

# Quantum mechanical model of proton transfer in a fluctuating potential field of the active site of $\alpha$ -chymotrypsin

B. A. Grishanin, Yu.M. Romanovskii, A. Yu. Chikishev, and E. V. Shuvalova

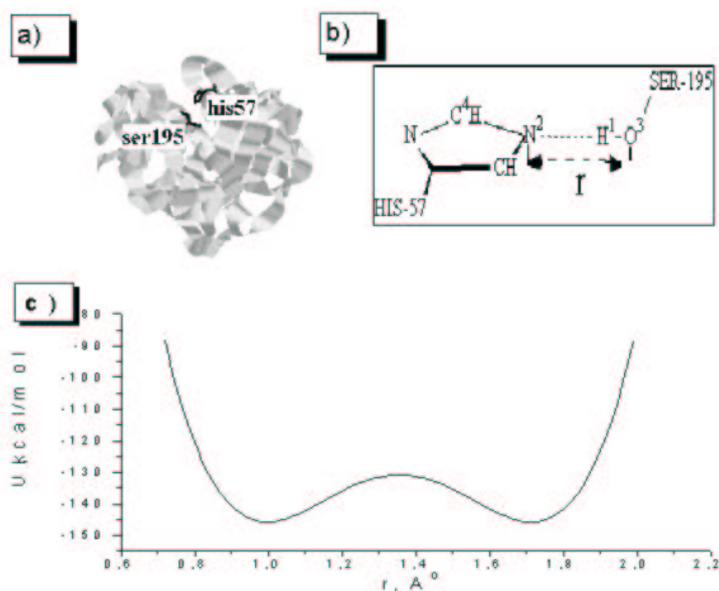
International Laser Center and Department of Physics, M. V. Lomonosov Moscow State University, 119899 Moscow, Russia

**Abstract.** We studied the process of proton transfer from oxygen of serine 195 to nitrogen of the imidazole ring of histidine 57 that takes place in the active site of the enzyme  $\alpha$ -chymotrypsin (CT). We studied the dynamics of the proton in a non-stationary potential of the active site of CT with regard to the fluctuations determined by the oscillations of the clusters. In addition to tunneling in the non-stationary potential we observed an incoherent dynamic irreversible process of the over-barrier transfer, that is caused by the noise action. The fluctuations of the potential field of the active site were described by either white or colored noise. Probability and energy parameters were obtained for both cases. We studied the influence of the amplitude and frequency of the colored noise and the asymmetry of the potential wells of the non-stationary two-minimum potential on the proton dynamics. It was demonstrated that over-barrier proton transfer plays the most important role.

## 1 Introduction

Conformational changes of the enzyme molecule are related with transitions of the multi-stable system from one equilibrium state into another under the action of, for example, thermal fluctuations or some other external factors (light quantum, chemical reaction, etc.). Proteins consist of thousands of atoms and, therefore, the calculation of this process with the use of molecular dynamics is quite difficult. It is assumed that protein molecules consist of relatively rigid clusters, that is why such transitions between the multi-stable states and the fluctuation motions can be described by the methods of classical cluster dynamics (see, e.g., Shidlovskaya, Schimansky-Geier, Romanovsky 2000, Netrebko et al 1994, Romanovsky 1997, Shaitan 1994). Molecule as a whole can be considered with the use of classical dynamics, whereas the active site must be considered as a quantum system. Below we consider a particular model of the enzyme. According to the X-ray data [Birktof, Blow1972; Havsteen1989, 1991] CT molecule consists of two subglobules each of which consists of six more or less rigid clusters. The structure of the molecule is stabilized by H-bonds. One of the key stages of the catalytic act is related with proton transfer is the H-bond between serine 195 and histidine 57 [Fersht1977]. Note that such a proton transfer is typical for other hydrolytic enzymes (e.g., acetylcholinesterase)[Quinn 1987, Romanovsky

et al.1999]. Similar problems are met in the case of consideration of the problems related with proton transfers in a chain of H-bonds [Davydov 1985, Nylund et al.1993; Manevich et al. 1994]. We study proton transfer in a local potential energy profile in a pocket of CT active site (Fig. 1). The profile was calculated by semi-empirical method PND for a free active site and the complex with the ligand. In the latter case the peptide bond of the substrate was positioned in the close vicinity of the H- bond of the catalytic group. Proton transfer takes place in the potential field of the atoms that belong to different clusters. In the absence of the substrate the potential profile is asymmetric and the potential barrier is high (about 30 kcal/mole). Substrate binding causes a series of local conformational changes in the active site that result finally in the symmetrization of the potential relief and lowering of the barrier [Romanovsky, Khurgin & Chikishev(1988)]. The characteristic time of the conformational changes is about 100 ps [Rubin (1987)] which is much larger than the period of oscillations of clusters. That is why in our model we calculated the proton transfer under adiabatic approximation with regard to only thermal fluctuations of the clusters and assuming symmetrization of the potential profile. Related problems are discussed in monograph [Chernavsky, Chernavskaya 1999].



**Fig. 1.** a) Two-domain structure of  $\alpha$ -chymotrypsin. Shown are the amino acid residues serine 195 and histidine 57 of the active site; b) a scheme of the fragment of the active site with the H-bond Ser195-His57 in which the proton transfer takes place along the coordinate  $r$  (Å); c) symmetric one-dimensional potential profile of the H-bond Ser195-His57.

## 2 Method of calculation of proton dynamics in a stochastic potential

The calculated symmetric profile  $V(r)$  was approximated by a sum of two Morse potentials,  $U(r + \Delta/2)$  and  $U(-r + \Delta/2)$ , and the polynomials of even orders:

$$V_{\Delta}(r) = U\left(r + \frac{\Delta}{2}\right) + U\left(-r + \frac{\Delta}{2}\right) + \sum_n C_n (r - r_0)^{2n}, \quad (1)$$

where

$$U(r) = D_0 \{ \exp[-2\alpha(r - r_0)] - 2 \exp[-\alpha(r - r_0)] \}.$$

Here  $D_0$  is the depth of a single Morse potential and  $r_0$  is the position of its individual minimum as well as the center of the barrier;  $\Delta$  determines an equilibrium distance between the wells' minima; coefficients  $C_n$  are calculated to fit experimental data on the transition frequencies. All the random processes of cluster dynamics lead to fluctuation changes of the distance between the N and O atoms in the H-bond. That is why the time dependence of the stochastic two-minimum non-stationary potential is determined by the change of the distance between the minima  $\Delta(t) = \Delta + \xi(t)$ . Here  $\xi(t) = \xi(\xi_0, \Omega_0, t)$  is the classical noise vibration with the characteristic frequency  $\Omega_0$  and amplitude  $\xi_0$  of the oscillations of the clusters. The latter were estimated as [Romanovsky, Tikhomirova & Khurgin(1979)]:

$$\Omega_0 \approx 10^{11} \div 10^{12} \text{ Hz}, \quad \xi_0 \approx 0.1 \div 0.2 \text{ \AA} \quad (2)$$

In this work we consider proton transfer under the action of delta-correlated external action and random oscillations of the clusters. We studied the influence of the asymmetry of the potential profile, amplitude of the colored noise and the detuning of the central frequency of the colored noise from the resonance frequency of the system on the probability of proton localization in one of the wells of the potential profile.

We used a quantum trajectories approach to the proton dynamics basing on calculation of the time-dependent wave function governed by the Schrödinger equation in the presence of classical noise. Wave function is localized initially in one of the wells. The probability of the proton transfer and the total energy of the proton are determined by the wave function. Fluctuation processes related with interactions of the enzyme molecule with environment are taken into account by means of introduction of the stochastic potential into the Hamiltonian of the system under study:

$$\hat{H} = \hat{H}_0 + \hat{V}_{\xi}, \quad \hat{H}_0 = \frac{\hat{p}^2}{2m} + \hat{V}_0, \quad \hat{V}_{\xi} = V_{\Delta+\xi(t)}(\hat{r}) - \hat{V}_0. \quad (3)$$

Here  $\hat{p}, \hat{r}$  are the operators of the momentum and coordinate and  $\xi(t)$  is the classical noise. Undisturbed potential  $\hat{V}_0 = V_0(\hat{r})$  is given by Eq. (1) with no shift of

the distance  $\Delta$ . Noise perturbed operator of the potential energy  $\hat{V}_\xi$  is approximated as

$$\hat{V}_\xi = \left. \frac{\partial \hat{U}(\xi)}{\partial \xi} \right|_{\xi=0} \xi. \quad (4)$$

Proton dynamics was calculated with the use of the computer codes based on symmetrization of the evolution operator [Kosloff 1988]. For the the system described by the Hamiltonian  $\hat{H}(t) = \hat{p}^2/(2m) + V(\hat{r}, t)$  the unitary transformation of the wave function for a time step  $\Delta t$  is represented in the symmetric form

$$S(\Delta t) \approx \exp \left[ -i \frac{V(\hat{r}, t)}{2\hbar} \Delta t \right] \exp \left( -i \frac{\hat{p}^2}{2m\hbar} \Delta t \right) \exp \left[ -i \frac{V(\hat{r}, t)}{2\hbar} \Delta t \right].$$

This representation minimizes the error due to non-commutativity of operators  $\hat{p}^2$ ,  $V(\hat{r}, t)$  and provides the possibility to simply apply the transformation to the wave function  $\psi$  as a non-operator multiplication, if only each time  $\psi$  is converted to a proper choice of either  $r$  or  $p$ -representation.

We suggest that the initial state wave function  $\psi(r, 0)$  is localized either in the first or second well and belongs to the tunnel-split minimum energy state of the unperturbed Hamiltonian  $\hat{H}_0$ :

$$\psi(r, 0) = \frac{1}{\sqrt{2}} [\psi_s(r) \pm \psi_a(r)], \quad (5)$$

where  $\psi_{s,a}$  are the eigen symmetric/antisymmetric eigen functions,  $\hat{H}_0 \psi_{s,a} = E_{s,a} \psi_{s,a}$ . If the noise perturbation is neglected, these states evolve exactly like the ones of a two-level system so that the other eigen states  $\psi_n$  of  $\hat{H}_0$  are not involved into dynamics. Relaxation takes place in the system described by the Hamiltonian (3) under the action of perturbation (4). Perturbation (4) is classical and the relaxation process is determined by the dephasing mechanism discussed in [Burstein 1963]. The characteristic time of relaxation of the system is given by [Fine 1972]:

$$\tau_r = (2W)^{-1} = \frac{2\pi}{\hbar^2} |V_{12}|^2 g(\omega_0 - \omega). \quad (6)$$

$V_{12}$  is the matrix element of the perturbation;  $\omega_0$  is the resonance frequency of the system, and  $\omega$  is the noise frequency. Formula (6) is valid under the condition of sufficient smoothness of the spectral power density of the noise  $g(\omega)$ .

White noise is used for simulation of fast non-correlated vibrational motions of the valence bonds by which N and O atoms are bound to the clusters. The random variation of the distance  $\xi(t)$  between the minimums of the potential in the case of the non-correlated perturbation (white noise) was modeled as a discrete time sequence with statistically independent random values, introduced properly to represent the process with the correlation function

$$K_\xi(t', t'') = K_\xi(t' - t'') = 2\pi G_0 \delta(t' - t''). \quad (7)$$

Therefore,  $\xi(t)$  represents the  $\delta$ -correlated process with the constant spectral density  $G_\xi(\omega) = 2\xi_0^2/\pi = G_0$ . As the changes of the length of the H-bond due to stretching vibrations of the corresponding atoms are not large, the amplitude of the white noise is much smaller than that given by (2):  $\xi_0 = 0.01$  Å. The absolute difference between the energies corresponding to the minimal and maximal distances does not exceed  $k_B T = 0.6$  kcal/mole. Random cluster oscillations caused by the action of the medium on the enzyme molecule are simulated by colored noise [Schimansky-Geier, Zulicke 1990], the amplitude and frequency of which are determined by (2). Transformation  $L$  of the white noise  $\xi(t)$  into colored noise  $x(t)$  is determined by:

$$Lx = \ddot{x} + 2\delta\dot{x} + \omega_0^2 x = \xi(t). \quad (8)$$

This is stochastic Langevin equation of the second order. Spectral power density of the colored noise determined by the equation (8) is given by:

$$g(\omega) = \frac{G_0}{(\omega^2 - \omega_0^2)^2 + 4\delta^2\omega^2}. \quad (9)$$

The width of the contour  $g(\omega)$  is  $F = \omega/Q$ , and the corresponding damping is  $\delta = \omega/(2Q)$  and the responding quality factor is  $Q \approx 10$  [Romanovsky, Khurgin & Chikishev 1988]. In our calculations we varied the frequency  $\omega$  and  $G_0$ . Studying the influence of the colored noise on the dynamics of the proton in the stochastic potential we varied the detuning  $\delta\omega = \omega_0 - \omega_{\text{res}} = nF$  ( $n$  is an integer) of the central frequency of the noise  $\omega_0$  from the resonance frequency of the system  $\omega_{\text{res}}$  and the amplitude according to (2).

We analyzed the time evolution of probability of proton localization in one of the potential wells. The corresponding dependencies allow one to determine the time of the proton transfer. Time dependence of probability in the case of white noise action can be approximated by [Lax 1968]:

$$P(t) = \frac{1}{2} + \frac{1}{2} \cos(2\pi\nu_1 t) \exp\left(-\frac{t}{\tau_0}\right). \quad (10)$$

The time of the transfer is determined in this case as the time  $\tau_0$  of relaxation to the stationary state. The relaxation time for the system in the case of colored noise action is determined after selection of the local maxima and approximation of this set by a function:

$$P^{\text{approx}}(t) = \frac{1}{2} + \frac{1}{2} \exp\left(-\frac{t}{\tau_0}\right). \quad (11)$$

### 3 Proton dynamics in a non-stationary profile

The characteristic times of the proton transfer in the stochastic potential with different parameters are summarized in Table 1. The tunneling frequency for the

symmetric stationary potential is about  $17 \text{ ps}^{-1}$  (splitting is  $\Delta E = 2 \cdot 10^{-2}$  kcal/mole). Figure 2 shows the relaxation of the probability  $P(t)$  to the stationary level for the case of the white noise action. Approximation parameters (see (10)) for this dependence are:  $\tau_0 = 12 \text{ ps}$  and  $\nu_1 = 17 \text{ ps}^{-1}$ , the latter virtually coincides with the tunneling frequency of the stationary potential. Calculation of  $\tau_0$  with the use of the formula (6) yields the value:  $\tau_0^{\text{theor}} = 13 \text{ ps}$ . It is seen from Fig. 2b that the total energy of the proton increases, which provides evidence of the proton transition to the highest states.

<b> Characteristic times of the proton transfer.</b>						
<b>System parameters</b>			<b>Results</b>			
$n = \frac{\Delta\omega}{\omega_0} Q^*$	$\xi_0$ [A <sup>0</sup> ]**	q***	T [ps] <sup>4*</sup>	$\tau_0^{\text{teor}}$ [ps] <sup>5*</sup>	$\tau_0$ [ps] <sup>6*</sup>	$\tau^{\text{con}}$ [ps]
<b>Unperturbed potential</b>						
0	-----	0	5.984	-----	-----	100
5	-----	0.03	3.91	-----	-----	
65	-----	0.2	0.619	-----	-----	
<b>Potential under the action of the white noise</b>						
0	0.01	0	5.984	12.554	12	
0	0.01	0.03	3.9	13.962	18.66	
0	0.01	0.2	-----	647.24	250	
<b>Potential under the action of the colored noise</b>						
-5	0.18	0	-----	14.143	10.02	
-3	0.18	0	-----	20.265	15.17	
0	0.18	0	-----	23.096	20.3	
3	0.18	0	-----	17.21	9.7	
5	0.18	0	-----	10.639	8.76	
5	0.01	0	5.984	3447		
0	0.18	0.03	-----	95.3	93	
5	0.18	0.03	-----	90.7	88.8	
0	0.18	0.2	-----	377	223	
65	0.18	0.2	-----	2.02	9.5	

\* $\Delta\omega = \omega - \omega_0$ ,  $\omega$ - noise frequency,  $\omega_0 = 1.0495 \text{ ps}^{-1}$  eigen frequency, Q-quality.

\*\* noise amplitude

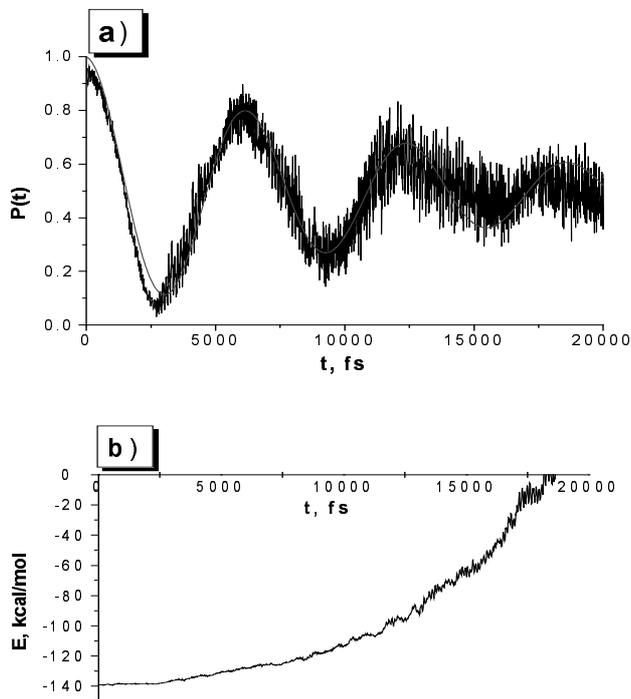
\*\*\* asymmetry coefficient.

4\* tunneling period.

5\* theoretical relaxation time.

6\* relaxation time.

**Table 1.** Characteristic times of the proton transfer in stochastic potentials with different parameters.



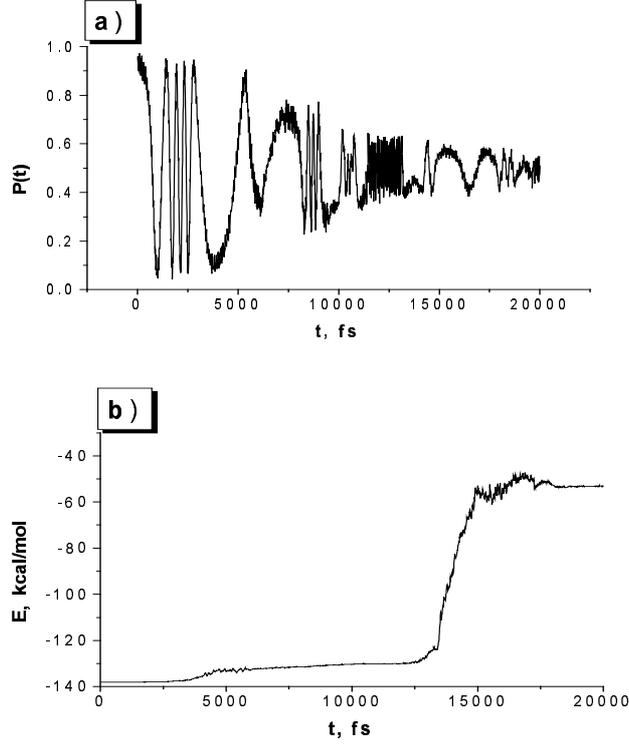
**Fig. 2.** Proton dynamics in a stochastic potential under the action of the white noise: a) probability of proton localization in one of the potential wells (solid line shows the approximation curve); b) total energy of the proton.

We calculated the time dependencies of the probabilities for the case of the colored noise action and determined the transfer times  $\tau_0$  for the amplitude  $0.18 \text{ \AA}$  at the range of (2) and the detunings  $\Delta\omega = -5F, -3F, 0, 3F, 5F$ . Here  $F$  is the width of the contour of the spectral density of the colored noise (9). The calculated relaxation times were compared with those determined theoretically according to formula (6) (see Table 1).

Figure 3 shows time dependence of the probability and total energy of the proton for the amplitude of the colored noise  $0.18 \text{ \AA}$  and the detuning  $\Delta\omega = 5F$ .

Characteristic time for the probability (Fig. 3a, formula (11)) was determined to be  $\tau_0 = 9 \text{ ps}$ . The theoretical value (formula (6)) is  $\tau_0^{\text{theor}} = 11 \text{ ps}$ . It was found out that for the case of the colored noise the relaxation time is inversely proportional to the square of the noise amplitude. For the amplitude  $\xi_0 = 0.01 \text{ \AA}$  and the detuning  $\Delta\omega = 5F$  (Fig. 4) the theoretical value of the transfer time is  $\tau_0^{\text{theor}} = 3447 \text{ ps}$ .

The probability of the proton transfer is maximal for the case of the symmetric potential profile. The asymmetry is much more critical for tunneling than for over-barrier transfer.



**Fig. 3.** Proton dynamics in a stochastic potential under the action of the colored noise with the detuning  $\Delta\omega = 5F$  of the central frequency  $\omega_0$  from the resonance frequency of the proton transition between the lowest tunnel-split states;  $\xi_0 = 0.18 \text{ \AA}$ : a) the probability of proton localization in one of the wells; b) total energy of the proton.

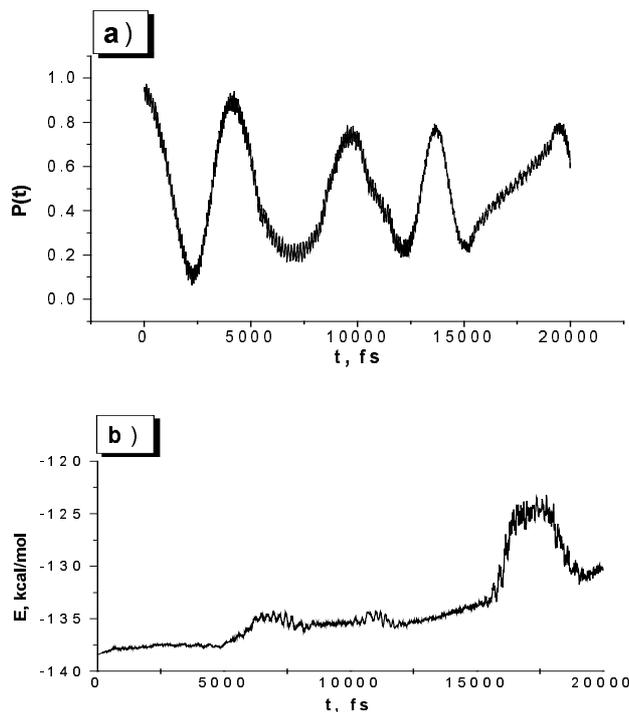
We studied the potential:

$$V(r) = U(r) + (1 - q)U(-r + \Delta r) \sum_n C_n (r - r_0)^n, \quad (12)$$

where  $U(r)$  is given by formula (1) and  $q$  is the degree of the asymmetry. We performed calculations for two differences of the depths:

$$\Delta U = \begin{cases} 2.29 \cdot 10^{-2}, & q = 3 \cdot 10^{-2}; \\ 1.529 \cdot 10^{-1}, & q = 3 \cdot 10^{-1}. \end{cases} \quad (13)$$

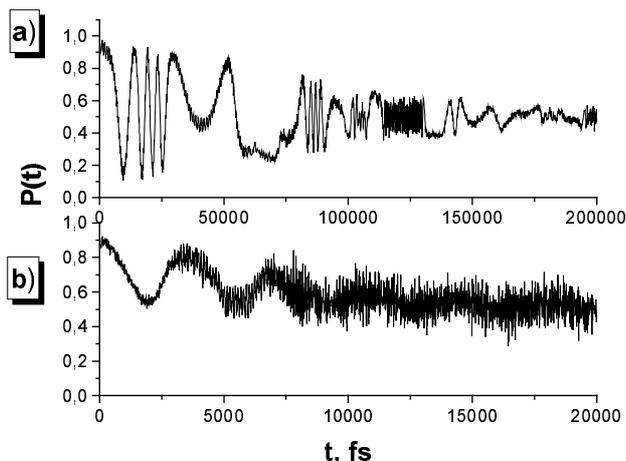
In the first case  $\Delta U \approx \Delta E_{\Delta U=0} \approx 10^{-2}$  kcal/mole; in the second case  $\Delta U \gg \Delta E_{\Delta U=0}$  ( $\Delta E = 1.58 \cdot 10^{-2}$  kcal/mole (1)). Tunneling is impossible for both cases. For the smaller asymmetry and white noise  $\xi_0 = 0.01 \text{ \AA}$  (see Fig. 5a) the transfer time is  $\tau_0 = 19 \text{ ps}$  ( $\tau_0^{\text{heor}} = 14$ ). Over-barrier transfer is possible for the larger asymmetry as well (Fig. 5).



**Fig. 4.** Proton dynamics in a stochastic potential under the action of the colored noise with the detuning  $\Delta\omega = 5F$  of the central frequency  $\omega_0$  from the resonance frequency of the system;  $\xi_0 = 0.01$  Å: a) the probability of proton localization in one of the wells; b) total energy of the proton.

## 4 Discussion

In the stochastic potential an irreversible process of phase relaxation of the probability of proton localization in one of the wells takes place. The energy of the proton increases and the proton reaches the levels above the barrier. The mechanism of phase relaxation (dephasing) is determined by the interaction with the highest states that plays the most important role in the over-barrier transfer. In our model we do not take into account the relationship between the position of the proton and the shape of the potential profile. That is why reversible tunneling does not describe proton transfer in contrast to irreversible over-barrier transfer. In addition, the probability of tunneling is much less than the probability of the over-barrier transfer in the asymmetric non-stationary potential. Thus, we assume that irreversible incoherent over-barrier transfer resulting from the fluctuation changes of the shape of the potential profile determines the mechanism of the proton transfer in the active site of the enzyme. Note that the problem of transfers in different non-stationary two-minimum potentials was addressed in many works [Grossmann 1991; Hesse, Schimansky-Geier 1991; Elyutin, Ro-



**Fig. 5.** Time evolution of the probability of proton localization in of the potential wells of the asymmetric profile ( $\Delta U = 2.29 \cdot 10^{-2}$  ( $q = 3 \cdot 10^{-2}$ ),  $\Delta U \gg \Delta E_{\Delta U=0} \approx 10^{-2}$  kcal/mole under the action of a) white noise (solid line shows approximation curve) and b) colored noise with the amplitude  $\xi_0 = 0.18 \text{ \AA}$  and the frequency  $\omega = 1.05 \cdot 10^{12}$ .

govenko 1999]. The most important results are reported in [Kagan 1991], where it is demonstrated that under certain conditions over-barrier transfer dominates over tunneling.

## 5 Conclusions

An irreversible relaxation dynamics of a proton in a two-well potential was described with use of stochastic Schrödinger equation. Localization of the proton in one of the wells turned to be a random event, which probability at the level of 0.5 takes place under the influence of both white and colored noise. The energy of the proton in the stochastic potential increases. Thus, the over-barrier proton transfer occurs. We calculated the characteristic times of the proton transfer in the stochastic potentials with different parameters. Under the action of the colored noise the relaxation time is maximal for the case when the central frequency of the noise coincides with the resonance frequency of the system corresponding to splitting of the first tunneling level. In the case of the colored noise the relaxation time is inverse proportional to the amplitude of the noise. In the case of the asymmetric potential tunneling is impossible. The action of the colored noise makes the over-barrier transfer possible for small asymmetries:  $\Delta U \approx \Delta E_{\Delta U=0} \approx 10^{-2}$  kcal/mole. Whereas, the action of the white noise makes over-barrier transfer possible for both small  $\Delta U \approx \Delta E_{\Delta U=0}$  and large  $\Delta U \gg \Delta E_{\Delta U=0}$  asymmetries.

In the future studies of the proton transfer we plan to take into account the relationship between the proton motion and the shape of the potential profile. We

also plan to construct the potential profiles by means of *ab initio* calculations and to compare the new profiles with those obtained by means of the semi-empirical methods. We also plan to consider dynamics of the proton in 2D and 3D profiles. It is worthwhile to consider also the following problems. 1) It was demonstrated earlier [Shidlovskaya et al., 2000] that classical Fermi-resonance can take place in 2D potential wells. Note that this problem was posed for the first time by Fermi who calculated the splitting of levels in a system with 2:1 ratio of transition frequencies [Fermi, 1931]. That is why we plan to study the problems of quantum Fermi resonance in 2D profiles. 2) The phenomena similar to stochastic resonance [Anischenko, et al., 1999], [Anischenko, Vadivasova, Astakhov, 1999], [Reinmann, Hanggi, 1997] must be studied in the case of quantum transitions between two potential wells.

## Acknowledgements

The work has been supported by the Center of Fundamental Natural Sciences (Ministry of High School, Russia), the State Program “Scientific Schools of Russia” (grant no. 96-15-97782), Russian Foundation for the Basic Research (grant no. 98-03-331191a).

The authors are grateful to Dr. A. A. Kubasov for calculation of the potential landscapes and to Dr. P. V. Elyutin for helpful discussions.

## References

1. Anishchenko V.S., Vadivasova T.E., Astakhov V.V., Nonlinear dynamics of chaotic and stochastic systems, Izd. Saratovskogo Universiteta, Saratov, 1999 (In Russian).
2. Anishchenko V.S., Neiman A.B., Moss F., Schimansky-Geier L., v. 42, No 1, 7 (1999).
3. Biretoft J.J., Blow D.M., *J. Mol. Biol.*, 68, 187 (1972).
4. Burstein A.I., *PSB*, 5, 1243 (1963) (in Russian).
5. Chernavsky D.S., Chernavskaya N.M., Protein-machine. Biological macromolecular constructions, Moscow: Moscow Univer., 1999 (in Russian).
6. Chikishev A.Yu., Netrebko N.V., Romanovsky Yu.M., Ebeling W., Schimansky-Geier L., Netrebko A., *Inter. J. of Bifurcation and Chaos*, v. 8, No 5, pp. 921–926 (1998).
7. Davydov A., Solitons in molecular systems. D. Reidel Publishing Company, Dordrecht, 1985; Ebeling W. & Schimansky-Geier L., In: *Noise in Nonlinear Dynamical Systems*, (F. Moss, P.E.V. McClintock, eds.), Cambridge, Cambridge University Press, 1989.
8. Elyutin P.V., Rogovenko A.N., *quant-ph/9912026* (1999).
9. Fermi E., *Zs. f. Phys.*, 71, 250 (1931).
10. Fersht A., Enzyme structure and mechanism. Freeman, Reading, San Francisco, 1977.
11. Fine V.M., Photons and nonlinear media, v. 1, *Quantum radiophysiks*, Moscow, 1972 (in Russian).
12. Grossmann F., Dittrich T., Jung P., Haenggi P., *Phys. Rev. Let.* 67, 516–519 (1991).
13. Havsteen B., *J. Theor. Biol.*, 140, 101 (1989); *J. Theor. Biol.*, 151, 557 (1991).

14. Hesse J.J., Schimansky-Geier J., *Z. Phys. B*, 84, 467–470 (1991).
15. Kagan Yu., *Phys. Chem.* 95 (3), 411 (1991).
16. Kosloff R., *J. Phys. Chem.*, 92, 2087 (1988).
17. Lax M., *Fluctuations and Coherence Phenomena in Classical and Quantum Physics*, (New York: Gordon & Breach), 1968.
18. Manevich L., Mikhlin Yu., Pilipchuk V., *Normal Vibrations Technique for Nonlinear Systems*. Moscow, Nauka, 1989 (In Russian).
19. McDonald K.M., Thorson W.R., Choi J.H., *J. Chem. Phys.* 99, 4611 (1993).
20. Netrebko A., Netrebko N., Romanovsky Yu., Khurgin Yu., Shidlovskaya E., 2, 26–43 (1994) (In Russian).
21. Nylund E., Lindenberg K., Trisons G., *J. Stat. Phys.*, 70, 163–173 (1993).
22. Quinn D.M., *Chem. Rev.*, V.87, 955–979 (1987).
23. Reinmann P., Hanggi P., *Stochastic Dynamics*, ics. Springer, pp. 127–139, Eds. Scimansky-Geir L., Poshel Th., 1997.
24. Romanovsky Yu.M., Netrebko A.V., *Applied nonlinear dynamics*, v.6, No. 4, pp. 31–44 (1998).
25. Romanovsky Yu.M., In: *Stochastic Dynamics*, Shimansky-Geier L., Poeschel T., Eds., Ser. Lecture Notes on Physics, Springer Verlag, Berlin, 1–13 (1997).
26. Romanovsky Yu.M., Tikhomirova N.K., Khurgin Yu.I., *Biophysika*, v. 24, 442 (1979) (In Russian).
27. Romanovsky Yu.M., Khurgin Yu.I., Chikishev A.Yu., *I. Mol. Catalysis*, v.47, 235–240 (1988).
28. Romanovsky Yu.M., Netrebko A.V., Netrebko, N.V., Kroo S.V., Chikishev A.Yu., Sakodynskaya I.G., Molodozhnya V., In: *Proc.SPIE*, v. 3599, *Optical Diagnostics of Biological Fluids IV*, Eds.: Priezzhev A.V., Asakura Toshimitzu, pp. 167–179 (1999).
29. Rubin A.B., *Biophysika*, High School, 1987 (In Russian).
30. Schimansky-Geier L., Zulicke Ch., *Z. Phys. B*, 79, 451–458 (1990).
31. Shidlovskaya E., Schimansky-Geier L., Romanovsky Yu.M., *Z. Phys. Chem. Leipzig* (2000) (in press).
32. Zundel G., *Proton polarizability of hydrogen bonds and proton transfer processes, their role in electrochemistry and biology*, Munchen: Univers. Munchen, 1997.