Biophysics, Vol. 45, No. 3, 2000, pp. 397–403. Translated from Biofizika, Vol. 45, No. 3, 2000, pp. 407–413.
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MOLECULAR BIOPHYSICS

Effect of the Fluctuation Amplitude on the Friction Coefficient of a Brownian Oscillator in Aqueous Medium

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Received April 27, 1999

Abstract—The methods of molecular dynamics and correlation functions of coordinates were applied to a study of damping molecular oscillations in water solutions upon variation of the fluctuation amplitude. It was found that as the fluctuation amplitude exceeded the threshold value (0.3–0.45 Å in water), the force of friction increased sharply, and the vibration mode changed into the mode of limited diffusion. The consistency of the results with the theory of the Moessbauer effect and the Brownian oscillator model for the conformational mobility in biopolymers is discussed.

Key words: dynamics of proteins, dynamics of aqueous medium, Brownian oscillator, limited diffusion, damping of molecular oscillations

INTRODUCTION

About 20 years ago, a theory of the Moessbauer effect in proteins was proposed for description of the conformation mobility in biopolymers [1–3]. This theory was based on the model of the Brownian oscillator with strong damping. In a number of modifications this theory has earned a certain popularity [4–10], and is widely used in theoretical biophysics and related fields [11–15]. These ideas are based on indirect estimation of the friction coefficient in conformation displacements [1, 2]. The latter term is understood as displacements of atomic groups in biopolymers with amplitudes significantly larger than those of the valence vibrations, or 0.1 Å. The data of Moessbauer spectroscopy [1, 2] show that in a condensed medium, atomic displacements with amplitudes of 0.3 Å or larger obey the diffusion mechanism. This motion mechanism can also be described in terms of the Brownian oscillator with a strong damping [16]. In this case, the friction coefficient is so large that the inertial terms in the Langevin equation for the oscillator can be neglected. The limiting case of strong damping is realized in the situation when there is no free volume to include the displacement of the atomic group, and to make such motion possible it is necessary that a fluctuation cavity ("hole") [17] be formed owing to collective dynamic effects in a condensed medium. In this case, the well-known Stokes equation [18] can be used for estimation of the friction coefficient. Displacements with amplitudes less than 0.1 Å, e.g., the valence vibrations, are characterized by lower values of the friction coefficient, and typical values of damping times fall into the picosecond range [19]. Upon an increase of the molecular oscillator amplitude, the mode of slowly damping oscillations should change into the mode of limited diffusion, with the damping time constant (which is proportional to the friction coefficient) on the order of the intrinsic oscillator frequency. We have studied this transition using the methods of molecular dynamics for molecular oscillators placed into water drops of 64 and 256 molecules.

MOLECULAR–DYNAMIC MODELS FOR AN OSCILLATOR IN WATER

In calculations of the molecular oscillator behavior in a water environment, we used models of three-dimensional and one-dimensional oscillators. A two-atom molecule similar to that of ethane was

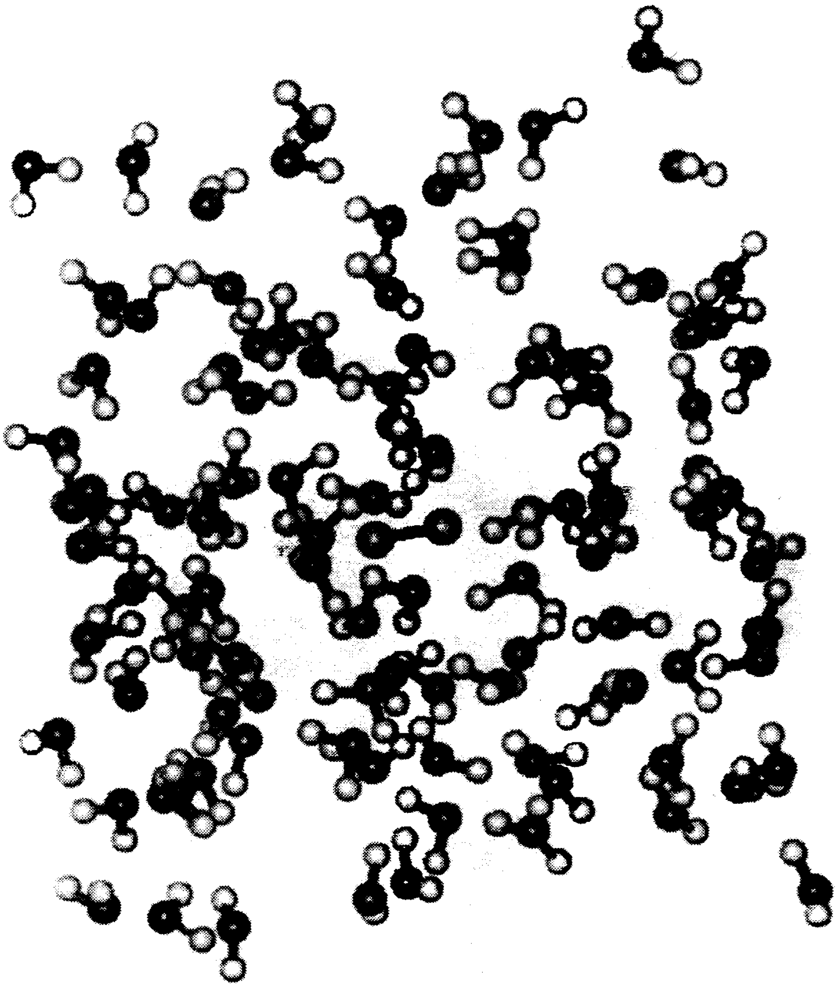

Fig. 1. Molecular-dynamic model of an oscillator in a drop of 64 water molecules. The ethane molecule is in the center (hydrogen atoms in this molecule are not shown).

chosen as the three-dimensional oscillator; the hydrogen atoms were taken into account in the framework of the heavy-atom approximation [20, 21]. The initial CH_3–CH_3 bond length was chosen equal to that in the ethane molecule ($\approx$1.53 Å). One of the heavy atoms of the molecule was fixed in space, which ensured the spherical symmetry of the three-dimensional oscillator.

A one-dimensional oscillator was simulated by a three-atom system similar to the propane molecule, in the same heavy-atom approximation. To reduce the system's dimension as well as the volume of the hydrate coating, the distance between the first and the second carbon atoms was fixed at 0.54 Å. The distance between the second and the third atoms was fixed at $\approx$1.53 Å, as in the ethane molecule. The first and the second carbon atoms were fixed in space, the valence angle C1–C2–C3 was also fixed at 180°. The angle was fixed using the rigid potential of the valence angle, with the rigidity constant of 999.9 kcal/(mol rad). The valence angle and the two first atoms were fixed to prevent rotation of the oscillator.

The "ethane" molecule was surrounded by a shell of 64 or 256 water molecules (see Fig. 1), and the "propane" molecule was surrounded by 256 molecules of water. The water molecules were described by the SP3 model, with valence and hydrogen bonds positioned at the angles of a tetrahedron. Periodic

Table 1. Parameters of valence, electrostatic, and van der Waals interactions, and of hydrogen bonds for water

Atom	van der Waals interaction		Hydrogen bond		Valence bond		Valence angle		Atomic charge
	ε	$r_{\min}$, Å	ε	$r_{\min}$, Å	K_{OH}, kcal/(mol Å^2)	$r_{\min}$, Å	K_{HOH}, kcal/(mol rad^2)	θ, deg	q, e
O	0.15	3.3	0.5	1.95	1106	0.96	94	104.5	–0.834
H	0.02	2.0							0.417

boundary conditions were chosen for the system of water molecules [20, 21]. The average mass density of the system was equal to 0.98. A system of AMBER potentials [22] was used in the calculations, and the van der Waals interactions and hydrogen bonds were taken into account. The parameters of the interactions of water molecules are presented in Table 1.

The rigidity constant of the C–C bond was varied in the range from 0.02 to 800 kcal/(mol Å^2) (in the real ethane molecule this bond is characterized by a rigidity constant of 520 kcal/(mol Å^2)).

We did not take into account the van der Waals interactions between carbon atoms, thus neglecting the hydrodynamic effects caused by sharp collisions of the carbon atoms at low values of the rigidity constant, when the amplitude of the molecular oscillator fluctuations exceeds the characteristic valence bonds lengths. The van der Waals interactions of the first and the second carbon atoms of propane with water molecules were also disregarded, thus avoiding perturbations of the linear one-dimensional oscillator induced by these interactions. The PUMA package [20, 21, 23] was used in the molecular dynamics calculations. The trajectory length was 150 ps, with an integration step of 0.0001 ps. The system temperature was maintained constant (300 K) with the aid of a Berendsen cryostat.

The time-domain autocorrelation function of coordinates was used for interpretation of the molecular dynamics calculations, which was compared with the expected dependence for the Brownian oscillator.

THE MODEL OF THE BROWNIAN OSCILLATOR

The dynamics of thermal fluctuations of atoms in molecules is usually described by the Langevin equations for the Brownian oscillator:

$$m\ddot{x} + \gamma\dot{x} + m\omega_0 x^2 = F(t). \tag{1}$$

Here m is the effective mass of the moving atomic group; γ is the friction coefficient; $\omega_0^2 m = K$ (K is the force constant); $F(t)$ is an accidental force, or thermal noise, describing the interaction of the oscillator with molecules of the surrounding medium. The accidental force is related to the friction coefficient by the fluctuation-dissipative theorem [16]:

$$\langle F(t)F(0)\rangle = 2kT\gamma\delta(t).$$

In the following, we shall consider the autocorrelation function of the coordinate $\varphi(t) = \langle x(t)x(0)\rangle$, where the angle brackets denote averaging. The Fourier transform of the correlation function of coordinate is [16]:

$$\varphi(\omega) = 2\int_0^\infty dt\varphi(t)\cos\omega t = \frac{2kT\gamma}{m^2(\omega_0^2 - \omega^2)^2 + \gamma^2\omega^2}. \tag{2}$$

Reversing the Fourier transform (2), one gets the expression for the correlation function at arbitrary values of the velocity of the vibrational relaxation:

$$\varphi(t) = \frac{kT}{m(\omega_1 - \omega_2)}\left\{\frac{e^{i\omega_1 t}}{\omega_1} - \frac{e^{i\omega_2 t}}{\omega_2}\right\}, \tag{3}$$

where ω_1 and ω_2 are the poles of $\varphi(\omega)$:

$$\omega_{1,2} = i\frac{\gamma}{2m} \therefore \varepsilon 6 \sqrt{\omega_0^2 - \frac{\gamma^2}{4m^2}}. \tag{4}$$

In the limiting cases $(\gamma/2m) \ll \omega_0$ and $(\gamma/2m) \gg \omega_0$ we obtain, respectively:

$$\varphi(t) = \frac{kT}{m\omega_0^2}\cos\omega_0 t \exp\left(-\frac{\gamma}{2m}t\right), \tag{5}$$

$$\varphi(t) = \frac{kT}{m\omega_0^2}\exp\left(-\frac{\omega_0^2 m}{\gamma}t\right). \tag{6}$$

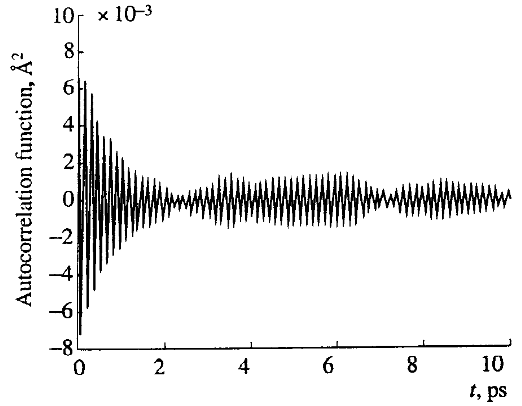

Fig. 2. Autocorrelation function of oscillations of the carbon atom in the model system with an intermediate-rigidity C–C bond (64 kcal/(mol Å^2)).

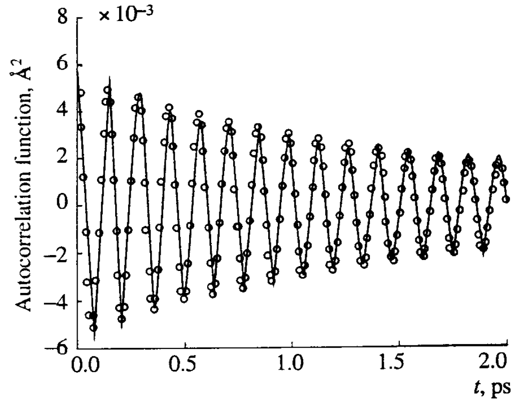

Fig. 3. Approximation of the autocorrelation function. The solid curve – numerical experiment; open circles – results of approximation at the rigidity constant for the C–C bond 74 kcal/(mol Å^2).

The value $\varphi(0) = kT/m\omega_0^2$ is the mean squared amplitude of the particle with energy kT. In these two limiting situations, one observes different ways of particle motion in the harmonic potential. In the first case this is the oscillation with frequency ω and with the damping time $\tau = 2m/\gamma$. Increasing the friction coefficient γ in (5) results in reduction of τ, i.e., in an increase of the vibrational relaxation rate. Upon an increase of the friction coefficient above the critical value $2m\omega_0$ the movement regime changes radically. Equation (6) describes the limited diffusion of a particle in a harmonic potential. By contrast to the low friction mode, in this case the correlation time is proportional to the friction coefficient: $\tau = \gamma/m\omega_0^2$. The reason is that the diffusion rate declines with increasing friction or viscosity of a medium.

Thus, variation of the dimensionless parameter $\gamma/2m\omega_0$ in region 1 should qualitatively change the time dependence of the autocorrelation function of coordinate. According to the reasons discussed above, the friction coefficient for a molecular oscillator in a liquid depends on the oscillation amplitude. In the case of amplitudes comparable with interatomic distances, the friction coefficient should approach the hydrodynamic limit, the latter being determined by the Stokes equation. In this case we definitely get into the regime of limited diffusion [1, 2].

This transition may be demonstrated by a "measurement" of the dependence of the imaginary part of ω_2 on the mean square amplitude of the molecular oscillator in water, $kT/m\omega_0^2$; this dependence is divided into two branches. In the region where $\gamma/2m\omega_0 \le 1$, the value $\mathrm{Im}\,\omega_2$ behaves as $\gamma(kT/m\omega_0^2)/2m$. (Here the dependence of the friction coefficient on the oscillation amplitude is shown explicitly.) In the entire region of its existence this function is increasing, and its derivative is positive and finite.

In the region where $\gamma/2m\omega_0 \ge 1$, the function under consideration is

$$\mathrm{Im}\ \omega_2 = \frac{\gamma}{2m} - \sqrt{\frac{\gamma^2}{4m^2} - \omega_0^2}. \qquad (7)$$

Differentiation of the function (7) over $kT/m\omega_0^2$, taking into account that the derivative of γ over this argument is positive, shows that in the region where $\gamma/2m\omega_0 \ge 1$ the function (7) decreases, and at the point $\gamma/2m\omega_0 = 1$ there is a *radical diversity*. This means that there is a characteristic λ-point at $\gamma/2m\omega_0 = 1$, which may be used for determination of parameters.

DISCUSSION

We have calculated a series of molecular dynamic trajectories at the described above conditions for the two molecular systems. Molecules were placed into water, and the solution density was 0.98 (Fig. 1). The rigidity constant for the C–C bond was varied with fixed values of other parameters. For each trajectory the autocorrelation functions of coordinates of

Table 2. Theoretical and calculated parameters for a three-dimensional spherically symmetrical oscillator in water environment

$K = m\omega_0^2$, kcal/(mol Å^2)	$kT/m\omega_0^2$ Å^2	ω_0, ps^{-1}	ω_0, ps^{-1} calcd.	γ/m, ps^{-1}
0.1	6.1967	1.6760	1.6377	13.6640
0.4	1.0723	3.3520	3.9369	13.4946
1	0.5917	5.3000	8.7851	13.1289
1.6	0.3698	6.7040	8.7637	11.7134
2	0.2958	7.4953	7.6441	13.1646
2.6	0.2276	8.5460	11.4095	7.7971
4	0.1479	10.6000	14.2529	4.2794
6	0.0986	12.9823	12.8596	4.2706
14	0.0423	19.8308	18.3243	2.1167
30	0.0197	29.0293	31.4018	5.8515
32	0.0185	29.9813	33.4122	2.8845
34	0.0174	30.9040	32.9224	3.8561
36	0.0164	31.8000	30.8992	4.5890
38	0.0156	32.6714	34.5605	2.8820
40	0.0148	33.5201	35.3065	3.6842
46	0.0129	35.9463	37.8272	2.4668
54	0.0110	38.9469	41.5567	2.9220
56	0.0106	39.6616	41.2172	2.8623
64	0.0092	42.4000	43.8675	3.0011
100	0.0059	53.0000	54.3110	2.2857
520	0.0011	120.8586	120.6330	0.2785

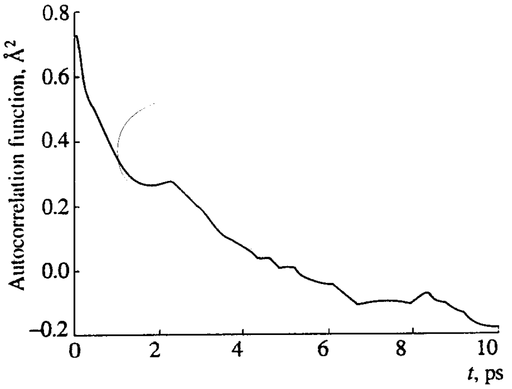

Fig. 4. Autocorrelation function of the carbon atom oscillations in a model system at a C–C bond rigidity constant of 0.02 kcal/(mol Å^2).

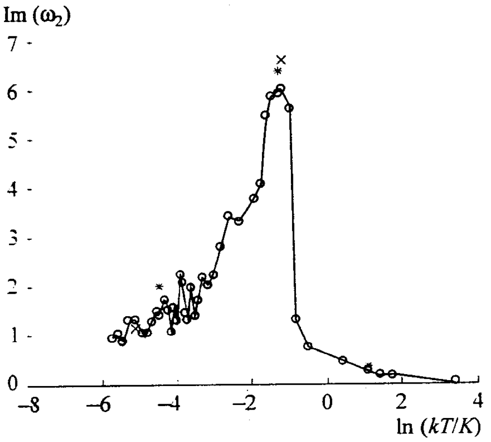

Fig. 5. Dependence of the imaginary part of ω_2 (ps^{-1}) on ln(kT/K). Mean square amplitude measured in Å^2; open circles pertain to a three-dimensional spherically symmetrical oscillator in a drop of 64 water molecules; asterisks pertain to the same oscillator in a drop of 256 molecules; crosses pertain to a linear oscillator in a drop of 256 water molecules.

the unfixed carbon atom were calculated (averaging was performed along the trajectory):

$$\varphi(t) = \langle x(0)x(t)\rangle, \qquad (8)$$

where x is the radius vector for the declination of the movable carbon atom from the equilibrium position. The autocorrelation functions (8) presented in Figs. 2–4 are in good agreement with the Brownian oscillator model for different regimes of motion. At high rigidity constants, which are inherent in valence vibrations, a classical pattern of vibrations with relatively slow damping is observed (Fig. 2, 3). In Fig. 2, in the time range of 10 ns, beats are observed, which are most probably caused by interference with waves reflected by the boundaries of the liquid drop. In the shorter time interval of 2 ns, we observe a good agreement of equation (5) with the numerical experiment (Fig. 3). Reduction of the rigidity constant is accompanied, at the initial stage, by increased damping, and then the motion regime changes, and a transition to the limited diffusion in a parabolic potential is observed (Fig. 4).

The values of $\gamma/2m$ and ω_0 determined from the calculated correlation functions according to equation

(3) are presented in Table 2. We failed to obtain a satisfactory result in the comparison of calculated and theoretical dependences, and in the determination of $\gamma/2m$ at fixed values of ω_0 and the oscillator mass. Only simultaneous variation of both parameters, $\gamma/2m$ and ω_0, produced a satisfactory fit (see Table 2). In certain cases it was necessary to vary also the average oscillator amplitude. Figure 5 shows on the logarithmic scale the dependence of the oscillator damping on the fluctuation amplitude. The left side of the plot reflects an increase of the friction coefficient with increasing oscillator amplitude in water. Inside a comparatively narrow interval on the x axis, the λ-point is seen corresponding to a change of the motion regime. The λ-point coordinate lies in the interval of amplitudes $x_0 = [\varphi(0)]^{1/2}$ from 0.3 to 0.45 Å (see Table 2 and Fig. 5). The right side of the plot reflects the increase in the relaxation time of limited diffusion in a parabolic potential with increasing motion amplitude (i.e., decreasing rigidity constant).

Note that the frequency values ω_0 in Table 2 differ somewhat from those determined by the rigidity constant and the oscillator mass. This can be caused by added mass effects, influence of the potential field of water molecules, and by the crudity of the white noise approximation in the Langevin equation.

CONCLUSION

The investigation of damping of the molecular oscillator placed in a water drop, performed by the methods of molecular dynamics, showed that the effective friction coefficient in a liquid medium increased by a factor of some tens with the oscillation amplitude increasing from 0.03 Å (the amplitude of valence vibrations of the C–C bond) to 2 Å (on the order of amplitudes of the conformational motion). Increasing the amplitude above the threshold value of 0.3–0.45 Å is accompanied by a change of the vibrational motion regime into the limited diffusion in the parabolic potential. The one-dimensional and three-dimensional oscillators behave practically in the same way. Using the Stokes's equation, and assuming the particle radius to be 1 Å, one can estimate the effective microviscosity of water at motion amplitudes on the order of 1 Å at about 0.18 cP, i.e., about five times less then the macroviscosity. It should be noted that the spherically symmetrical oscillator considered here approximately reproduces the conformational degree of freedom corresponding to the rotation about the C–C bond. The one-dimensional oscillator simulates motion under strong steric limitations.

The results of calculations are almost insensitive to the water drop volume (64 or 256 water molecules). One should expect only minor changes in the threshold amplitude of motion (of about 0.1 Å) for the transition of the molecular oscillator into the regime of limited diffusion in other liquid media. The threshold amplitude values obtained by the methods of molecular dynamics are in good agreement with the results of the Moessbauer spectroscopic studies of macromolecular systems.

ACKNOWLEDGMENTS

This work was partly supported by the Russian Foundation for Basic Research, project no. 98-04-48479, and the Ministry of Education, grant no. 220-7.

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