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EFFECT OF SILICA SURFACE ON HYDROLYSIS OF ACETYLSALICYLIC ACID: THEORETICAL SIMULATION

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Using methods of quantum chemistry, the mechanisms of hydrolytic degradation of acetylsalicylic acid have been considered in aqueous solution at pH values from 2 to 4 and from 4 to 8.5 as well as those involving silica surface. The results of calculations have been confirmed the experimental data on intramolecular catalysis of hydrolysis of acetylsalicylic acid at pH 4 to 8.5. It has been shown that the activation energy of surface reaction of hydrolysis is lower than that in aqueous solution due to specific interaction between silica surface and molecules of water and acetylsalicylic acid.

INTRODUCTION

In practical use of topical medications, a problem arises on their stability under storage [1]. Adsorption of organic molecules on silica surface alters their reactivity compared to free states [2]. It is known [3] that adsorption of acetylsalicylic acid (ASA) on silica surface promotes its hydrolytic destruction what casts doubt on the feasibility of using silica as an excipient in medicinal products containing ASA. However, the mechanisms of surface effect on this process has not yet defined. One can only assume that the hydrolysis of acetylsalicylic acid can involve silica surface with partially dissociated surface groups and its mechanism is similar to that of enzymatic catalysis of sucrose [4] or proteins [5, 6] hydrolysis. Therefore a quantum study on the elementary acts of ASA hydrolysis and on the effect of silica surface on this process is actual.

OBJECTS AND METHODS

When examining the hydrolysis mechanisms, complexes of reactants were considered composed of ASA with geometrical and electronic parameters described in [7, 9] and water molecules as well as intermolecular complexes of reaction products (salicylic [10] and acetic acid) and related transition states. The silica surface with partially dissociated silanol groups was simulated by disilicic acid anion ($[Si_2H_5O_7]^-$) and cubic cluster ($[Si_8H_7O_{20}]^-$) [11]. In order to provide electroneutrality of the models, a hydrogen cation (H_3O^+) was added to each structure stabilized by three water molecules. The calculations were performed using density functional theory (DFT) with the B3LYP exchange-correlation functional and basis set 6-31G(d,p). The effect of aqueous environment was simulated within supermolecular approximation and within the continuous solvent model (point charge model, PCM [12]), using the US GAMESS program package [13]. Equilibrium spatial structures of the molecules of reactants and reaction products within elementary stages as well as configurations of the transition states were determined by the gradient norm minimization [14]. The stationarity of minimum energy structures obtained was proved by the absence of negative eigenvalues in corresponding Hessian matrices, and the availability of transition states was confirmed by the existence of transient vectors, according to the Murrell-Laidler theorem [15]. The Gibbs energy values of the respective channels of hydrolysis were defined according to the formula:

$$\Delta G_{react.} = \Delta G^0_{298\ (reaction\ products)} - \Delta G^0_{298\ (reactants)}.$$

The free activation energy was found as follows:

$$\Delta G_{act.} = \Delta G^0_{298\ (transition\ state)} - \Delta G^0_{298\ (reactants)}.$$

The Gibbs energy values were found due to the formula:

$$\Delta G^0_{298} = \Delta E_{0K} + \Delta ZPE + \Delta\Delta G_{0\rightarrow 298K},$$

where ΔE_{0K} is the difference between the total energy values for ion-pair and molecular states, and the differences between both zero point energy values (ΔZPE) and the $\Delta\Delta G_{0\rightarrow 298K}$ values

were evaluated via calculation of the Hesse matrices for both these states [16].

RESULTS AND DISCUSSION

Hydrolysis of acetylsalicylic acid in the free state. It is known from experimental data [17] that the rate of hydrolysis of ASA depends on the pH value. At pH from 2 to 4, hydrolysis occurs with a relatively low velocity constant, as for the author, with participation of a neutral molecule of acetylsalicylic acid and water molecules (solvolysis); at pH from 4 to 8.5 – intramolecular base catalysis occurs with greater rate constant of hydrolysis. This increase in the hydrolysis rate constant in [17] is explained by the fact that ASA has pK_a = 3.75, so in the acidic aqueous solution (pH=2–4) its molecules are hydrolyzed without dissociation, and at higher pH (4) the molecules of acetylsalicylic acid in aqueous solution dissociate to form hydroxonium cations (H_3O^+) and ASA anions ($[C_9H_7O_4]^-$), the latter being involved into hydrolysis. Possible mechanisms of these schemes are shown in Figure 1.
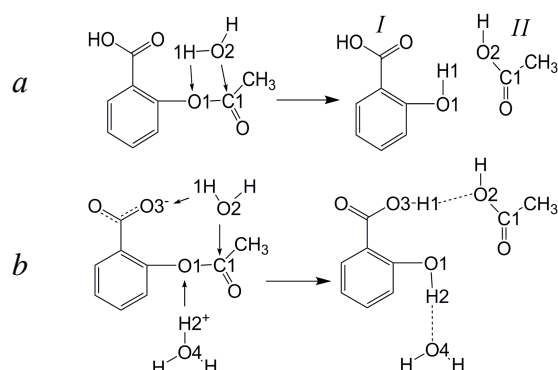

Fig. 1. Probable hydrolysis mechanisms of acetylsalicylic acid in aqueous solution at different values of medium acidity:
(*a*) – pH=2 – 4, (*b*) - pH=4 – 8.5.

While the mechanism of hydrolysis by (*a*) (Fig. 1), the oxygen atom (O2) of water molecule attacks the carbon atom (C1) of acetylsalicylic acid molecule; at the same time, the hydrogen atom (H1) of water molecule attacks the oxygen atom (O1) of ASA molecule. So, the acyl-oxygen bond (O1–C1) is terminated to form molecules of both salicylic (I) and acetic (II) acids. According to the mechanism (*b*) (Fig. 1), the oxygen atom of water molecule (O2) attacks the carbon atom (C1) of carbonyl group as well as in the previous case. However, the hydrogen atom (H1) to water molecule is connected to the oxygen atom (O3) of carboxyl group of acetylsalicylate anion. At the same time, the proton (H2) formed due to dissociation of acetylsalicylic acid attacks the oxygen atom (O1) of the same molecule. This mechanism is so-called intramolecular base catalysis [17]. The geometry parameters have been found for prereaction complexes, transition states, and reaction products for both the mechanisms (Fig. 2).
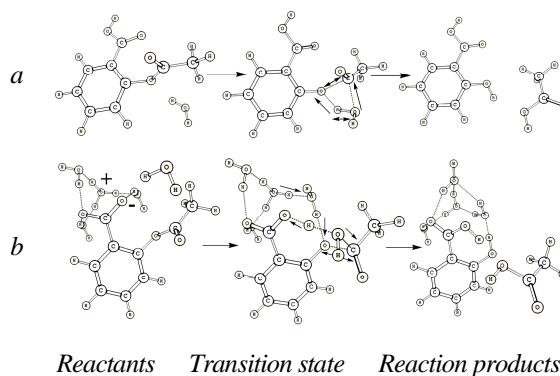

Reactants   Transition state   Reaction products

Fig. 2. Elementary acts of acetylsalicylic acid hydrolysis in aqueous solution at pH (2 – 8.5):
a – solvolysis, *b* – a mechanism of intramolecular base catalysis (arrows on the transition states show displacements of atoms caused by the transition from the reactants complex to the reaction products)

Table 1. Energy characteristics of different channels of aspirin hydrolysis in aqueous solution (kJ/mol)

Mechanism	Method of calculation	Activation energy		The energy effect of reaction		Reaction rate constant (exp., $k_{obs}*10^{-5}$, s^{-1}) [2]
		$\Delta E_{act.}$	$\Delta G_{act.}$	$\Delta E_{react.}$	$\Delta G_{react.}$	
solvolysis (*a*)	B3LYP/6-31G(d,p)	142.5	139.7	-31.6	-33.1	1.0
	B3LYP /6-31G(d,p)/PCM	156.7	154.6	-34.8	-40.0	
intramolecular base catalysis (*b*)	B3LYP/6-31G(d,p)	82.3	83.4	-41.8	-48.8	6.3
	B3LYP/ 6-31G(d,p)/PCM	101.5	113.9	-26.0	-16.6	

The calculation results are presented in Table 1. Both two mechanisms are thermodynamically favorable, i.e. $\Delta G_{react.} < 0$, and the activation energy for hydrolysis of acetylsalicylic acid in aqueous solution by intramolecular basic mechanism is less than that for solvolysis what confirms the experimental data. Using PCM leads to an increase in the activation energy of hydrolysis reactions for both mechanisms.

Hydrolysis of acetylsalicylic acid on the silica surface. Let us consider the effect of silica surface on the mechanism of hydrolysis of acetylsalicylic acid. A mechanism is proposed similar to the enzymatic hydrolysis of sucrose. It is possible in the tablets after mixing ASA with non-calcined silica where silica surface can bear physically adsorbed water molecules and some dissociated silanol groups. We believe that when ASA molecule interacts with water one, the proton (H1) moves to the oxygen atom (O1) of dissociated silanol group (Fig. 3). Meanwhile the oxygen atom (O2) attacks the carbon atom (C1) and the proton another silanol groups (H2) passes to the oxygen atom (O3) of ASA molecule, so resulting in brokening acyl-oxygen bond (O3–C1) to form salicylic and acetic acid molecules. It should be noted that the gross composition of silica surface after hydrolysis of ASA remains unchanged.
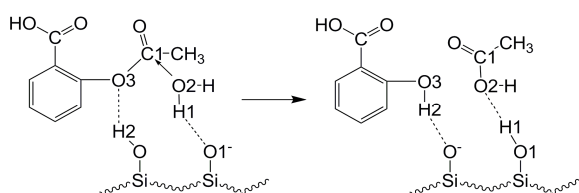

Fig. 3. The mechanism of ASA hydrolysis over silica surface

It should be noted that according to [3], acetylsalicylic acid is weakly adsorbed from aqueous solution onto silica surface, so under such conditions the hydrolysis reaction unlikely follows this mechanism. In order to simulate the effect of silica on the mechanism of hydrolysis of acetylsalicylic acid, the spatial structures has been optimized of the models for adsorption complexes of reactants, transition states, and reaction products, the former involving disilicic acid anion $[Si_2H_5O_7]^-$ and a complex with gross composition of $[Si_8H_7O_{20}]^-$. The models

simulated for hydrolysis involving silica surface bearing dissociated silanol groups are shown in the Fig. 4.

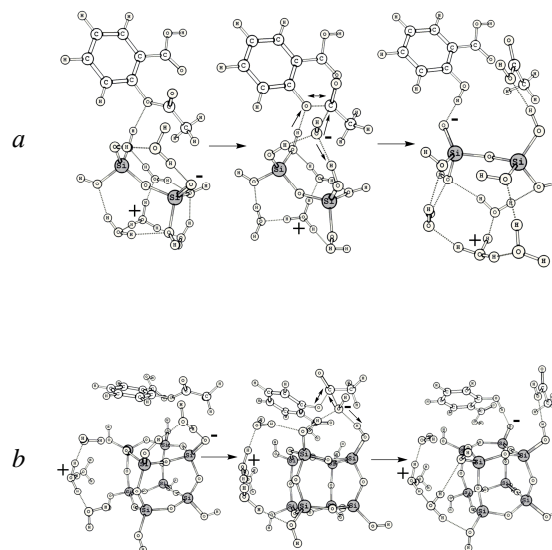| Reactants | Transition state | Reaction products |

Fig. 4. Elementary acts of acetylsalicylic acid hydrolysis on silica surface involving different size models with dissociated silanol groups: $a - [Si_2H_5O_7]^-$, $b - [Si_8H_7O_{20}]^-$

Table 2 presents the results of calculations of kinetic ($\Delta E_{act.}$, $\Delta G_{act.}$) and thermodynamic ($\Delta E_{react.}$, $\Delta G_{react.}$) characteristics of the hydrolysis of acetylsalicylic acid on silica surface carried out by B3LYP/6-31G(d,p)/PCM method. When comparing the $\Delta G_{act.}$ values from the Table 1 with those from the Table 2, one can conclude that regardless of the selected models for silica surface, the values of free activation energy of acetylsalicylic acid hydrolysis are lesser than those for similar reactions in aqueous solution. This can be easily explained by the fact that a dissociated sylanol group can easily pick up a proton from a water molecule that takes part of the ASA hydrolysis so that the attacking nucleophilic oxygen atom has a greater negative charge. In addition, the hydrogen bond in the reactant complex ($l(H2 \cdots O3) = 1.73$ Å, see Fig. 3) is shorter than that in aqueous solution ($l(H2 \cdots O3) = 2.32$ Å, see Fig. 1, *b*). The geometry of adsorbed reactants slightly differ from that related to the transition state (Fig. 4) unlike the situation in aqueous solution (Fig. 2), so that the activation energy of ASA hydrolysis

in the latter case is somewhat higher as compared to that related to the adsorption state.

Table 2. Energy characteristics of hydrolysis of acetylsalicylic acid on silica surface (kJ/mol)

Model for silica surface	Activation energy		The energy effect of reaction	
	$\Delta E_{act.}$	$\Delta G_{act.}$	$\Delta E_{react.}$	$\Delta G_{react.}$
$Si_2H_6O_7$	80.8	78.3	-43.3	-30.1
$Si_8H_8O_{20}$	82.5	80.1	-32.7	-26.5

CONCLUSIONS

The results of simulation of the mechanisms of the hydrolysis of acetylsalicylic acid in aqueous solutions with different pH agree well with the experimental data on the rate constants of the process. The free activation energy of hydrolysis reactions involving silica surface has been found to be lesser (82 kJ/mol) than that in aqueous solution (113.9 kJ/mol), so indicating a catalytical effect of silica surface on the reaction of ASA hydrolysis due to the specific interaction between silica surface and acetylsalicylic acid molecules. That is why silica should not be used as an adjuvant in the manufacture of drugs containing ASA.

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Вплив поверхні кремнезему на гідроліз ацетилсаліцилової кислоти: теоретичне моделювання

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За допомогою квантовохімічних методів розглянуто механізми гідролітичної деструкції ацетилсаліцилової кислоти у водному розчині при pH від 2 до 4 та від 4 до 8,5, а також за участю поверхні кремнезему. Розрахунками підтверджені експериментальні дані щодо внурішньомолекулярного каталізу в гідролізі ацетилсаліцилової кислоти при pH від 4 до 8,5. Показано, що за рахунок специфічної взаємодії поверхні кремнезему з молекулами води і ацетилсаліцилової кислоти енергія активації реакції її гідролізу менша, ніж у водному розчині.

Влияние поверхности кремнезема на гидролиз ацетилсалициловой кислоты: теоретическое моделирование

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С помощью квантовохимических методов рассмотрены механизмы гидролитической деструкции ацетилсалициловой кислоты в водном растворе при pH от 2 до 4 и от 4 до 8,5, а также при участии поверхности кремнезема. Расчетами подтверждены экспериментальные данные о внутримолекулярном катализе гидролиза ацетилсалициловой кислоты при pH от 4 до 8,5. Показано, что за счет специфического взаимодействия поверхности кремнезема с молекулами воды и ацетилсалициловой кислоты энергия активации реакции ее гидролиза меньше, чем в водном растворе.