Physical Chemistry

Proton migrations in associates of two molecules of formic acid with one molecule of hydrazine or hydrogen peroxide

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The mechanisms of the proton transfer in associates of two molecules of formic acid with one molecule of hydrazine or hydrogen peroxide were studied using *ab initio* (SCF/6-31G**) method. The mechanism of cooperative (concerted, one-step) four-proton transfer is realized in the associate with the hydrazine molecule. The proton transfer occurs stepwise *via* an intermediate in the associate with a hydrogen peroxide molecule. The calculated activation barriers to the proton transfer in the associates investigated are 34.7 kcal mol^{-1} and 27.1 kcal mol^{-1}, respectively.

Key words: formic acid, hydrazine, hydrogen peroxide; associate; one-step four-proton transfer; potential energy surface, *ab initio* calculations.

The process in which a receptor recognizes a substrate and involves it in a chain of enzymatic transformations starts with stabilization of the substrate by the active groups of the enzyme.[1–5] The variety of stabilizing interactions used by enzymatic systems for selective recognition of a substrate is relatively wide and includes hydrogen bond,[5–8] van-der-Waals,[7–9] electrostatic,[7–10] and stacking interactions.[8,10] Taken together, they ensure selective attraction of the substrate, its activation, and progress along the reaction pathway. In complex systems, it is almost impossible to separate one interaction from another in order to understand the importance of each of them at individual stages of the reaction pathway. Therefore, simplified molecular models have been developed, which simulate enzymatic reactions at their different stages.[1–4,6,10–15]

Hydrogen bonding plays a determining role in all reactions related to proton transportation; it is one of the most easily-modelled types of intermolecular interactions.[14–18] Amidine, carboxylic, NH_2-, NRH-, and OH-groups are most frequently used as models of H-bonding enzymatic centers. Asymmetry of the interaction between an enzyme and a symmetric substrate is achieved if they form not less than three intermolecular bonds between each other (the Ogston effect)[13,19], *i.e.*, no less than three hydrogen bridges must be formed in the H-bonded system.

In this work, the interaction between an enzyme and a substrate is simulated using two formic acid molecules capable of forming four hydrogen bridges. Hydrazine and hydrogen peroxide, which are extremely toxic substances for a living organism,[13,20–22] were chosen as the

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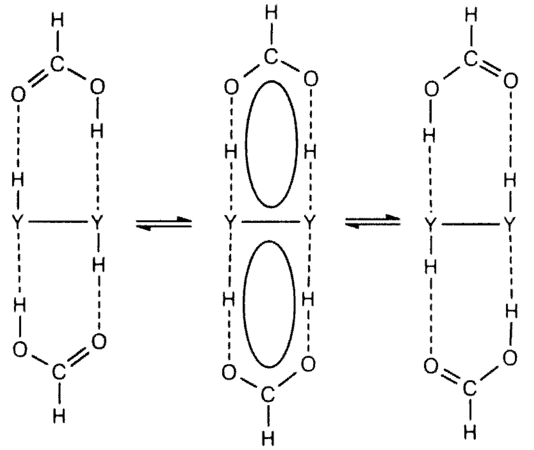
simplest substrates. The simulation of their interaction with the active centers of an enzyme is important for understanding the nature of the origin of various types of damage in a cell. The main objective of this work was to study the stereochemistry of the stabilization of hydrazine (Y = NH) and hydrogen peroxide (Y = O) by two formic acid molecules and the mechanism of intermolecular proton transfer (1) in associates **1** by the *ab initio* RHF/6-31G** method. A calculation procedure described previously[10] was used in this work.



1a **2** **1b**

(1)

Mechanisms of proton transfer

The associate of two formic acid molecules and one hydrazine molecule (1a; Y = NH), according to calculations, corresponds to the energy minimum (λ = 0; hereinafter λ denotes the number of negative eigenvalues of the Hesse matrix at a given critical point).[23] The calculated energetic and geometric characteristics of structures **1** and **2** are presented in Table 1 and in Fig. 1.

Table 1. Total (*E*, a.u.) and relative (Δ*E*, kcal mol^{-1}) energies, the number of negative eigenvalues of the Hessian (λ), and the two minimum (ν_1, ν_2/cm^{-1}) or imaginary (iν/cm^{-1}) frequencies predicted by the *ab initio* (RHF/6-31G**) method

Structure	$-E^a$	Δ*E*	λ	ν_1,ν_2/iν
Y = NH (C_2)	488.76427	0	0	30; 42
Y = NH (C_2)	488.70902	34.7	1	i447.0
Y = NH (C_2)	299.97344	—	0	73; 141
Y = O (C_2)	528.35622	0	0	29; 40
Y = O (C_s)	528.32204	21.4	0	31; 36
Y = O (C_1)	339.56554	—	0	71; 164
Y = O (C_1)	528.31310	—	1	i1512.3
HC(O)OH (C_s)	188.77057	—	0	692; 712
H_4N_2 (C_2)	111.18352	24.9^b	0	478; 947
H_2O_2 (C_2)	150.77696	23.9^b	0	387; 1150

^{a} 1 a.u. = 627.5095 kcal mol^{-1}. ^{b} Relative energies of three separated molecules, E_H(**1**).

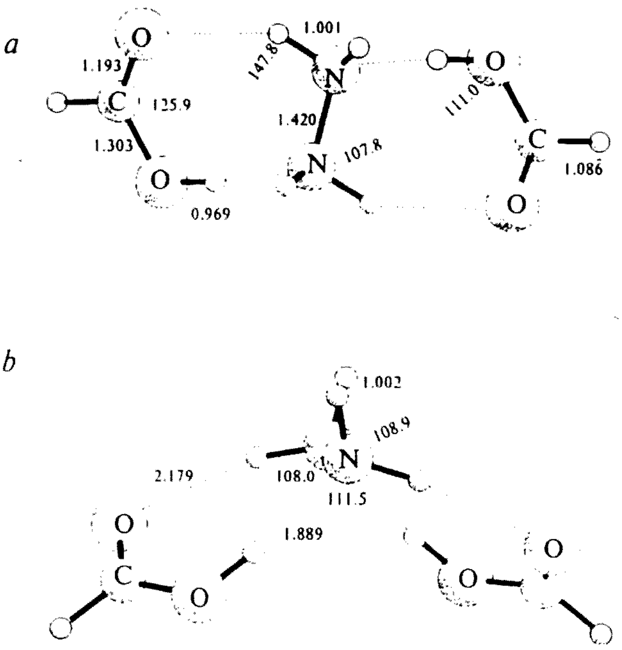


Fig. 1. Geometric characteristics of associate **1a** (Y = NH): *a*, the top view from the plane passing through four oxygen atoms; *b*, the side view. The bond lengths (*d*) and bond angles (ω) are given in Å and degrees, respectively.

Associate **1a** is nonplanar and is stabilized by four hydrogen bridges with the energy $E_H(\mathbf{1})$ = 24.9 kcal mol^{-1}. The geometry of the O...HN and OH...N hydrogen bridges in structure **1** strongly deviates from the "ideal" linear form,[6] which indicates that they are strained in this associate. The lengths of the H-bridges lie within the standard limits for similar associates of various organic compounds.[6,8,24,25] In the successive formation of the H-bonded hydrazine complex first with one molecule of formic acid (**3**) and then with two molecules (**1**), the geometric characteristics of the latter change insignificantly, whereas the N—N bond length increases monotonically to a length ~0.005 Å greater than that characteristic of the hydrazine molecule in the gas phase (see Fig. 2), *i.e.*, this bond is activated in association.

It is of interest to note that the formation energy of the two H-bonds in the associate (**3**) of one formic acid molecule with one hydrazine molecule $E_H(\mathbf{3})$ is 12.1 kcal mol^{-1} (see Table 1). The difference $\Delta E_{coop} = E_H(\mathbf{1}) - 2E_H(\mathbf{3}) \approx 0.6$ kcal mol^{-1} can be considered to be the cooperative effect of the formation of four hydrogen bonds in structure **1** as compared to two H-bridges in complex **3**. However, it should be noted that the definition of the cooperative effect in the formation of H-bonds is ambiguous. The cooperative effect can also be determined as $\Delta E'_{coop} = 12.7 - E_H(\mathbf{3}) \approx$ 0.6 kcal mol^{-1}, where the first term is the formation energy of two additional H-bonds in structure **1** upon addition of a formic acid molecule to associate **3**. The

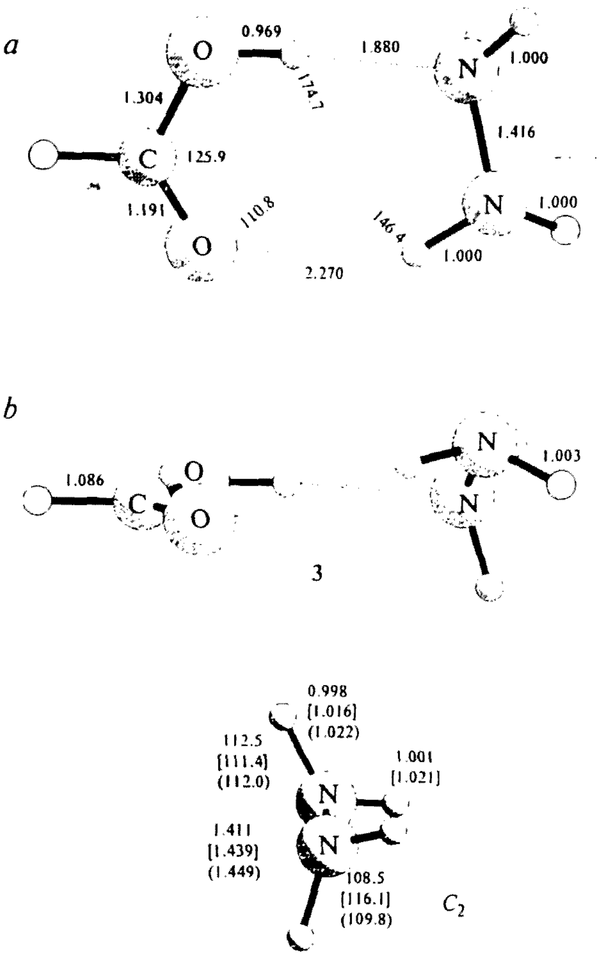


Fig. 2. Geometric characteristics of associate **3** and the hydrazine molecule: *a*, the top view from the plane passing through four oxygen atoms; *b*, the side view (*d*/Å; ω/deg). The results of calculations by the MP2/6-31G*[27,28] method are given in brackets, experimental data[28] are in parentheses.

values of ΔE_{coop} and $\Delta E'_{\text{coop}}$ differ very little from each other. However, it should be noted that the existence of a cooperative effect in the formation of multiple H-bonds and its calculation procedures remain the subject of discussion.[6,8,19,25]

The hydrazine molecule in associates **1** and **3** holds its *gauche*-conformation, the most stable in the gas phase. It can be seen from a comparison of the theoretical[26,27] and experimental[28] data for hydrazine presented in Fig. 2, that they are in fairly good agreement.

According to *ab initio* calculations, bicyclic structure **2** with C_{2v} symmetry corresponds to the saddle point ($\lambda = 1$) on the potential energy surface (PES) and a transition state (see Fig. 3) in reaction (1).

This points to the fact that the four-proton transfer (1) for Y = NH consistently follows the one-channel pathway $\mathbf{1a} \rightleftharpoons \mathbf{2} \rightleftharpoons \mathbf{1b}$. The calculated activation barrier (34.7 kcal mol^{-1}) is significantly higher than that for the intermolecular proton transfer in dimers of carboxylic acids (~14 to 18 kcal mol^{-1}).[14,29,30] However, according to calculations of the double proton transfer in the system

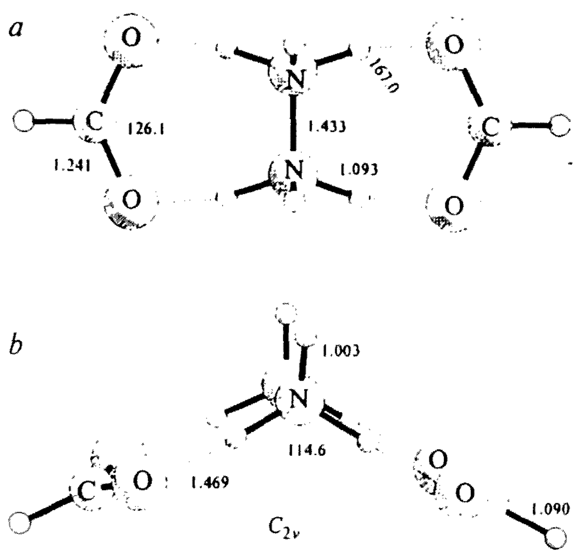


Fig. 3. Geometric characteristics of transition state **2** (Y = NH) in the reaction of four-proton transfer (1): *a*, the top view from the plane passing through four oxygen atoms; *b*, the side view (*d*/Å; ω/deg).

$$N_2H_4 + N_2H_2 \rightleftharpoons N_2H_2 + N_2H_4,$$

the allowance for the electronic correlation decreases the energy barrier from 67.2 (RHF/6-31G*) to 17.1 kcal mol^{-1} (MP2/6-31G*);[26] therefore, if the electronic correlation is taken into account, one can also expect a significant decrease in the barrier to reaction (1).

It is of interest to note that the protons in structure **2** are shifted towards hydrazine; therefore, structure **2** can be considered as a diprotonated form (in an eclipsed configuration) stabilized by two carboxylate anions. The eclipsed conformation of the hydrazine molecule in transition state **2** points to the fact that the rotation of two NH-groups not participating in the formation of the hydrogen bridges occurs simultaneously with the displacement of four protons in process (1).

The associate of two formic acid molecules and one hydrogen peroxide molecule (1a, Y = O), according to calculations, corresponds to the energy minimum ($\lambda = 0$) on the PES. The calculated energetic and geometric characteristics of structure **1** (Y = O) are presented in Table 1 and in Fig. 4.

Associate **1a** (Y = O) is stabilized by four hydrogen bridges, which are shorter than those in complex **1a** (Y = NH) considered above. The calculated value of the energy of formation of the four hydrogen bridges in structure **1a** (Y = O) is 23.9 kcal mol^{-1}. As can be seen from a comparison of Fig. 4 and Fig. 5, the geometric

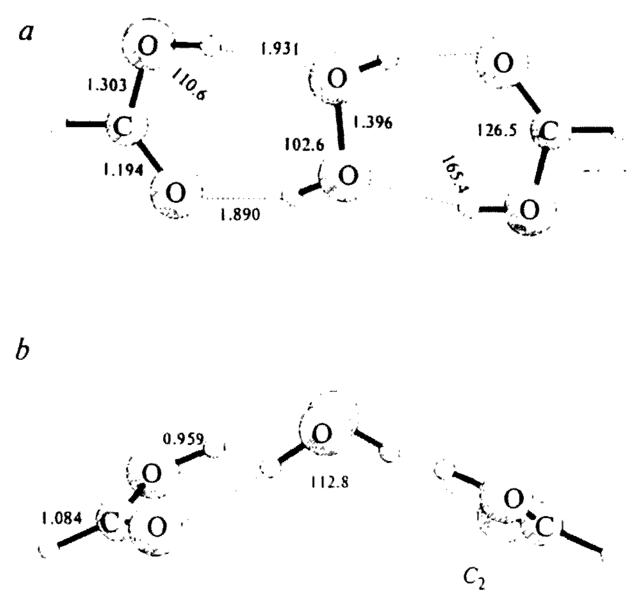


Fig. 4. Geometric characteristics of associate **1a** (Y = O): *a*, the top view from the plane passing through four oxygen atoms; *b*, the side view (*d*/Å; ω/deg). Dihedral angle HOOH is 112.8°.

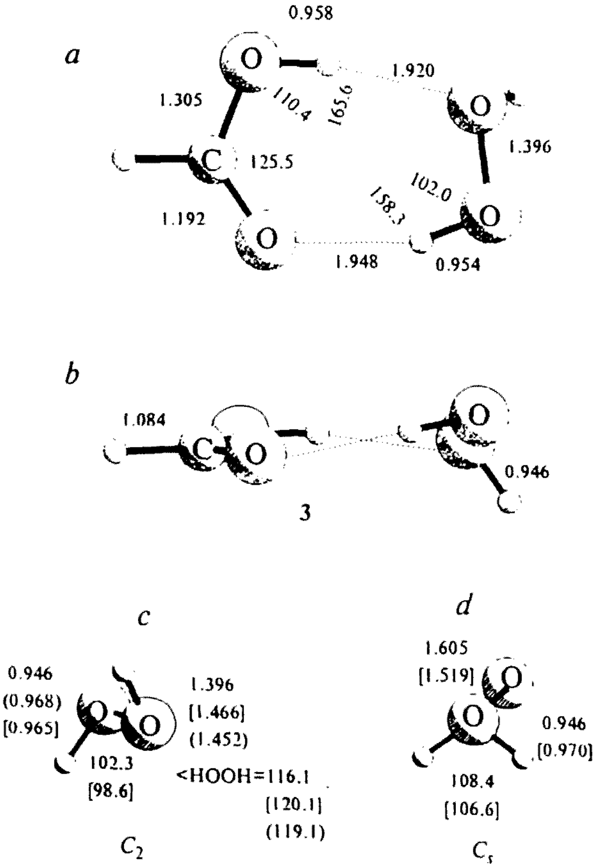


Fig. 5. Geometric characteristics of associate **3**, and HOOH and OOH_2 molecules: *a*, the top view from the plane passing through four oxygen atoms belonging to two formic acid molecules; *b*, the side view; *c*, HOOH; *d*, OOH_2 (*d*/Å; ω/deg). The results of calculations by the MP2/6-31G* method are given in brackets, experimental data[28] are in parentheses.

characteristics of the formic acid molecules and, which is surprising, of the hydrogen peroxide molecule remain virtually unchanged by the formation of associate **1a** (Y = O).

However, it should be noted that the length of the O—O bond (1.396 Å) in the isolated molecule of hydrogen peroxide (see Fig. 5), calculated in the Hartree—Fock approximation, is significantly shorter than that experimentally measured (1.452±0.004 Å).[28] This points to the necessity of taking into account the electronic correlation when describing this bond. The energy of formation of the two H-bonds in associate **3** (Y = O) is 11.3 kcal mol^{-1} (see Table 1). Correspondingly, the cooperative effects $\Delta E_{\text{coop}} \approx \Delta E'_{\text{coop}} \approx 1.3$ kcal mol^{-1} for associate **3** are more than 2 times higher than those for associate **1** (Y = NH). The hydrogen peroxide and hydrazine molecules in associates **1** and **3** hold their *gauche*-conformations, the most stable in the gas phase.

According to *ab initio* calculations, the nonplanar bicyclic structure **2** (Y = O) (see Fig. 6) with C_s symmetry corresponds to the minimum ($\lambda = 0$) on the PES and is an intermediate of reaction (1), which indicates the stepwise character of the latter.

The lengths of the O...HO bonds in intermediate **2** (Y = O) are appreciably shorter than those in associate **1** (Y = O). A comparison of the O—O bond lengths of the OOH_2 fragment in intermediate **2** (1.456 Å) and those in the free state (1.605 Å) (see Fig. 5, *d*) points to an substantial stabilization of the OOH_2 system by two formic acid molecules.

The reaction $\mathbf{1} \rightleftharpoons \mathbf{2}$ proceeds through an intermolecular 1,2-H-shift *via* an asymmetric transition state **4** (C_1), presented in Fig. 7, and results in the formation of the OOH_2 molecule. It is likely that the latter, in its turn, decomposes into a water molecule and a singlet oxygen atom. The calculated activation barrier to this

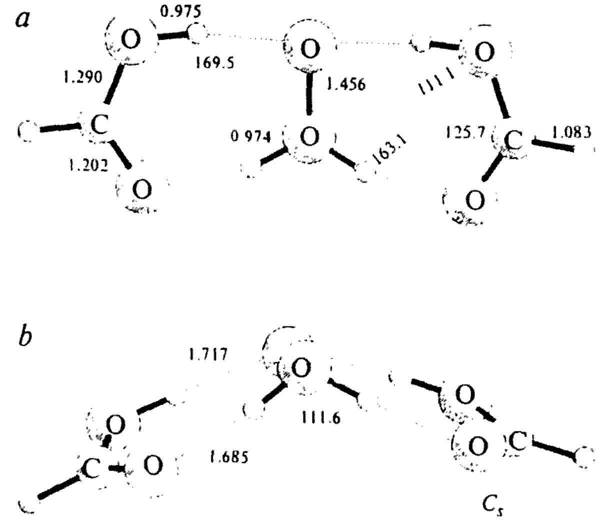


Fig. 6. Geometric characteristics of intermediate **2** (Y = O *a*, the top view from the plane passing through four oxyge atoms; *b*, the side view (*d*/Å; ω/deg).

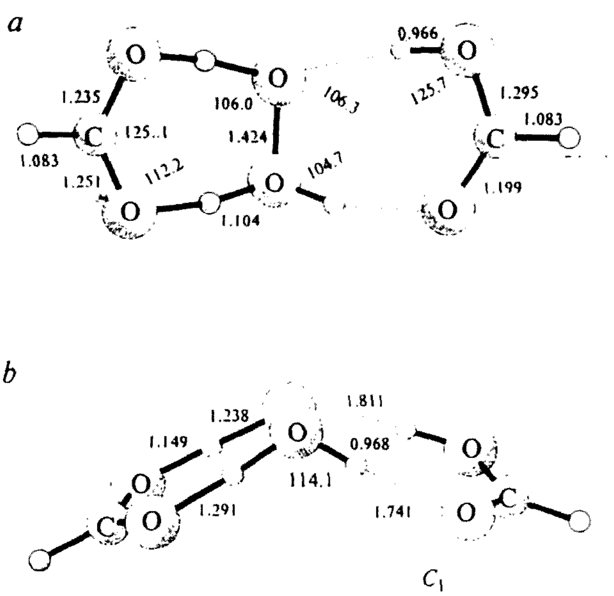


Fig. 7. Geometric characteristics of the transition state **4** (Y = O) in the proton-transfer reaction (1): (*a*), the top view from the plane passing through four oxygen atoms belonging to two formic acid molecules; (*b*), the side view (*d*/Å; ω/deg).

reaction is 27.1 kcal mol^{-1}, which is somewhat lower than that to cooperative proton transfer in associate **1** (Y = NH).

Thus, the calculations performed show that nonplanar associates, potentially capable of stereoselective bonding to symmetric substrates, are formed during stabilization of the hydrazine and hydrogen peroxide molecules by two formic acid molecules. The N—N bond of hydrazine is activated when associate **1** (Y = NH) is formed. The proton exchange in structure **1** (Y = NH) follows a concerted (cooperative) mechanism, in which four-proton transfer occurs simultaneously *via* a hydrazine molecule. At the same time, the similar reaction in associate **1** (Y = O) proceeds stepwise *via* intermediate **2**.

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