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1993 J. Phys.: Condens. Matter 5 861

(http://iopscience.iop.org/0953-8984/5/7/012)

J. Phys.: Condens. Matter 5 (1993) 861–866. Printed in the UK

Molecular mechanisms for proton transfer in alpha-helical proteins

S Ichinose† and T Minato‡

† Fukuoka University of Education, Munakata, Fukuoka 811-41, Japan
‡ Nara University Computer Centre, Nara University, 1500 Misasagi-cho, Nara 631, Japan

Received 16 October 1992

Abstract. Likely mechanisms for proton transfer in alpha-helical proteins are explored. The fundamental structural element is assumed to be continuous chains of hydrogen bonds formed from the peptide groups, and a molecular example is presented. Using the PM3 semi-empirical molecular orbital method, we study the potential energy surfaces for the proton transfer processes in such systems. The results obtained can be used to explain some basic transport phenomena in biological systems.

1. Introduction

The last decades of research in bioenergetics have increasingly focused attention on the transport of protons as an intermediate mechanism in energy transduction. Many publications have been devoted to the problem of protonic charge transport along the hydrogen bonds of the protein side groups, such as the hydroxyls of serine, theonine, and tyrosine, and the carboxyls of aspartic and glutamic acids [1, 2]. The hydrogen-bonded chain is a simple OH---OH---OH--- chain, where the charge transport is connected with the motion of hydronium (H_3O^+) and hydroxyl (OH^-) ions. An important property of such hydrogen bonds is that the proton potential energy curve has the form of a symmetric well with two minima corresponding to two equilibrium positions of a proton [3–14].

Although the migration of uncharged excitations over protein molecules appears to be an established fact and it plays an important physiological role in certain cases, proton transfer in the protein molecule itself remains questionable as yet. The purpose of the present paper is to explore some molecular mechanisms by which protons may move in protein molecules of which the detailed molecular structure is known. Among these, the alpha-helical protein is a typical molecular system in which three hydrogen-bonded chains of peptide groups stabilize the helical structure of the protein molecule. Careful inspection of the alpha-helical structure of proteins reveals three channels oriented approximately in the longitudinal direction with the sequence O=C–N–H---O=C–N–H---O=C–N–H etc, where the dashed lines represent hydrogen bonds.

0953-8984/93/070861+06$07.50

2. Asymmetric hydrogen-bonded chain

Since biological processes do not take place in a vacuum but in an aqueous medium, the medium and the temperature are of great importance in the processes of charge transport. In order to deal with proton transport along the hydrogen-bonded chain, we need to understand the mechanism of injection of protons into the chain. In fact, there are always H_3O^+ ions present in water, so a proton from the ion may attach itself to the oxygen atom of a peptide group. Under the influence of an electric field the hole injected through the protonation process may move in the valance band of the alpha-helical protein molecule. At least some of the circuits of the corresponding proton transfer in the alpha-helical protein will consist of one-dimensional hydrogen-bonded chains running zigzag through the helical structure.

As a model, we consider a one-dimensional chain formed by the formamide molecule (CH_3NO). This type of molecule has two types of chemical structure, so that one of the states, the keto (O=C–N–H) structure, has lower energy than the other state, the enol (H–O–C=N) structure. The interaction between formamide molecules, constituting the chain under study, is through the hydrogen bonds. Such a single channel, called a formamide chain $(CH_3NO)_n$, as shown in figure 1, serves as a model for one of the three chains in the alpha-helical protein molecule. In contrast to the case of the ice lattice, the transport of protons along the *asymmetric* hydrogen-bonded chains requires a fair amount of energy. After a proton in the hydrogen bridge goes over the local potential barrier, the covalent bond and hydrogen bond exchange places. Then, the relevant formamide molecule transposes its chemical structure from the keto state to the enol state, or vice versa.

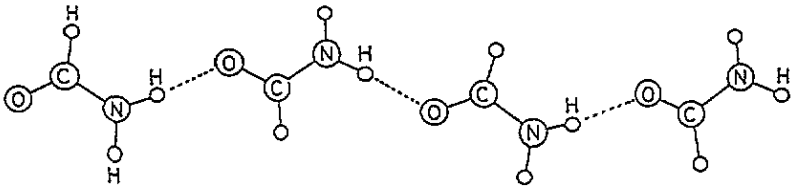

Figure 1. A portion of a hydrogen-bonded chain formed by formamide molecules.

If it is possible to learn the principles of self-organization from the biological world and apply that principle to organic materials then we will be opening a door on a new and powerful technology. It would permit the design and fabrication of materials the properties of which can be varied over nanometre dimensions. At the heart of molecular electronics is the dual concept of conformational change and charge localization and control. In the following section we will demonstrate opportunities for using conformational changes in the charged states in formamide chain systems (protonated formamide chains).

3. Molecular mechanisms for proton transfer in the hydrogen bridges

Two non-equivalent backbone geometries can be envisioned for formamide: the keto form (which is thermodynamically the most stable form) and the enol form. The

keto form is converted into the enol form upon heating. Such conversion may promote transfer processes of protons in the hydrogen bridges. To see whether the idea described above makes sense from a theoretical standpoint, we examine the proton transfer reactions in the protonated formamide chain $H^+(CH_3NO)_n$. Quantum chemistry can bring useful contributions to these reaction mechanisms by molecular orbital calculations of $H^+(CH_3NO)_n$ macromolecules. The calculations were performed using the MOPAC (version 5.0) program [15]. Planarity of the formamide chain was assumed, while the other geometrical parameters were optimized. The structures of protonated formamide dimers under consideration are shown in figure 2. It can be seen how a hydrogen-bonded dimer can transport a proton from the left to the right side of figure 2. The transition state (TS) is in between the keto (PT(0)) and enol (PT(1)) forms, and is characterized by confirming one negative eigenvalue in the Hessian matrix [16].

The presence of low-frequency hydrogen-bond stretching vibrations in the flexible intermolecular proton transfer system allows a comparatively easy compression of the hydrogen bond. In fact, the hydrogen-bond length in the dimer system $H^+(CH_3NO)_2$ is variable, i.e. the energy of activation of the proton transfer is pooled into the hydrogen-bond stretching vibration which shortens the hydrogen-bond length. As a consequence, the barrier for the proton transfer is reduced. Note that the model dimer system $H^+(CH_3NO)_2$ has an asymmetric potential energy surface as shown in figure 3. We used the conjugate reaction coordinate method, in which a conjugate pair of bonds, r_1 and r_2 in this case, are selected as the reaction coordinates. The activation barrier $\Delta E^{\neq}$ and the energy of reaction ΔE of the present dimer system $H^+(CH_3NO)_2$ are shown in table 1. The proton affinity (PA), defined as the difference between the energy of the protonated state and the energy of the neutral state, is also shown.

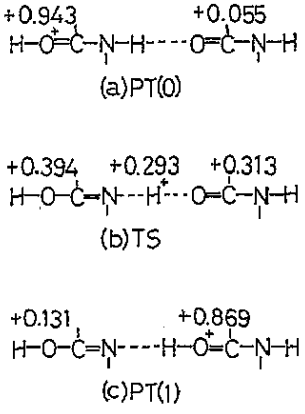

Figure 2. Charge distribution around the proton in the hydrogen bridge of the protonated formamide dimer $H^+(CH_3NO)_2$: (*a*) charge distribution of the dimer with keto (PT(0)) form; (*b*) charge distribution of the dimer in the transition state (TS); (*c*) charge distribution of the dimer with enol (PT(1)) form.

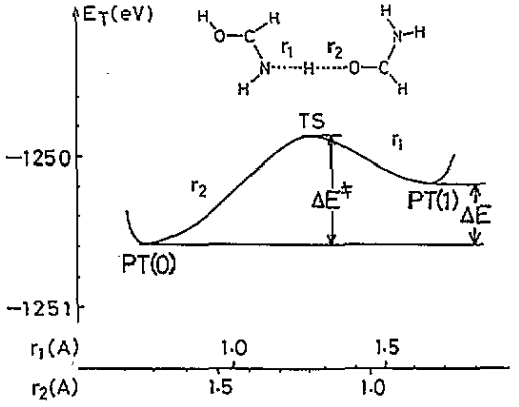

Figure 3. Potential energy surface of the protonated formamide dimer $H^+(CH_3NO)_2$.

Table 1. Calculated energies (kcal mol^{-1}) involved in the proton transfer reactions in $H^+(CH_3NO)_n$, $n = 2$, 3, and 4.

	Dimer	Trimer	Tetramer
$\Delta E^{\neq}$ (kcal mol^{-1})	16.5	12.9	16.0 (11.9)
ΔE (kcal mol^{-1})	9.3	2.1	8.2 (0.1)
PA (kcal mol^{-1})	202.9	209.0	211.7

We also examined the energetics of the proton transfer reaction for model systems $H^+(CH_3NO)_n$ with $n = 3$ and 4 as shown in figures 4 and 5. The flexible intermolecular proton transfer systems studied are subject to a stepwise reaction mechanism. In each step only one proton jumps along the hydrogen bridge in the model chain systems $H^+(CH_3NO)_n$. It is understandable that it costs too much energy to transfer a number of protons along the hydrogen bridges at the same time. The reaction profiles are then asymmetric as indicated schematically in figure 6, where the protons move in a stepwise fashion along the asymmetric potentials. It can be observed from table 1 that the energy of reaction for the model systems $H^+(CH_3NO)_n$ seems to remain constant with increasing size of molecule except for the trimer.

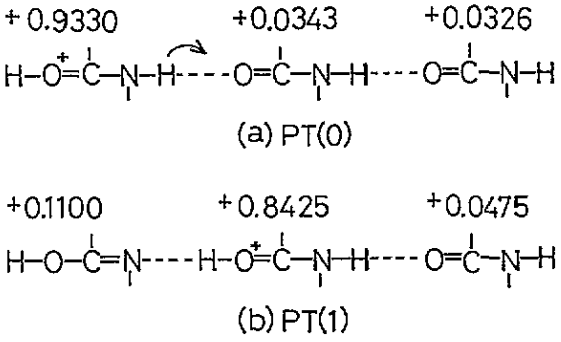

Figure 4. Intermolecular proton transfer accompanied by charge accumulation in the protonated formamide trimer $H^+(CH_3NO)_3$: (*a*) trimer with keto (PT(0)) form; (*b*) trimer with enol (PT(1)) form.

So far we have discussed the most essential features of our model systems $H^+(CH_3NO)_n$ based on the results obtained by quantum chemistry. The most interesting feature here is that the proton transfer may couple strongly with the keto–enol transition of the formamide molecules. In this case the low-frequency hydrogen-bond stretching vibration modulates the hydrogen-bond length and induces the keto–enol transition of the formamide molecules. These features are expressed in figures 2, 4, and 5. In effect, the keto–enol transition of the formamide molecule may favour the tranfer process of the proton along the hydrogen bridge. Such coupling, in fact, plays a crucial role in making the proton transfers on different hydrogen bridges couple strongly with each other to produce a cooperative excitation.

In contrast, we also examined the case without the keto–enol transition, where the proton transfer may not couple cooperatively with the charge accumulation along the hydrogen bridge. As a consequence, proton transfer may induce an electric dipole moment around the proton in the hydrogen bridge. This feature is depicted

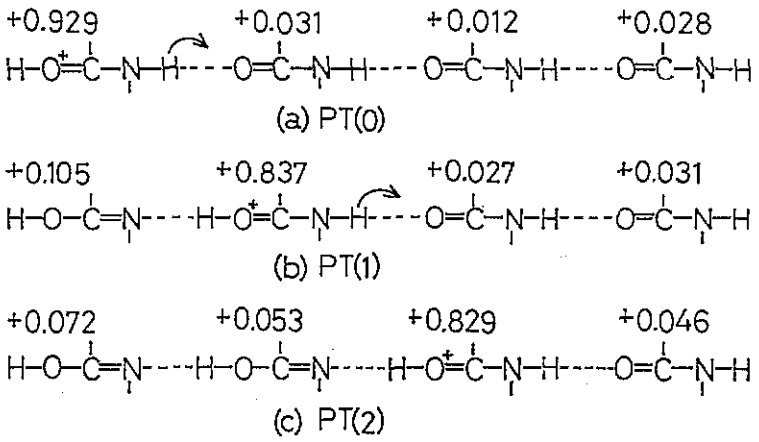

Figure 5. Stepwise intermolecular proton transfer accompanied by charge accumulation in the protonated formamide tetramer $H^+(CH_3NO)_4$: (*a*) tetramer with keto (PT(0)) form; (*b*) tetramer with one proton transferred (PT(1)); (*c*) tetramer with two protons transferred (PT(2)).

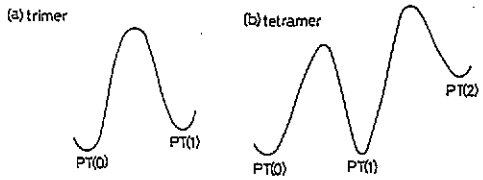

Figure 6. Potential energy surfaces of the protonated formamide chain molecules $H^+(CH_3NO)_n$ for (*a*), $n = 3$; (*b*), $n = 4$.

in figure 7. In this case it costs too much energy to break the bond of a proton to its neighbouring atom as shown in table 2. Thus, we propose for the intermolecular proton transfer system a reaction mechanism according to figures 2, 4, and 5.

Table 2. Comparison of the energies (kcal mol^{-1}) involved in the two types of reaction for the proton transfer processes.

	Keto–enol transition	No keto–enol transition
$\Delta E^{\neq}$ (kcal mol^{-1})	16.0	26.1
ΔE (kcal mol^{-1})	8.2	24.8

4. Discussion

We have presented a simplified model for proton transfer in the alpha-helical protein molecule. Our model is quite specific as regards proton motion, which is presumed to be a universal feature. In the case of intermolecular proton transfer reactions, stepwise reaction pathways are realized accompanied by the keto–enol transition of the molecules; in each step only one proton jumps. Each step carries only a fraction

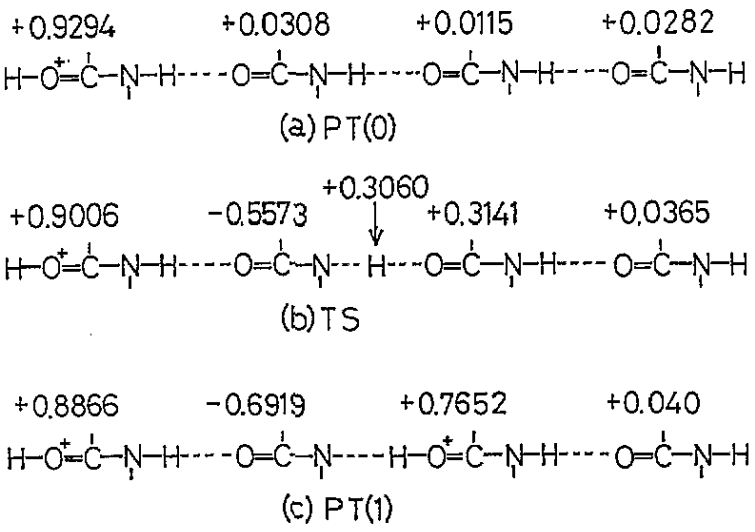

Figure 7. Intermolecular proton transfer without the keto–enol transition in the protonated formamide tetramer $H^+(CH_3NO)_4$: (*a*) charge distribution in the PT(0) state; (*b*) charge distribution in the transition state (TS); (*c*) charge distribution in the (PT(1)) state.

of the charge. One feature of our mechanism that should be emphasized is that the individual steps taken by the protons involve energy of the order of kT, so these thermally activated steps are fast. We think that there is a very good possibility that the basic proton transport mechanisms that we have adapted will play a central role in proton transport and bioenergetics. The calculations described here were carried out on the Nara University ACOS-430/70 computer.

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