 10%) with the variation in m.

Table

Results of our approximations of experimental data for K_c from [1, 2] by expression (8)

m	Values obtained from initial data in [1] and [2]					
	ρ		W_d/k, K		A	
	[1]	[2]	[1]	[2]	[1]	[2]
2.0	3.330	2.500	–5879	–6392	$2.96 \cdot 10^4$	28.5
1.5	3.321	2.500	–6034	–6545	$8.59 \cdot 10^5$	817
1.0	3.319	2.501	–6188	–6697	$2.49 \cdot 10^7$	$2.35 \cdot 10^4$
0.5	3.318	2.502	–6343	–6851	$7.23 \cdot 10^8$	$6.80 \cdot 10^5$
0.0	3.316	2.503	–6498	–7003	$2.10 \cdot 10^{10}$	$1.96 \cdot 10^7$
–0.5	3.314	2.504	–6653	–7156	$6.09 \cdot 10^{11}$	$5.64 \cdot 10^8$
–1.0	3.313	2.505	–6808	–7309	$1.77 \cdot 10^{13}$	$1.63 \cdot 10^{10}$

Notes. 1. The data used are from studies by Silvestrini et al. [1] and Sakamoto et al. [2]. 2. The variation in T was accepted within 300 ± 15 K.

We can conclude from this analysis that if the measurement errors of $K_c(T)$ are more than a few tenths of a percent, information about the magnitude of m cannot be extracted from the experimental data captured within the thermal range of variation in T, and also that variations in the quantity m have only a negligible effect on the degree to which Eq. (8) can reproduce the experimental data on the equilibrium constant of reaction (1). Consequently, we can assume that $m = 0$ in expression (8) for simplicity; this will not make the error of such an approximation worse within the variation range of temperatures characteristic for biomolecules.

So, if the given experimental errors are acceptable to the researcher, it is possible to use the following approximation for the equilibrium constant:

$$\mathrm{P} + \mathrm{M} \leftrightarrow \mathrm{P}_{\mathrm{i1}} + \mathrm{P}_{\mathrm{i2}} + \mathrm{M}. \tag{11}$$

Unfortunately, the constant A cannot be theoretically calculated for biomolecules with acceptable accuracy (no worse than 10–15%), because, as noted above, there are no data on many parameters appearing in existing theories.

Degrees of association and dissociation

Let the thermal dissociation of a biomolecule P simultaneously proceed through several decay channels of the type

$$\mathrm{P} + \mathrm{M} \leftrightarrow \mathrm{P}_{\mathrm{i1}} + \mathrm{P}_{\mathrm{i2}} + \mathrm{M}. \tag{12}$$

Each ith reaction corresponds to its own equilibrium constant K_{ci}, numerically equal to

$$K_{ci} = C_{P_{i1}}^2 / C_P, \tag{13}$$

because $C_{P_{i1}} = C_{P_{i2}}$. Here C_P is the concentration of molecules P preserved throughout all reactions of type (12).

Let us define the quantity β as the ratio of the concentration C_P of all undissociated molecules P to the concentration C_{P_0} of potentially existing molecules P (for example, at low temperatures, when thermal dissociation is negligible, or as the number of molecules of 'dry' matter per unit volume of solution), i.e., as

$$\beta = C_P / C_{P_0}. \tag{14}$$

We assume that the solution of molecules P is weak, such that C_{P_0} is much lower than the concentration of solvent molecules, and the presence of a solute does not affect the volume of the solution. The following equality holds true for a fixed volume of such solution:

$$C_P + \sum_i C_{P_{i1}} = C_{P_0}. \tag{15}$$

Then, given that $C_{P_{i1}} = \sqrt{K_{ci} C_P}$, we obtain the following expression in accordance with Eq. (13):

$$\beta = \left(1 + \sum_i \sqrt{K_{ci}} \Big/ \sqrt{C_P} \right)^{-1}. \tag{16}$$

Expression (15) is transformed into a quadratic equation with respect to $\sqrt{C_P}$:

$$C_P + \sqrt{C_P} \sum_i \sqrt{K_{ci}} - C_{P_0} = 0, \tag{17}$$

Its physically reasonable solution takes the form

$$\sqrt{C_P} = \sqrt{\frac{1}{4}\left(\sum_i \sqrt{K_{ci}} \right)^2 + C_{P_0}} - \frac{1}{2} \sum_i \sqrt{K_{ci}},$$

and it follows then that

$$\frac{\sum_i \sqrt{K_{ci}}}{\sqrt{C_P}} = \frac{2}{\sqrt{1+4C_{P_0}\left(\sum_i \sqrt{K_{ci}}\right)^{-2}}-1}.$$

Substituting this equality into expression (16), we obtain the formula

$$\beta = \left[1+\frac{2}{\sqrt{1+4C_{P_0}\left(\sum_i \sqrt{K_{ci}}\right)^{-2}}-1}\right]^{-1}. \quad (18)$$

The values of K_{ci} can be calculated by the formula for approximating the equilibrium constant (11).

The variable $\beta(T)$ represents the degree of association, while the quantity

$$\alpha(T) = 1-\beta(T) = \sum_i C_{P_{i1}} \Big/ C_{P_0} \quad (19)$$

is the degree of dissociation of molecules P.

If the molecule P can dissociate through only one possible channel, i.e., if the probabilities of decay through other channels are negligible, then expressions (18) and (19) are transformed, respectively, into the following expressions:

$$\beta(T) = \left(1+\frac{2}{\sqrt{1+4\,C_{P_0}/K_c}-1}\right)^{-1}; \quad (20)$$

$$\alpha(T) = 1-\beta(T) = C_{P_1}/C_{P_0}. \quad (21)$$

Fig. 3 shows the time-dependent association degree for β-dimers of SARS-CoV-2 protease at different concentrations of these molecules in aqueous solution. The calculation is performed in this paper based on the data from [1], in accordance with expression (20); the function $K_c(T)$ was calculated using expression (9).

Obtaining new information based on the known data

Let us establish the relationship between the quantities that can be measured experimentally (or whose measurement results are available in the literature) with those that cannot be measured directly so that the values of the latter can be calculated. An additional task is to find the simplest yet physically reasonable relationship, i.e., the one containing as few selected parameters as possible to improve the conditionality of the problem. Figuratively speaking, we will prepare an 'indirect experiment' of sorts, i.e., we use the known experimental data as a source for finding the necessary information about the unknown parameters.

We assume that we can either measure the dependence $C_p(T)$ or that such a dependence is given in the literature (the methods for measuring $C_p(T)$ are described, for example, in [1]). First, we assume that the studied molecule P dissociates through a single possible channel. If Eq. (11) can be used to approximate $K_c(T)$, then we obtain from expression (20):

$$C_P(T) = C_{P_0}\left[1+\frac{2}{\sqrt{1+4\frac{C_{P_0}}{A}\exp\left(\frac{W_d}{kT}\right)}-1}\right]^{-1}. \quad (22)$$

Then the variable $C_p(T)$ can be approximated by the following expression:

$$C_P(T) \approx A_1 \left[1 + \frac{2}{\sqrt{1 + 4A_2 \exp\left(\frac{A_3}{T}\right)} - 1} \right]^{-1}, \quad (23)$$

containing only three parameters to be tailored: A_1, A_2 and A_3 (see curve *1* in Fig. 4).

Because approximation (23) is considerably nonlinear and linearization is impossible, the Levenberg–Marquardt method should be used to find the numerical values of the parameters [13]. After finding the values of the approximation parameters A_1, A_2 and A_3, we can calculate the values of C_{P_0}, A and W_d in accordance with expression (22).

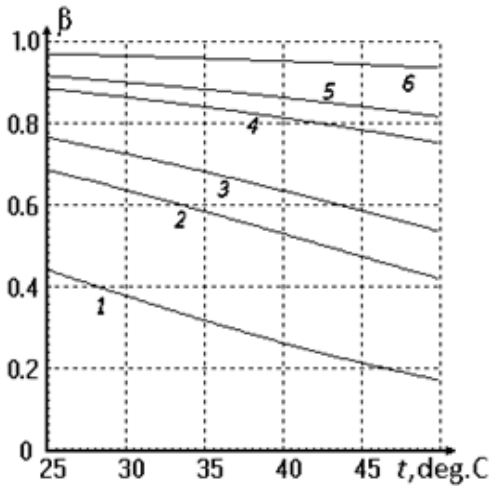

Fig. 3. Calculated temperature dependences for association degree of β-dimers of SARS-CoV-2 protease in aqueous solution at different inlet concentrations C_{P_0}, μmol/l: 10 (*1*), 50 (*2*), 100 (*3*), 500 (*4*), 1000 (*5*), 10,000 (*6*)
Calculations are performed based on data from [1]

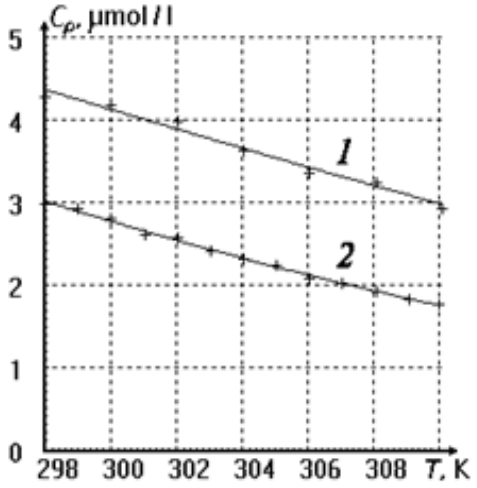

Fig. 4. Experimental (symbols) and approximated (lines) temperature dependences of the concentration of undissociated molecules in an aqueous solution (C_{P_0} = 10 μmol/L) for two cases: *1*, there was one dissociation channel of the dimer-monomer of the SARS-CoV-2 protease [1] (discrepancy of 1.7%); *2* (model), two simultaneous dissociation channels (discrepancy of 1.3%)
The approximation by expression (23) was performed based on the data from [1]

Approximating the data from [1], we obtain that the root-mean-square (RMS) integral discrepancy is 1.72 %; $A_1 = 9.701$, $A_2 = 1.93 \cdot 10^{-4}$, $A_3 = 6503$.

Calculations of regression uncertainty, as well as the degree of multicollinearity, are complicated, as the approximation is strongly nonlinear. However, the parameter values obtained from the approximation should be compared for control with those known from the experiment (if such data are available). For example, the parameters in expression (22) included the quantity C_{P_0} that was known from the experiments in [1] and is equal to 10 μmol/L. The approximation gave a value of $C_{P_0} = 9.70$ μmol/l; the error was 3%, which is quite satisfactory.

Thus, the measurement results for one dependence $C_p(T)$ are sufficient for estimating the concentrations of the 'dry' substance C_{P_0}, the dissociation energy of the molecule W_d, as well as the pre-exponential factor A in Eq. (11). Notably, if analysis of biological fluids in organisms is carried out *in vivo*, the quantity C_{P_0} cannot be measured directly, since biomolecules with temperatures in the thermal range are largely dissociated. Knowing the quantity C_{P_0} can be extremely important for determining the state of the organism.

If the thermal dissociation of a molecule can proceed through several different channels (see reaction (12)), the problem is reduced to the following approximation:

$$C_P(T) = C_{P_0}\left[1 + \frac{2}{\sqrt{1 + \frac{4C_{P_0}}{\left(\sum_i \sqrt{A_i}\exp\left(-W_{di}/2kT\right)\right)^2}} - 1}\right]^{-1}. \qquad (24)$$

Apparently, expression (24) contains the sum of decreasing exponents, where the numerical values of the pre-exponential factors and exponents are to be determined. It was established in [13–15] that such a problem is generally ill-conditioned, and its solution is extremely unstable with respect to small errors in the initial experimental data, without an explicit guarantee of obtaining satisfactory results.

However, in the particular case when one of the values that W_{di} takes is much smaller than the others, all the terms with these other quantities are negligibly small in Eq. (24) compared to the term with the minimum value of W_{di}, and the problem is reduced to problem (22), (23) with one exponent, considered above.

In another particular case when there are several minimum W_{di} values that are slightly different in magnitude, control model calculations indicate that the same expression as (22) and (23) can be taken for approximation. However, now the parameter A_3 no longer coincides with the dissociation energy for some specific reaction of type (12), serving instead as simply a fitting parameter. Nevertheless, the quantity C_{P_0} can still be determined with acceptable accuracy. An example of such an approximation is shown in Fig. 4 (Curve *2*); the case of two simultaneous dissociation channels is considered here. The model equilibrium constants (in μmol/l) were taken as follows:

$$K_{c1}(T) \approx 2.1 \cdot 10^{10} \exp\left(-\frac{6498}{T}\right);\ K_{c2}(T) \approx 3 \cdot 10^{10} \exp\left(-\frac{7003}{T}\right).$$

The value of C_{P_0} in the model was taken equal to 10 μmol/l. The model 'experimental data' for $C_p(T)$ were calculated as a solution to Eq. (17) and then complemented with a random error, giving an RMS integral discrepancy of 1.2%. As a result, the following values of the approximation parameters were found (23):

$$A_1 = 10.60,\ A_2 = 5.5 \cdot 10^{-10},\ A_3 = 6593.$$

We should note that approximation (23) here gave a value $C_{P_0} \approx 10.6$ μmol/l (the error was 6%), suggesting that the quantity C_{P_0} is reproduced with satisfactory accuracy. As expected, other parameters can be compared with the parameters of the equilibrium constants only by order of magnitude.

Conclusion

We have established that a priori, purely theoretical quantitative calculation of the equilibrium constant $K_c(T)$ cannot be performed with acceptable accuracy, since it is not yet possible to theoretically calculate the pre-exponential factor A in the Arrhenius equation with acceptable accuracy for biomolecules. The reason for this is that there are no quantitative data on many of the parameters included in the expressions proposed by existing theories.

However, we also found that establishing the temperature dependence for the proportion of undissociated dimers $C_p(T)$ not only to allows to determine the concentration of 'dry' matter computationally C_{P_0}, but also to reconstruct the dissociation energies of the dimer, as well as the temperature dependences for the equilibrium constant and degrees of association/dissociation of biological molecules.

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