INTRAMOLECULAR RELAXATION OF MACROMOLECULES

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An asymptotic description is obtained for the relaxation of an individual polymer molecule.

It is an extremely difficult problem to present a really elementary description of the relaxation processes taking place in polymer structures, owing to the complicated kinematic structure of the polymer molecules. Because of the wide variety of forms assumed by the conformational mobility, the kinetic characteristics of an individual polymer chain in solution involve an extremely wide spectrum of relaxation times. The difficulties encountered in describing the dynamics of an individual macromolecule theoretically limit the possibilities of describing the nonequilibrium properties of the polymer in mass form [1] very severely.

A consideration of the intramolecular relaxation process is of fundamental importance in the case of one very important class of natural polymers: proteins. It is well known that all the molecules in a globular protein of a particular type assume the same conformation in solution; the molecules are usually turned into this unique (and essentially nonperiodic) structure quite spontaneously from any initial conformation. It is reasonable to consider that this structure is the one corresponding to the universal minimum free energy of the molecule [2]. On the other hand, if we consider the extremely large dimensions of the molecule (mol. wt. 10^4-10^5, number of internal-rotation angles of the order of 10^3) we may well expect that the relaxation process will occupy a very long time [3]. In actual fact, the number of local potential minima increases on the statistical combination principle with increasing number of internal-rotation angles; the contribution of the universal minimum to the statistical sum is very small, even if its depth relative to the other (local) minima amounts to tens of kilocalories. In the absence of quantitative estimates this question, nevertheless, remains subject to discussion. Thus, Lumry and Biltonen [4], referring to experiments on the spontaneous recombination of sulfohydryl groups into disulphide bonds during the renaturing of a protein molecule, assert that their results " . . . exclude all these carefully developed kinetic theories based on the kinetic preference of local structures serving as nuclei for a subsequent coagulation process . . . . These data provide an adequate reason for preferring thermodynamic mechanisms of conversion into the stable state, rather than the complicated kinetic alternative."

One of the several possible ways of estimating the order of magnitude of the "search time" required for a macromolecule to find the universal minimum (within the framework of various idealized models) may be formulated as follows. It is well known that many problems of conformational statistics are formally equivalent to diffusion problems in a multidimensional space [1]. The analog of the potential function describing the interaction between a diffusing particle and the ambient is in this case the intramolecular energy $U(\varphi_1, \ldots, \varphi_i, \ldots, \varphi_n)$, where φ_i are the angles of internal rotation. The desired kinetic parameters may be estimated in terms of the activation energies on the basis of the theory of absolute reaction rates [5].

Diffusion is here considered as a random walk of the penetrant (penetrating) particle around the minima of the potential function, while the transition probabilities are defined by the equation for the specific activity of the velocity constant,

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*Deceased.

$$K = \varkappa \frac{kT}{h} e^{-\frac{\Delta F}{RT}}, \tag{1}$$

where $\varkappa$ is the so-called transmission coefficient, equal to unity for the majority of diffusion problems.

It is well known that the diffusion coefficient may be expressed in terms of the characteristic velocity constant K in the form

$$D = <\lambda^2> K. \tag{2}$$

The activation energy for the intramolecular relaxation of a polymer molecule over a large part of the phase volume is chiefly determined by short-range interactions; various estimates of the activation energy may be obtained on the basis of the theoretical conformation analysis of oligomers [6, 7].

The quantity $\langle \lambda^2 \rangle$ is clearly determined by the multiplicity q of the potential function of the monomeric unit,

$$\lambda = \frac{2\pi}{q}. \tag{3}$$

At this stage we must make some comments on the characteristics of the metric describing the space of internal-rotation angles. Firstly, since the essential mutual relationship is chiefly associated with the internal rotations in the principal chain, it is convenient to consider the set of the corresponding dihedral angles as the sole basis. The limitations imposed on this by the presence of mobile side radicals may be taken into account by introducing an effective multiplicity factor of the corresponding potential barriers.

Secondly, the effects of the phase volume excluded as a result of self-intersections may be taken into account by reducing the number of dimensions in the problem, as is customary in the conformation statistics of polymers [8]. In the polypeptide case of present interest we may make use of the estimate made by Knaell and Scott [9] for the statistical tangle (globule) of poly-L-alanine; these authors obtained an expression describing the self-intersection coefficient as a function of the degree of polymerization M in the form

$$\omega = 0.13 \left[\frac{M-3}{M+1.91} \right]^{0.88}. \tag{4}$$

Thus, in the problem of the intramolecular relaxation of a protein molecule the effective dimensions of the potential function should be taken as being equal to

$$n = 2m\omega, \tag{5}$$

the multiplicity of the assumed internal-rotation potential may take any values in the range 3-6, according to the amino acid composition of the molecule [6].

Let us now assume that the polypeptide molecule is characterized by a unique universal minimum, sharply distinguished as regards depth. In the absence of kinetic factors leading to the stabilization of this structure (model A), the potential cross section along a line of arbitrary shape passing through the universal minimum should take the form schematically illustrated in Fig. 1a. If any structural singularities directing the self-assembly process of the globule (model B) exist, the corresponding potential profile assumes the form of Fig. 1b.

If we process adequate information regarding the structure of the potential function, we may in principle obtain a general solution to the diffusion equation in discrete form [10],

$$c_k(t) = \sum_{n=0}^{N} e^{-\lambda n t} \left[\sum_{i=0}^{N} c_i(t_0) e^{-\frac{\Delta F_i}{RT}} \psi_i^{(n)} \right] \psi_k^{(n)}, \tag{6}$$

where λ_i and $\bar{\psi}_i$ are, respectively, the eigenvalues and eigenvectors of the matrix of mutual transitions between the minima, the elements of this matrix

$$a_{ij} = -K_{ni} + \left(\sum_{j=0}^{N+1} K_{ji} \right) \delta_{ni}, \tag{7}$$

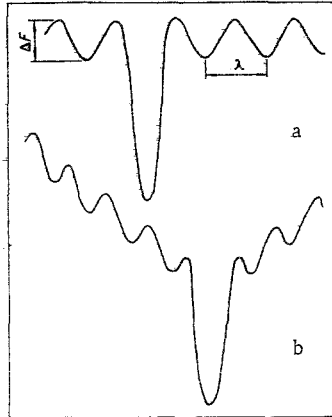while $c_k(t_0)$ is the initial distribution of populations.

Fig. 1   Fig. 2

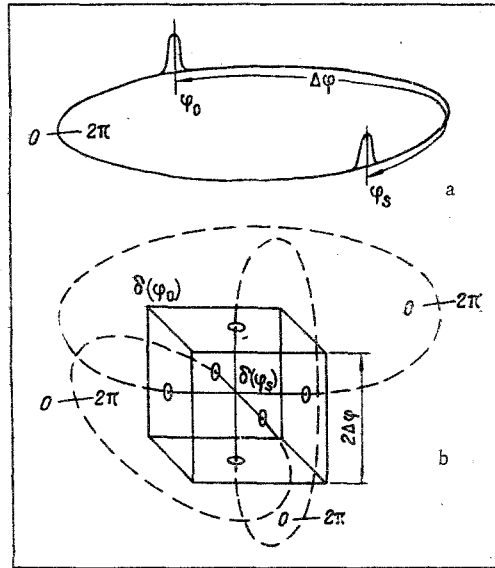Fig. 1. Schematic representation of cross sections through a universal potential minimum.

Fig. 2. Schematic representation of the original conformation and the universal minimum in the case of model A.

However, in problems of interest from our present point of view, the dimensional index c of the vectors is very large, and it becomes appropriate to pass to a continuous model. Let the mutual disposition of the delta-type source (original conformation) and sink (universal minimum) in the cross section associated with each internal-rotation angle be given as in the scheme of Fig. 2a. In the case of independent relaxation with respect to each angle φ_i the dynamics of the probability density are determined by the product of the independent density functions in each section,

$$U(\overline{\Phi}, t) = \prod_i u(\varphi_i, t), \tag{8}$$

where $\varphi_i \in \overline{\Phi}$.

If the original conformation corresponds to one of the vertices of an N-dimensional cube with a side $2\Delta\varphi$, having the universal-minimum in its center (Fig. 2b), the relaxation process is described by a diffusion equation which (in dimensionless independent variables) may be written in the form

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial \varphi^2} - \alpha u^N \delta(\varphi - \varphi_s), \tag{9}$$

which corresponds to the introduction of the dimensionless time t = Dt' and the "stacking constant"

$$\alpha = \frac{K}{D} = \frac{1}{<\lambda^2>}.$$

We furthermore have the periodic boundary conditions

$$u\big|_{\varphi=0} = u\big|_{\varphi=2\pi} \tag{10}$$

and the initial condition

$$u\big|_{\varphi=0} = \delta(\varphi - \varphi_0). \tag{11}$$

On the time scale so defined, the experimentally observed relaxation times of the self-assembly process are of the order of 10^4–10^6, so that it is sufficient to obtain an estimate of the asymptotic behavior of the solution to Eq. (9) for large values of t.

We shall seek the solution to Eq. (9) in the form

$$u = \sum_{n=-\infty}^{\infty} a_n(t) e^{in\varphi}.$$ (12)

The coefficients of the Fourier series (12) are determined from

$$a_m = \frac{1}{2\pi} \int_0^{2\pi} u e^{-im\varphi} d\varphi.$$ (13)

The integral transformation (12)–(13) automatically satisfies the boundary condition (10) and transforms the boundary problem (9)–(11) into an infinite system of ordinary differential equations,

$$\frac{da_m}{dt} = -m^2 a_m - \frac{\alpha}{2\pi} u_s^N e^{-im\varphi_s}, \quad -\infty < m < \infty$$ (14)

with the initial conditions

$$a_m(0) = \frac{1}{2\pi} e^{-im\varphi_0}.$$ (15)

Here we have introduced the notation

$$u_s(t) \equiv u(t, \varphi_s).$$ (16)

Using system (14), we may derive an integral equation for the boundary problem (9). The solution to the system (14), subject to the conditions (10) and (11), takes the form

$$a_m(t) = \frac{1}{2\pi} e^{-im\varphi_0} e^{-m^2 t} - \frac{\alpha}{2\pi} e^{-im\varphi_s} \int_0^t u_s^N(\tau) e^{-m^2(t-\tau)} d\tau.$$ (17)

Hence, by substituting (17) into (12), we obtain

$$u(t, \varphi) = \frac{1}{2\pi} \sum_{m=-\infty}^{\infty} e^{-m^2 t} e^{-im(\varphi_0 - \varphi)} - \frac{\alpha}{2\pi} \sum_{m=-\infty}^{\infty} e^{-im(\varphi_s - \varphi)} \int_0^t u_s^N(\tau) e^{-m^2(t-\tau)} d\tau,$$ (18)

i.e., the solution to Eq. (9), expressed in terms of the unknown function $u_s(t)$.

Putting $\varphi = \varphi_s$ in Eq. (18), we obtain a nonlinear integral equation for determining the function $u_s(t)$, and hence an integral equation for the boundary problem (9)–(11),

$$u_s(t) = \frac{1}{2\pi} K_\psi(t) - \frac{\alpha}{2\pi} \int_0^t K_0(t-\tau) u_s^N(\tau) d\tau.$$ (19)

In Eq. (19) we have introduced the following notation:

$$K_\psi(t) = \sum_{m=-\infty}^{\infty} e^{-m^2 t} e^{-im\psi},$$

$$K_0(t) = \sum_{m=-\infty}^{\infty} e^{-m^2 t},$$ (20)

$$\psi = \varphi_s - \varphi_0.$$

It follows from the numerical estimates that Eq. (19) contains two large parameters $t > 10^4$–10^5 and $N \sim 10^2$–10^3; we must therefore find an asymptotic solution to the integral equation (19).

We note that

$$K_\psi(t) = 1 + 2 \sum_{m=1}^{\infty} e^{-m^2 t} \cos m\psi,$$ (21)

and hence as $t \to \infty$

$$K_\psi(t) \simeq 1 + 2e^{-t} \cos \psi t + \ldots \qquad (22)$$

On the other hand, it follows from the Poisson summation formula [11] that

$$K_\psi(t) = \sqrt{\frac{\pi}{t}} e^{-\frac{\psi^2}{4t}} \left[1 + 2 \sum_{m=1}^{\infty} e^{-\frac{(\pi m)^2}{t}} \operatorname{ch}\left(\frac{\pi m \psi}{t}\right) \right]. \qquad (23)$$

We obtain the corresponding results for the kernel of the integral equation $K_0(t)$ by putting $\psi = 0$ in the latter equations:

$$K_0(t) = 1 + 2 \sum_{m=1}^{\infty} e^{-m^2 t}, \qquad (24)$$

$$K_0(t) = \sqrt{\frac{\pi}{t}} \left(1 + 2 \sum_{m=1}^{\infty} e^{-\frac{(\pi m)^2}{t}} \right). \qquad (25)$$

Let us introduce some new variables (dependent and independent) into Eq. (19) by means of the equations

$$\xi = \frac{1}{t}, \ \eta = \frac{1}{\tau} \qquad (26)$$

and

$$V(\xi) = u_s\left(\frac{1}{\xi}\right). \qquad (27)$$

We then write (19) in the form

$$V(\xi) = \frac{1}{2\pi} K_\psi\left(\frac{1}{\xi}\right) - \frac{\alpha}{2\pi} \int_{\xi}^{\infty} K_0\left(\frac{1}{\xi} - \frac{1}{\eta}\right) V^N(\eta) \frac{d\eta}{\eta^2}. \qquad (28)$$

Let us consider the behavior of the kernel $K_0[(\eta - \xi)/\xi\eta]$ as $\xi \to 0$ ($t \to \infty$). From Eqs. (24) and (25) we have

$$K_0\left(\frac{\eta - \xi}{\xi\eta}\right) \underset{\xi \to 0}{\simeq} \sqrt{\pi\xi} \left[1 + 2 \sum_{m=1}^{\infty} e^{-(\pi m)^2 \xi} \right]. \qquad (29)$$

Allowing for (29), Eq. (28) now becomes

$$V(\xi) = \frac{1}{2\pi} K_\psi\left(\frac{1}{\xi}\right) - \frac{\alpha}{2\pi} \sqrt{\pi\xi} \left[1 + 2 \sum_{m=1}^{\infty} e^{-(\pi m)^2 \xi} \right] \int_{\xi}^{\infty} V^N(\eta) \frac{d\eta}{\eta^2}. \qquad (30)$$

Let us consider the expression

$$\Theta(\xi) = \sqrt{\pi\xi} \left[1 + 2 \sum_{m=1}^{\infty} e^{-(\pi m)^2 \xi} \right].$$

According to Eq. (25), this may be converted to the form

$$\Theta(\xi) = 1 + 2 \sum_{m=1}^{\infty} e^{-\frac{m^2}{\xi}},$$

when neglecting those terms which diminish exponentially as $\xi \to 0$ we have $\Theta(\xi) \underset{\xi \to 0}{\simeq} 1$.

Hence Eq. (30) may be written as follows:

$$V(\xi) = \frac{1}{2\pi} K_\psi\left(\frac{1}{\xi}\right) - \frac{\alpha}{2\pi} \int_{\xi}^{\infty} \frac{V^N(\eta)}{\eta^2} d\eta. \qquad (31)$$

Returning to the original variables, for fairly large values of t we have the integral equation

$$u_s(t) = \frac{1}{2\pi} K_\psi(t) - \frac{\alpha}{2\pi} \int_0^t u_s^N(\tau)\, d\tau,$$

where if we omit the exponentially diminishing terms we may put $K_\psi(t) = 1$ in accordance with Eq. (22).

Finally, for the unknown function $u_s(t)$, as $t \to \infty$ we have the equation

$$u_s(t) = \frac{1}{2\pi} - \frac{\alpha}{2\pi} \int_0^t u_s^N(\tau)\, d\tau. \tag{32}$$

It follows from this that

$$\frac{du_s}{dt} = -\frac{\alpha}{2\pi} u_s^N(t),$$

i.e.,

$$\frac{u_s(t)^{-(N-1)}}{N-1} = -\frac{\alpha}{2\pi} t + c,$$

and for large t the desired asymptotic solution takes the form

$$u_s(t) \simeq \left[\frac{\alpha}{2\pi}(N-1)t \right]^{-\frac{1}{N-1}}. \tag{33}$$

Since $u_s(t)$ is, in fact, none other than the probability density corresponding to the surroundings of the universal φ_s minimum, the development of the intramolecular relaxation process is determined by the equation

$$Q(\tau) = 1 - \frac{\alpha}{2\pi} \int_\tau^\infty u_s^N(t)\, dt = 1 - \frac{\alpha}{2\pi}(N-1)\left[\frac{\alpha}{2\pi}(N-1) \right]^{-\frac{N}{N-1}} \tau^{-\frac{1}{N-1}} \tag{34}$$

and since $N \gg 1$, we have

$$Q(\tau) \approx 1 - \tau^{-\frac{1}{N-1}}. \tag{35}$$

An important characteristic of the resultant solution is the universality of the asymptotic stage of relaxation, i.e., the complete independence of the solution relative to the initial distribution. The universality of the final stage of relaxation was first observed in [12] for physical problems of the type under consideration.

According to Eqs. (33)-(35), in fact, the flow of the process does not depend on the mutual disposition of the initial conformation and the universal minimum in the space of internal-rotation angles. On the one hand, this result justifies our arbitrary specification of the initial distribution in the form of a delta-type source at the vertex of an N-dimensional cube; on the other hand, we also find justification for the following important practical conclusion: If there are no kinetic limitations guiding the self-assembly of the globule at all, the hypothetical mechanisms "easing" this process during the biosynthesis of a protein molecule by providing it with a "starting" conformation close to the conformation of the universal minimum [13] are quite ineffective.

Let us discuss some of the numerical results emerging from Eq. (35), from which it follows that the activation energy ΔF and the effective number of potential barriers influence the results almost solely by way of a change in the scale of the dimensionless time $t = Dt'$. The influence of the multiplicity of the effective internal-rotation potential may then be entirely neglected (Table 1).

Figure 3 shows the time required for half the molecules to find the universal minimum, expressed as a function of the number of radicals in the polypeptide chain for various activation energies. It is easy to see that for cases of $m > 150$ we shall be concerned with very long time periods (10^{10} sec or over), greatly exceeding the experimentally observed renaturing relaxation times.
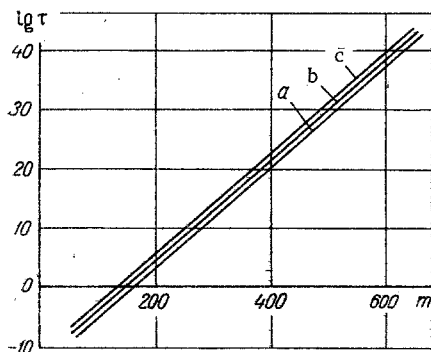
Fig. 3. Time τ (sec) required for half the molecules to find the universal minimum, as a function of the number of radicals in the polypeptide chain: a) for $\Delta u = 2$ $D = 0.98 \cdot 10^{12}$; b) for $\Delta u = 3$ $D = 0.18 \cdot 10^{12}$; c) for $\Delta u = 5$ $D = 0.0065 \cdot 10^{12}$.

TABLE 1. Degree of Completion of the Intramolecular Relaxation Process for $\tau = 1$ sec, Expressed as a Function of the Multiplicity q of the Effective Internal-Rotation Barrier ($\Delta F = 5$ kcal /mole)

Number of radicals in the molecule	Q	
	q	
	2	6
100	0,53	0,56
200	0,31	0,33
300	0,22	0,23
600	0,11	0,12
1000	0,07	0,08

We may therefore assert with complete confidence that the kinematic factors involved in the formation of a protein globule are an indispensable element in the mechanism underlying the realization of a unique spatial structure. The foregoing estimates show that in the absence of a system of intramolecular interactions directing the globularization process the time required to find the universal intramolecular energy minimum corresponding to the native structure would, in the majority of cases, exceed the lifetime of the molecule.

NOTATION

φ_i is the internal-rotation angles;

ΔF is the free activation energy of the transition;

$\varkappa$ is the transmission coefficient;

$\langle \lambda^2 \rangle$ is the mean square of the distance between neighboring potential minima;

q is the multiplicity of the potential function of the monomeric unit;

m is the number of amino acid radicals in the polypeptide chain;

$c_k(t)$ is the population of the k-th potential minimum;

λ_i, $\vec{q}_i$ are the eigenvalues and eigenvectors of the matrix of mutual transitions between the minima;

$Q(\tau)$ is the degree of completion of the process;

N is the degree of polymerization;

M is the effective number of internal degrees of freedom in the macromolecule.

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