

Brownian Motion of a Classical Particle Through Potential Barriers. Application to the Helix–Coil Transitions of Heteropolymers

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We discuss some properties of the one-dimensional Fokker–Planck equation, and in particular the time required to go through a potential barrier of arbitrary size and shape. We apply the resulting formulas to the melting of helical polymers made of two types of monomers (A and B) with different melting temperatures: We consider a restricted problem in irreversible melting, where one *single* boundary (separating a coil region from a helical region) moves through the chemical sequence. In a crude approximation the distribution function for the boundary point is then ruled by a simple Fokker–Planck equation. When the temperature T is equal to or higher than the average melting point \bar{T} , the boundary tends to move over macroscopic distances, thus extending the size of the coil regions. In an interval $\bar{T} < T < T^*$ the progression is predicted to be slow (logarithmic). At higher temperature $T > T^*$ essentially all barriers are overcome and the progression is fast.

KEY WORDS: Brownian motion ; helix–coil transitions ; activated jumps ; Fokker–Planck equations ; Ising model kinetics.

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1. INTRODUCTION

The transition from helix to coil of homogeneous polymer chains is reasonably well understood, at least as far as the static properties are concerned.² But if we go to a heteropolymer, with two constituents A and B that have different intrinsic melting temperatures T_A and T_B ($T_A > T_B$), we find a much more complex situation.

(a) The equilibrium melting curve cannot be calculated in closed form (and heavy numerical calculations are required) when the chemical sequence of A and B monomers is not periodic^(2,3) although information from the *wings* of the curve can be helpful even for very long DNAs.⁽⁴⁾

(b) The situation for kinetics is even worse. In fact, even for homopolypeptides, the standard kinetic description, based on a time-dependent Ising model,⁽⁵⁾ is often not satisfactory; for instance, the elimination (upon cooling) of a small coil region C between two helical portions H_1 and H_2 can take place only if the rod parts H_1 and H_2 are collinear and suitably positioned. Requirements of this sort are not properly included in the Ising picture. In this paper, we try to separate some effects of chemical heterogeneity on the kinetics; for instance, an A-rich region that does not melt easily may act as a barrier opposing the spread of a coil region.

In one favorable case these barrier effects become more tractable (and also the time-dependent Ising model is not too defective): Namely if we have only *one coil portion*, starting at one free end of the molecule, and growing at the expense of a long helix (Fig. 1). A similar problem was discussed previously for homopolypeptides.⁽⁶⁾ The assumption of a single coil portion is a severe restriction: In many cases, when the temperature T is raised,

² For an introduction to helix-coil transitions see Ref. 1.

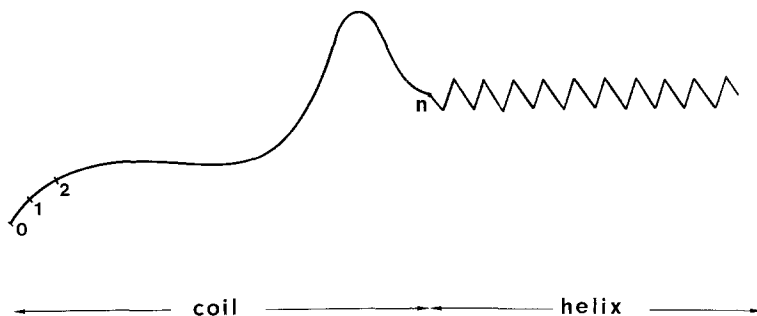


Fig. 1. At increasing temperatures a single-strand helical polymer is partially molten; the only conformations allowed for in the present paper correspond to a single coil region (from 0 to n).

nucleation of coils may occur separately at many points along the chemical sequence. However, (a) nucleation from the ends is favored, and (b) elastic forces tend to suppress nucleation inside one rigid rod, as explained in Ref. 6. Thus the assumption may hold, at least for times not too long.

Reference 6 was mainly concerned with a slowing down of the helix \rightarrow coil reaction due to hydrodynamic friction on the coil portion. In the present study, where activation energies are dominant, these hydrodynamic effects enter only into some unessential prefactors and will be completely omitted. The motion of the boundary point (labeled by an index n , giving its position along the chemical sequence) will be described by a simple Fokker-Planck equation, including the effects of both random jumps and energy barriers. For the rather strongly cooperative transitions of interest, it will be appropriate to treat the index n as continuous. Let us then call $f(n, t)$ the distribution function of the boundary point. It obeys an equation of the form

$$\frac{\partial f(nt)}{\partial t} + \frac{\partial J}{\partial n} = 0 \quad (1)$$

where J is the current

$$J = -D \left(\frac{\partial f}{\partial n} + f \frac{\partial U}{\partial n} \right) \quad (2)$$

containing (a) a diffusion term $-D \partial f / \partial n$ and (b) a flow term $-Df \partial U / \partial n$, describing the drift in a potential gradient: UT is the free energy required to transform the region $(0, n)$ from helix to coil:

$$UT = \sum_{m=1}^{m=n} [F_c(m) - F_h(m)] = \int_0^n dm [F_c - F_h] \quad (3)$$

Here $F_c(m)$ and $F_h(m)$ are the free energies of monomer m in the coil and in the helical state. In terms of the parameter S usually introduced for this type of transition⁽¹⁾ we can write

$$(1/T)[F_c(m) - F_h(m)] = \ln S_m \quad (4)$$

The m dependence of S_m describes the fact that, in heteropolymers, successive units do not have the same thermodynamic parameters.

Equation (3) contains an important hidden assumption, namely that the free energy due to the boundary region itself (E_f) is independent of the nature of the surrounding base pairs. Again returning to the usual notation,⁽¹⁾ this means that, in our model, the cooperativity parameter

$$\sigma = \exp(-2E_f/T) \quad (5)$$

is kept independent of n . In reality, as pointed out by Reiss,⁽¹²⁾ some modulation of σ must occur. However, for n large, we expect the fluctuations of U to

increase³ and to dominate over the fluctuations of σ , which remain bounded—thus justifying our assumption. We associate with each monomer site m an index μ_m giving the type of monomer:

$$\mu_m = \begin{cases} +1 & \text{type A} \\ -1 & \text{type B} \end{cases} \quad (6)$$

and write

$$\begin{aligned} \ln S_m &= -\Phi + \Delta\mu_m \\ \Phi &= C(T - \bar{T}), \quad \bar{T} = \frac{1}{2}(T_A + T_B); \quad \Delta = \frac{1}{2}C(T_A - T_B) \end{aligned} \quad (7)$$

Assuming $T_A - T_B \ll \bar{T}$ and $\sigma \ll 1$ (strong cooperativity), we can treat the factor C as temperature independent for all T of interest, and express it in terms of the reaction enthalpy H ,⁽⁴⁾

$$C \cong H/\bar{T}^2 \quad (8)$$

Both Φ and Δ will be taken much smaller than unity.⁴ Δ is independent of T , and Φ increases with T . In terms of Φ and Δ we may write the reduced potential energy $U(n)$ for the boundary point in the compact form

$$U(n) = -n\Phi + \sum_1^n \mu_m \cong -n\Phi + \Delta \int_0^n \mu \, dm = -n\Phi + U_1(n) \quad (9)$$

In Section 2 we shall discuss the Brownian motion of the boundary point in the presence of a given $U(n)$. Our aim is to extend the classical work of Kramers⁽⁷⁾ to more general barrier shapes. In Section 3 we go to a statistical problem, where the sequence $[\mu_1 \mu_2 \dots \mu_n \dots]$ is not known in detail, but only through certain averages. We take the overall average concentrations of A and B to be equal, and thus $\langle \mu_n \rangle \ll 0$ for all n . On the other hand, we do *not* assume that the different indices μ_m and μ_p are statistically independent. The correlation

$$\langle \mu_p \mu_m \rangle \ll g(m, p) \quad (10)$$

will be different from zero when $|m - p|$ is smaller than a certain “chemical correlation range” ξ_c . We shall also assume that $g(m, p)$ depends only on the difference $(m - p)$, i.e., that the material properties are homogeneous on the average.

In Section 4 we return to the nonstochastic problem, where the sequence $[\mu_1 \dots \mu_n \dots]$ is assumed to be known entirely; here the boundary point n may show a nearly stepwise progression (from one barrier to the next): High-resolution experiments might eventually detect these steps.

³ For large n the square deviation $\langle U^2(n) \rangle - \langle U(n) \rangle^2$ is linear in n .

⁴ It is in this limit only that n can be treated as a continuous variable.

This paper attempts to steer a middle course between the Charybdis of abstract statistical mechanics and the Scylla of unproven statements. Section 2 emphasizes the first aspect, and the reader who is more interested in practical denaturation problems should skip it, using only the final formula (45).

2. BROWNIAN MOTION THROUGH A POTENTIAL BARRIER

2.1. General Features

We consider a Brownian particle moving in one dimension (axis n) and hitting a potential barrier described (in units of T) by a potential function $U(n)$.

Various types of barriers are shown in Figs. 2 and 3. The simplest type (to be discussed first) is that of Fig. 2a: This is a purely repulsive barrier, of maximum height U_m . Experience and intuition both lead us to guess that the probability of overcoming the barrier is proportional to $\exp(-U_m)$. Our aim here is (i) to make this guess slightly more quantitative and (ii) to derive formulas for the jump rule that can apply to more general barrier shapes,

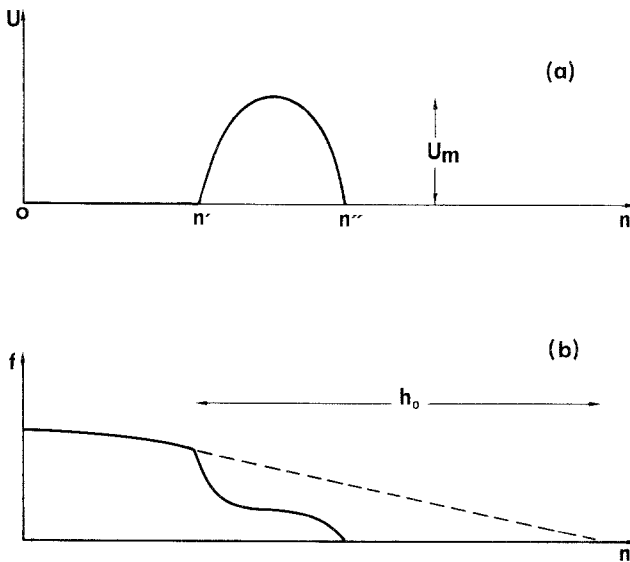


Fig. 2. (a) A simple (constantly repulsive) potential barrier. (b) The corresponding distribution function f for a Brownian particle starting from the left. It is assumed that the particle is trapped as soon as it has reached the right of the barrier. The distribution shown is reached when the particle has hit the barriers many times.

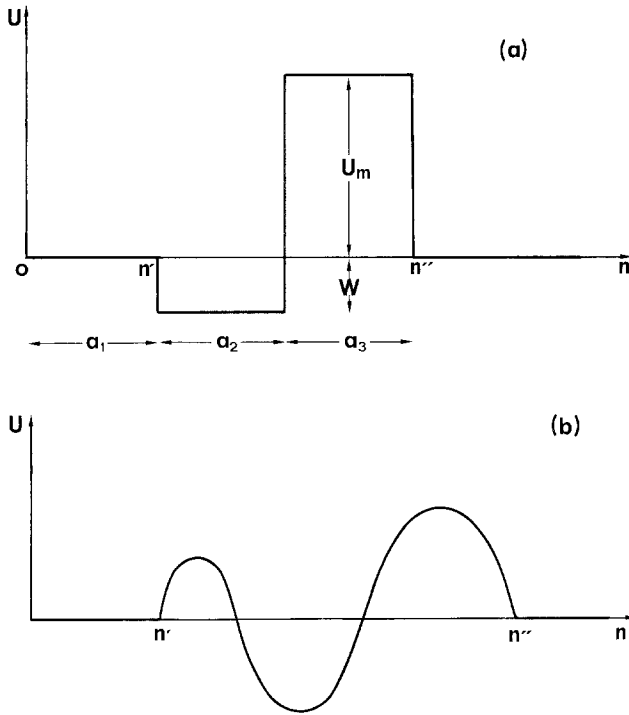


Fig. 3. A succession of wells and barriers: (a) simple model, (b) general case.

such as those depicted in Figs. 2b and 3. Our starting point is the Fokker-Planck equation defined in Eqs. (1) and (2) for the distribution function $f(n, t)$, which we rewrite, following Kramers,⁽⁷⁾ as

$$\frac{\partial}{\partial t} f(nt) = -D \frac{\partial}{\partial n} \left[e^{-U} \frac{\partial}{\partial n} (e^U f) \right] \tag{11}$$

We shall mostly be interested in factored solutions of the form

$$f(n, t) = f(n)e^{-t/\tau} \tag{12}$$

where $f(n)$ is governed by the time-independent equation

$$\frac{1}{\tau} f(n) = -D \frac{\partial}{\partial n} \left[e^{-U} \frac{\partial}{\partial n} (e^U f) \right] = \mathcal{H} f \tag{13}$$

The operator \mathcal{H} is not self-adjoint. However, if self-adjoint operators are desired (e.g., to define an orthogonal set of eigenfunctions), it is enough to introduce

$$\psi(n) = f(n) \exp[\frac{1}{2}U(n)] \tag{14}$$

The equation for ψ is then

$$\psi/\tau = \mathcal{H}\psi \tag{15}$$

where

$$\mathcal{H} = a^+ a \tag{16}$$

$$a = i(\partial/\partial n) + \frac{1}{2}U(n) \tag{17}$$

and a^+ is the Hermitian adjoint of a . The operator \mathcal{H} is now self-adjoint, and this implies that the eigenvalues $1/\tau$ are real. (In practice we shall not use \mathcal{H} any further.) Equations (13) and (15) have some similarity to a time-independent Schrödinger equation. However, this similarity is not very deep, and we shall see that the problem of transmission through barriers is very different for the two types of equations; in particular, the WKBJ approximation, which gives a powerful approach to the Schrödinger problem, is less fundamental for the Fokker–Planck problem.

2.2. The Kramers Problem ⁽⁷⁾

We now consider the form of $U(n)$ shown in Fig. 2a, and impose the following boundary conditions on the distribution function f .

(a) On the right-hand side of the barrier ($n = n''$) we set $f = 0$. This corresponds to a trap, capturing all particles that have gone through the barrier.

(b) At some point (0) on the left of the barrier ($0 < n'$) we put a reflecting wall.

(c) At time 0 we assume that the particle is located between 0 and n' . We want to know how long it will take for the particle to jump over the barrier and get trapped. The distribution function will then be of the form

$$f(n, t) = \sum_{k=0}^{\infty} e^{-t/\tau_k} f_k(n) C_k \tag{18}$$

where $f_0, f_1, \dots, f_k, \dots$ are the successive eigenfunctions of (13) and $1/\tau_0, 1/\tau_1, \dots, 1/\tau_k, \dots$ are the corresponding eigenvalues, with increasing magnitudes. The C_k are expansion coefficients to be determined from the form of $f(n, t = 0)$. For the problem at hand, the first coefficients C_0, C_1, C_2, \dots will be nonvanishing, and the long-time behavior of (18) will be of the form

$$f(n, t) \rightarrow \text{const} \times f_0(n) e^{-t/\tau_0} \tag{19}$$

Thus (as usual in linear transport problems for finite geometries) we may say that τ_0 is the time required to cross the barrier. From now on we shall concentrate on the ground state: f_0 and $1/\tau_0$ (for simplicity we shall omit the index 0 on both symbols).

Let us assume now that the barrier is strong, i.e., that the time τ is long when compared to the time that would be required to reach n'' by Brownian motion in the absence of any barrier. This suggests that in Eq. (13) the left-hand side (proportional to $1/\tau$) is small. In a first approximation we shall put it equal to zero; it will turn out that this is indeed acceptable if the barrier is *constantly repulsive and strong* ($U > 0$ and $U \gg 1$). Equation (3) can then be integrated twice, giving

$$-De^{-U} (d/dn)(e^{Uf}) = J = \text{const} \quad (20)$$

and

$$f(n) = (J/D) \int_n^{n''} dm \exp[U(m) - U(n)] \quad (21)$$

The integration limit in (21) ensures that $f(n'') = 0$ as prescribed. We can use (21) to calculate $f(n_-')$ at a point (n_-') immediately to the left of the barrier⁵

$$f(n_-') = (J/D) \int_n^{n''} dm \exp[U(m) - U(n)] = (J/D)h_0 \quad (22)$$

For $n < n'$, $U(n)$ is constant and $J = -D df/dn$. Thus we may express (22) as an effective boundary condition to be applied at the entrance of the barrier

$$-\frac{1}{f} \frac{df}{dn} \Big|_{n_-'} = h_0^{-1} \quad (23)$$

The length h_0 defined in (22) may be called the *extrapolation length* of the barrier at low frequencies ($1/\tau \rightarrow 0$). Its geometrical meaning is shown in Fig. 2b. The quantity

$$\frac{J}{f} \Big|_{n_-'} = \frac{D}{h_0} \quad (24)$$

could be called the *permeation velocity*. Finally, if we want to extract the lifetime for a particle initially trapped on the left-hand side, we must solve the free particle equation

$$(1/\tau)f = -D \partial^2 f / \partial n^2$$

on the interval $0 < n < n'$, together with the boundary condition (23) at $n = n'$, plus the condition $\partial f / \partial n = 0$ at $n = 0$. The solution is given by

$$\begin{aligned} f &= \text{const} \times \cos(qn) \\ q^2 &= 1/D\tau, \quad h_0 q \tan(qp) = 1 \end{aligned} \quad (25)$$

⁵ n_-' is infinitesimally close to n' and on the left of n' . This distinction between n_-' and n' is introduced to cover the case of square barriers, where U and f are discontinuous at n' .

In the limit of large τ , qp is smaller than one and the last equation gives

$$h_0 p q^2 = 1 \quad (26)$$

$$\tau = \frac{n' h_0}{D} = \frac{n'}{D} \int_{n'}^{n''} dm \exp[-U(n') + U(m)] \quad (27)$$

Apart from details in presentation, Eq. (27) is the formula derived by Kramers.⁽⁷⁾ It is restricted to strong positive barriers such as shown on Fig. 2a. Note the following consequences of (27): (a) For a square barrier of amplitude V , Eq. (27) gives of course the usual activation energy $\tau = \text{const} \times e^V$. (b) For a barrier with a simple, well-behaved maximum $U = U_m$ the integral h_0 (22) can be performed by expanding U near U_{max} in a Taylor series, and the leading factor in h_0 or τ is again e^{U_m} .

2.3. Barriers with an Attractive Part

Let us now consider the potential diagram of Fig. 3, where a square well (of depth W and width a_2) precedes a square barrier (of height U_m and width a_3). Both U_m and W are taken $\gg 1$. What is the effective activation energy for this case?

Clearly if a_2 is very small the activation energy should be U_m . On the other hand, if a_2 is large enough, the particle will first go into the well, stay there for a long time, and eventually come out to the right: The barrier to be overcome in this case is $U_m + W$. This can be confirmed by a complete solution, which we shall now describe briefly. Whenever $U(n)$ is discontinuous, the matching conditions to be satisfied are

$$f e^U \text{ continuous} \quad (28)$$

$$-\frac{J}{D} = \frac{df}{dn} + f \frac{dU}{dn} \text{ continuous} \quad (29)$$

as can easily be shown in the original equation (13). The ground-state solution of (13) is of the form

$$f(n) = \begin{cases} \cos q & 0 < n < a_1 \\ \alpha \cos qn + \beta \sin qn, & a_1 < n < a_2 + a_1 \end{cases} \quad (30)$$

where α and β are two constants, and q is related to the eigenvalue ($1/\tau$) by

$$1/D\tau = q^2 \quad (31)$$

The boundary conditions at a_1 give, after some manipulation,

$$\begin{aligned} \alpha &= [\cos^2(qa_1)]e^W + \sin^2(qa_1) \cong e^W \\ \beta &= (e^W - 1) \sin(qa_1) \cos(qa_1) \cong (qa_1)(e^W - 1) \end{aligned} \quad (32)$$

In the last form we used the fact that τ is large and q is small.) The boundary condition at $a_1 + a_2$ can be derived from the analysis of the last paragraph, and is

$$-\frac{1}{f} \frac{df}{dn} \Big|_{a_1+a_2-} = \frac{1}{h_1} \quad (33)$$

where h_1 is the extrapolation length for the repulsive part of the barrier, as measured from the bottom of the well

$$h_1 = a_3 \exp(U_m + W) \quad (34)$$

Inserting (33) into (30) and going to the limit of small q , we arrive at the condition

$$\alpha[h_1 q^2(a_1 + a_2) - 1] = \beta h_1 q \quad (35)$$

When compared with (32) this gives an explicit equation for q^2 (or for τ), namely

$$\tau = 1/Dq^2 = (h_1/D)(a_2 + a_1 e^{-W}) \quad (36)$$

Equation (36) shows the trends that we guessed earlier: If a_2 goes to zero, τ becomes proportional to $h_1 e^{-W}$: $\text{const} \times e^{U_m}$. On the other hand, as soon as

$$a_2 e^W > a_1 \quad (37)$$

The a_1 term may be omitted and τ becomes simply proportional to $h_1 = \text{const} \times e^{U_m+W}$. The criterion (37) amounts to saying that the particle, after reaching a local quasistationary state on the left of the barrier, spends more time in the well than in the zero-energy portion $(0, a_1)$.

Having an explicit form (36) for the lifetime τ , we can now compare it to the predictions of Eq. (27); setting $n' = a$ and $n'' = a_1 + a_2 + a_3$, we find from (27)

$$\tau = \frac{a_1}{D} (a_2 e^{-W} + a_3 e^{U_m}) \sim \frac{a_1 a_3}{D} e^{U_m}$$

i.e., the activation energy is expected to be U_m in all cases: Thus (27) clearly fails in the present case. In the next subsection, we shall show how the disease can be cured.

2.4. Improved Approximation

We now consider a rather general potential shape $U(n)$, as shown in Fig. 3b, including repulsive and attractive parts. Both parts are assumed to

be strong (i.e., $|U| > 1$ in most of the region considered). We start from Eq. (2) in the form

$$De^{-U} (d/dn)(e^U f) = -J$$

and integrate it to get

$$f(n) = D^{-1} \int_n^{n''} e^{U(m)-U(n)} J(m) dm \quad (38)$$

Then we turn to the conservation equation (1) (with $\partial f/\partial t = -f/\tau$) and also integrate it, obtaining

$$J(m) = J(n') + \tau^{-1} \int_{n'}^m f(p) dp \quad (39)$$

This can now be inserted into (38) to give an exact integral equation for f :

$$Df(n) = J(n')h_0(n) + \tau^{-1} \int_n^{n''} f m \int_{n'}^m dp e^{U(m)-U(n)} f(p) \quad (40)$$

where $h_0(n)$ is a natural generalization of the h_0 defined by (22):

$$h_0(n) = \int_n^{n''} dm e^{U(m)-U(n)} \quad (41)$$

In the second term (40) we shall now insert an approximate value of $f(p)$. We shall assume that in all the region preceding the main barrier the distribution function is close to its equilibrium form $f = \text{const} \times e^{-U}$:

$$f(p) \sim f(n_-') \exp[U(n_-') - U(n)] \quad (42)$$

This approximation would not be correct to compute derivatives df/dp , but is quite satisfactory for f itself in the limit of q small [where q is given by (31)]; this can be verified explicitly on Eqs. (30) and (32) for the square well plus square barrier problem. Inserting (42) into (40) and specializing to the barrier entry ($n \ll n_-'$), we get an explicit formula for the extrapolation length h :

$$h = \left[-\frac{1}{f} \frac{df}{dn} \Big|_{n_-'} \right]^{-1} = h_0 + \frac{S}{n'} \quad (43)$$

with

$$S = \int_{n'}^{n''} G(m) dm, \quad G(m) = \int_{n'}^m dp e^{U(m)-U(p)} \quad (44)$$

Equation (43) may also be transformed into an equation for the lifetime τ :

$$D\tau = n h_0 + S \quad (45)$$

Equations (44) and (45), together with Eq. (22) defining h_0 , will be of constant use in the next sections. Let us for the moment emphasize some of their general features:

(a) If the barrier is repulsive and strong as in Fig. 2a, the correction is small: From Eq. (44) one can show that S/h_0 is comparable to the size of the "non-strong" regions of the barrier (i.e., of the regions where $|U| < 1$, which were assumed small); for square barriers the corrections are completely negligible. Thus Eq. (27) may be used for the case of Fig. 2a.

(b) The correction is strong if there is a well to the *left* of a barrier so that both $U(m)$ and $-U(p)$ can be simultaneously large (by putting p in the well and m in the barrier). In particular for the "square well plus square barrier" problem of Fig. 3a one has

$$G(m) = \begin{cases} m - a_1 & a_1 < m < a_1 + a_2 \\ a_2 e^{U_m + w} + m - a_1 - a_2, & a_1 + a_2 < m < a_1 + a_2 + a_3 \end{cases}$$

Keeping only the dominant term, this gives after integration

$$\begin{aligned} S &\cong a_3 a_2 e^{U_m + w} \\ D\tau &= a_1 h_0 + S = a_3 e^{U_m} (a_1 + a_2 e^w) \end{aligned} \quad (46)$$

in agreement with the correct formula (36).

(c) Note also that there are no large contributions to S if the well is lying to the right of the barrier [because $m > p$ by definition in Eq. (44)], in agreement with physical expectations.

3. STOCHASTIC GROWTH OF ONE-COIL REGION

3.1. Creep versus Drift

We consider now the particular helix-coil conformation shown in Fig. 1 for a heteropolymer. A single coil region is assumed, extending from the beginning (0) of the chemical chain up to n . The associated potential energy is (in reduced units) $U(n)$ as defined by Eq. (9). It contains an average part, associated with a constant force Φ , and a random part U_1 :

$$U(n) = -\Phi n + U_1(n) \quad (47)$$

When we are just at the average melting temperature ($T = \bar{T}$) the force Φ vanishes, and U reduces to U_1 . The characteristics of $U_1(n)$ are shown in Fig. 4a. The fluctuations of $U_1(n)$ increase in magnitude when n becomes large. As a result there exist (in most cases) a number of energy barriers between 0 and n . When $T < \bar{T}$ the average force Φ is negative and tends to bring back the boundary point n near the origin 0 (Fig. 4b). The most

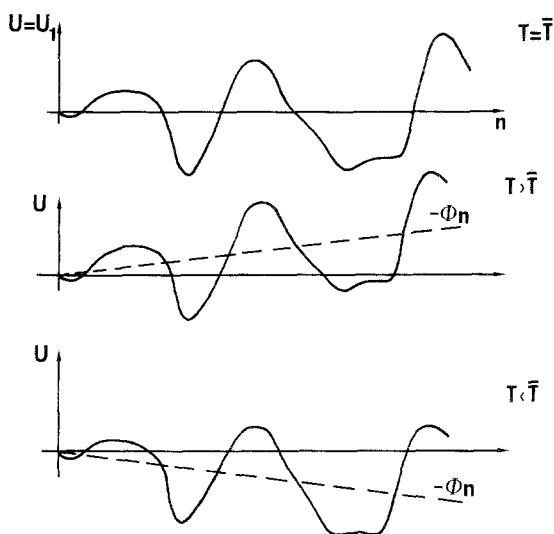


Fig. 4. Typical features of the potential $U(n)$ experienced by the boundary point n , for various temperatures. Note that the fluctuations of U increase with n .

interesting case corresponds to the opposite situation: $T > \bar{T}$. Here the force $\Phi > 0$ pulls the boundary to the right: If there were no barriers, the boundary point would drift off to infinity at a constant speed ΦD . The central question is to find whether the random barriers described by $U_1(n)$ will be able to suppress this drift or not.

The answer, to be derived below, depends on the magnitude of the force Φ . If Φ is smaller than a certain threshold, we predict that the drift is suppressed, and replaced by a slow “creep process,” where the abscissa (n) is not a linear function of time.

3.2. The Creep Law

We now treat the chemical sequence $\mu_1, \mu_2, \dots, \mu_n, \dots$ and the resulting potential $U_1(n)$ as stochastic functions: This means that we do not consider one specific sequence, but rather an ensemble of polymer chains with different sequences. Observations of calculations on an ensemble will necessarily cause certain fine structure to be lost—to which we shall return in Section 4—characteristic of a single chemical chain. But they will give us an average creep law around which the fine structure can later be built up.

Our aim is to estimate the average transit time $t(n)$ between 0 and n , through Eq. (45). The stochastic calculation shall mainly be concerned with rather large values of n , for which the potential curve $U(n)$ shows at least a

few deep minima and high maxima: Thus we are in a situation where the correction term S is dominant, and we can write Eq. (45) in the form

$$t(n) = D^{-1} \int_0^n dm \int_0^m dp \langle e^{U(m)-U(p)} \rangle \quad (48)$$

where the brackets denote an average over our stochastic ensemble of chemical sequences. We must first separate in U the average part and the fluctuating part:

$$U(m) - U(p) = \Phi(p - m) + U_1(m) - U_1(p) \quad (49)$$

For the large intervals $m - p$ of interest ($m - p > \xi_c$, where ξ_c is the range of correlations defined in Section 1) terms such as $U_1(m) - U_1(p)$ are the sum of many independent contributions and have a Gaussian distribution. Then

$$\langle e^{U(m)-U(p)} \rangle = \exp[\Phi(p - m)] \exp\langle \frac{1}{2}[U_1(m) - U_1(p)]^2 \rangle \quad (50)$$

$$= \exp[\Phi(p - m) + \frac{1}{2}\Delta^2 \iint_p^m dq dr \langle \mu_q \mu_r \rangle] \quad (51)$$

When the interval $m - p$ is large the double integral in (51) becomes

$$\iint_p^m dq dr g(r - q) \rightarrow 2\xi_c(m - p) \quad (52)$$

where ξ_c is now explicitly defined by

$$\int_0^\infty g(x) dx = \xi_c \quad (53)$$

Collecting these formulas, we find

$$t(n) = D^{-1} \int_0^n dm \int_0^m dp e^{g(m-p)}, \quad n \gg \xi_c \quad (54)$$

where

$$g = \Delta^2 \xi_c - \Phi = C(T^* - T) \quad (55)$$

Here we have made use of Eq. (7), and defined

$$T^* = \bar{T} + C^{-1} \xi_c \Delta^2 \quad (56)$$

Returning to Eq. (54), we see that we are faced with two possibilities, depending on the sign of g :

(a) If $g > 0$ ($T < T^*$), the exponent is positive, the integral in (54) is large, and the time of transit $t(n)$ is long. In this case the barriers are very effective. Also, the assumptions underlying Eq. (45) are satisfied, and the whole calculation is consistent.

(b) If $g < 0$ ($T > T^*$), the exponent is negative, the integral (54) is bounded, and the time of transit becomes short: The barriers are not very effective. In this regime we expect that there is a uniform drift. [However, we are not able to compute the average drift velocity because Eq. (45) is not a correct starting point for short transit times.]

This distinction between drift and creep regimes for a classical particle in a potential whose derivative (the force) is a stationary random variable may, in fact, be of interest in other branches of physics. Let us now consider in more detail the laws for the creep process occurring in the interval $\bar{T} < T < T^*$. Integrating (54), we get

$$t(n) = D^{-1}g^{-1} \int_0^n dm (e^{gm} - 1) \sim D^{-1}g^{-1} \int_0^n dm e^{gm} \quad (57)$$

$$\cong D^{-1}g^{-2}e^{gn}, \quad g > 0$$

Assuming that all relevant distributions are reasonably peaked, we can invert this formula and write that the length \bar{n} reached in a fixed time t is of order

$$\bar{n} = g^{-1} \ln(\omega t), \quad \omega = Dg^2 \quad (58)$$

(The dependence of ω on T is not very critical, since ω enters only through a logarithm.) The main features of Eq. (58) are then (a) the logarithmic dependence of \bar{n} on t , characteristic of a creep process, and (b) the temperature dependence of the coefficient g^{-1} [proportional to $(T^* - T)^{-1}$ according to Eq. (55)].

4. CONCLUDING REMARKS

4.1. Possible Fine Structure in the Melting Curve for One Chemical Species

For the stochastic ensemble considered in Section 3, the melting curve is expected to be essentially smooth: Any fine structure will be washed out by the average over different chemical structures. In this section, we return to the case where the chemical sequence is unique. Then we expect the irreversible melting curves to show (if the resolution is high enough) a more or less stepwise structure. The origin of this structure can be understood in terms of successive energy barriers, and is exemplified in Fig. 5. We consider here an irreversible melting curve obtained by raising the temperature through small successive jumps of magnitude δT and duration θ . To the time θ we can associate a characteristic barrier height (in reduced units) V such that

$$V = \log \omega_0 \theta \quad (59)$$

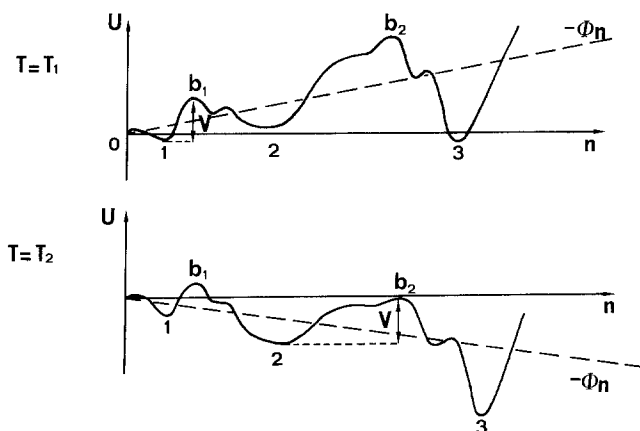


Fig. 5. Irreversible melting. The time scale θ of the experiments fixes the height V of the barriers that can be overcome. When the temperature T reaches T_1 the average slope of the potential ($-\Phi$) becomes small enough and the barrier b_1 can be overcome. The boundary point then exchanges between region 1 and region 2. When T reaches T_2 barrier b_2 can be overcome and the boundary point moves to region 3.

where ω_0 is a microscopic frequency (of order D/ξ_c). All barriers smaller than V will be overcome in time θ ; all larger barriers will not. Consider now the chemical sequence described by Fig. 5, and start (at $n = 0$) with a low temperature ($T < \bar{T}$). Then at first the boundary point will stay in the shallow well (1). When T is increased the average slope of $U(n)$ decreases, and finally at one temperature T_1 the first important barrier will be overcome; the representative point can reach region 2 and a local thermal equilibrium between 1 and 2 is achieved. When T increases above T_1 this equilibrium is progressively displaced toward 2. Still increasing the temperature, we reach later a value $T = T_2$ at which the next important barrier can be overcome. The representative point then moves to region 3, and (for the case shown in Fig. 5) region 2 is then completely depopulated. The process continues in a similar manner; the resulting irreversible melting curve is given as a plot of the average \bar{n} versus T in Fig. 6. Finally at a temperature close to T^* the drift regime takes over.

If a curve of the type shown in Fig. 6 is observed, it is of course tempting to define "subunits" along the chemical sequence, corresponding to the intervals (01), (12), (23),.... However, it must be realized that the resulting classification depends on the exact type of experiment which is performed. We discussed here a progressive heating with a fixed time per step θ . If we had operated differently, we might have found another set of subunits: (a) It is clear that a large increase of θ may change V and thus change the classification. (b) In the experiment described in Fig. 7a, a temperature jump

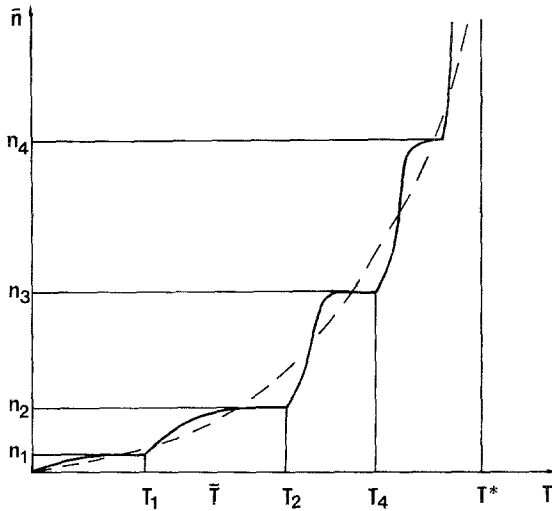


Fig. 6. Melting curve $\bar{n}(T)$ associated with the chemical sequence described by Fig. 5. The dashed line shows the smoothed curve calculated by stochastic arguments in Section 3.

has brought T suddenly from low values up to $T = \bar{T}$, where it is fixed. The later variations of n are recorded as a function of time. In this experiment we shall observe successive occupations of regions 1, 2, 3,.... However, if on the same chemical sequence we perform the first type of experiment, with progressive increases in T (as in Figs. 5 and 6), step 2 will not appear. This is clear from Fig. 7b: When θ is large enough to allow passage of the first barrier, the second barrier has been reduced strongly and is not efficient.

Thus, if certain fine structure appears in an irreversible melting curve, it may well depend on the particular choice of experimental conditions. Only when the chemical structure has very sharp accidents will the important barriers be the same for all practical types of experiments.

With these limitations in mind, we can still, to some extent, ask what is the average size of a subunit. The following represents a means of estimating an answer. For simplicity we consider the second type of experiment (fixed T) and fix $T = \bar{T}$. Equation (58) (with $g = \Delta^2 \xi_c$) tells us roughly the distance \bar{n} between the origin and the first barrier of amplitude larger than or equal to $V = \log \omega_0 t$. Identifying t and θ (and ignoring the difference between ω_0 and ω), we get an estimate of the size of the first subunit n_s

$$n_s \sim g^{-1}V = (\lambda^2/\xi_c) \log(\omega_0\theta) \tag{60}$$

Here we have introduced a length $\lambda = \Delta^{-1}$, which has the following physical interpretation: If (at $T = \bar{T}$) we have a long chain portion made up of only

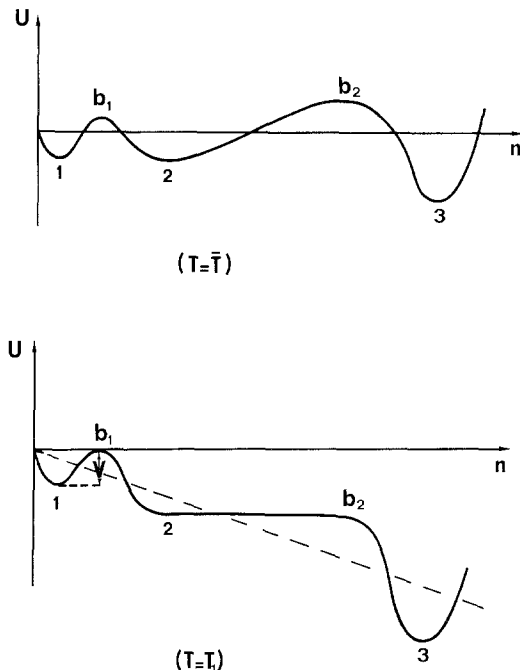


Fig. 7. (a) After a temperature jump from low temperatures to the average melting point \bar{T} , the system will go successively from 1 to 2, and after a longer time from 2 to 3. (b) When the same system is heated progressively at the temperature $T = T_1$ where it can overcome the first barrier b_1 , the second barrier b_2 has disappeared: The system jumps directly from 1 to 3.

the A monomers (those of high melting point), the coil region will penetrate it, on the average, only up to a length λ . We might thus call λ the *penetration depth*.

Equation (60) is extremely conjectural. But it points out an important fact, which is probably model independent, namely that the size of a subunit need not be comparable to the range of chemical correlations ξ_c .

4.2. The Case of Natural DNA'S

Nucleic acids are copolymers with two different types of melting units (the AT and GC pairs).⁶ Certain nucleic acids of intermediate length, such as mitochondrial yeast DNA or phage λ DNA, do show a melting curve with a certain fine structure, which is clearly due to the chemical heterogeneity.^(9,10) However, the current interpretation⁽¹⁰⁾ is *not* connected with the barrier

⁶ For an introduction to the physical aspects of DNA denaturation see, e.g., Ref. 8.

processes that were described above. It appears that the various steps found upon melting correspond to large segments of the molecule, with different AT/GC ratios, melting independently. Thus the two effects are probably quite different. It may be, however, that the hysteresis properties, which have been used ingeniously to assign the order of the segments,⁽¹¹⁾ are complicated by some of the barrier processes that we have described.

4.3. Summary of Results

The situation considered in this paper, where one single coil region grows from the end of a long helix, is extremely special and may be amenable to experiment only on rather small chains, where the stochastic considerations of Section 3 are not of great interest. However, the formula (45), describing the penetration through one barrier, may remain useful even for short chains. In a different direction, the distinction between creep and drift regions appears general; it may be of help even for problems involving simultaneously many coil regions in a partially molten system.

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