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Oxidation of 6-Methyl-2,4-dioxypyrimidine with Selenious Acid

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Abstract—The yield orotic aldehyde at the oxidation of 6-methyl-2,4-dihydroxypyrimidine was found to increase when selenious acid is used as an oxidizer. A comparative analysis of 6-methyl-2,4-dioxypyrimidine oxidation with selenium dioxide and selenious acid was performed using the *ab initio* quantum chemical method in the 6-31G** basis.

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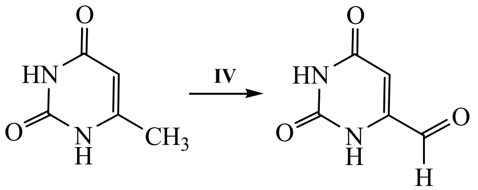
The reflux of the dilute solutions (2–4%) of 6-methyl-2,4-dioxypyrimidine **I** with selenium dioxide **II** in acetic acid for 6 h was found to afford orotic aldehyde **III** in ~32–50% yield. We studied the oxidation of 6.5% solution of compound **I** with selenious acid **IV** in a boiling acetic acid for 4 h. Under these conditions the yield of aldehyde **III** can be raised to 62%.



I **III**

It can be assumed that the oxidation of methyl moiety of compound **I** involves the mixed selenious and acetic anhydride, which is formed from the selenium derivatives **II** and **IV**. Analyzing the formation of mixed anhydride of acetic and selenious acids as one of the stages of 6-methyl-2,4-dioxypyrimidine oxidation with selenium oxide and selenious acid in acetic acid solution, we found that the formation energy for SeO_2 and H_2SeO_3, calculated by the quantum *ab initio* method in the 6-31G** basis [3], differ only slightly. Unlike original selenious and acetic acids, the mixed anhydride (Fig. 1) has a higher activity.

The charge on the selenium atom of the anhydride increases from 1.23 in selenium dioxide and 1.46 in selenious acid to 1.49. In addition, unlike selenium dioxide and selenious acid, the anhydride selenium atom has a greater spatial accessibility at the electrophilic attack of the 5-position of pyrimidine ring. Analysis of the reaction path of the anhydride

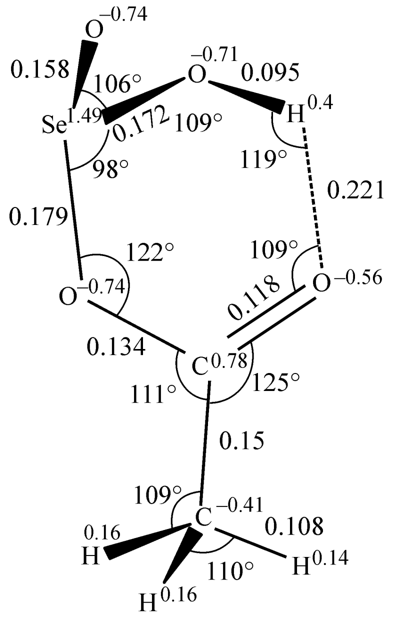
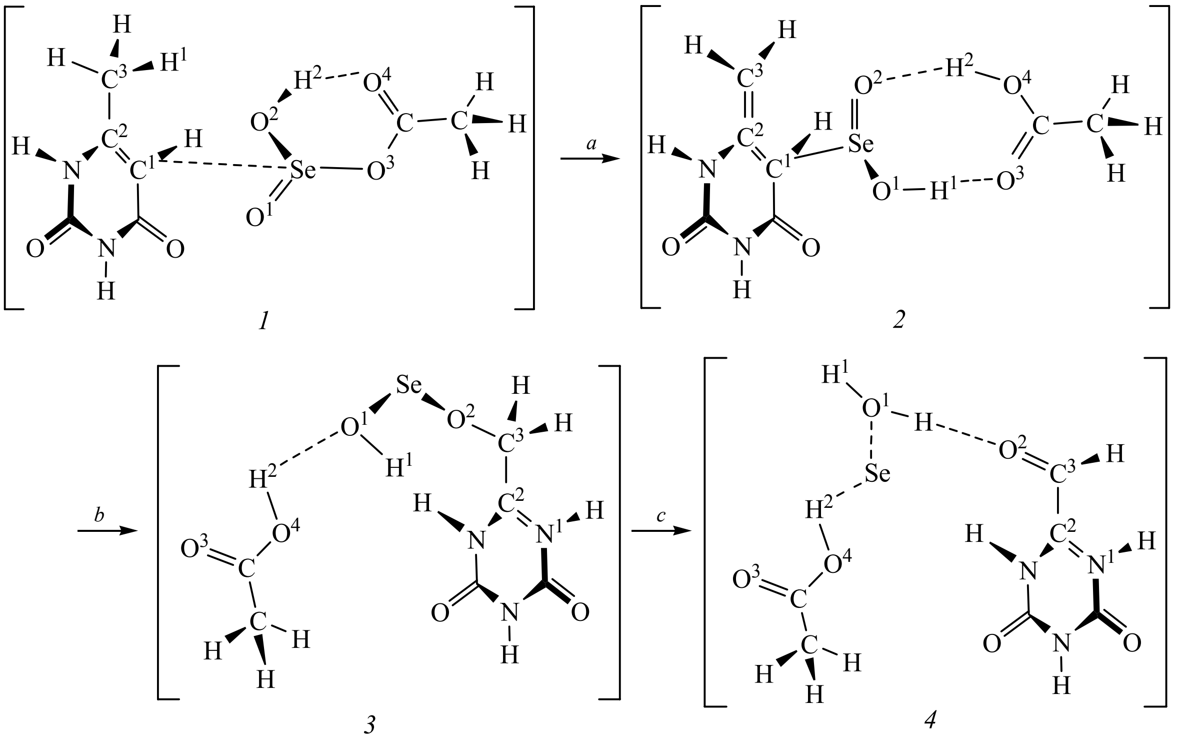


Fig. 1. Electronic and geometric structure of the mixed anhydride of selenious and acetic acids (total energy E_0 = –347994.4 kcal mol^{-1}, the charge is specified for the each atom, the distance between atoms is indicated above the bond, nm).



with 6-methyluracil identified three stages of the oxidation of the methyl group in 6-methyluracil.

As selenic anhydride (the selenium atom) approaches the electrophilic carbon atom C^1 of pyrimidine base, at a distance of 0.22 nm there is a point of the barrier with an activation energy of 47.5 kcal mol^{-1} (*a*). The geometric and electronic structure of the transition complex corresponding to this point is shown in Fig. 2. The charge on the carbon atom becomes more negative and increases to –0.615, and positive charge on the selenium atom increases to 1.541. Simultaneously, the ^{1}H hydrogen atom of the methyl group removes to the side of the Se–O^1 oxygen in the anhydride and occurs synchronous transfer of the hydrogen atom from the Se–OH group to the acyl radical followed by acetic acid release and the intermediate 6-methyl-5-pyrimidineselenious acid formation.

At the second stage (*b*) occurring with an activation energy of ~31.8 kcal mol^{-1}, the O^2 oxygen atom of selenious acid residue attacks the C^3 methylene carbon atom to form the transition structure (Fig. 3). After

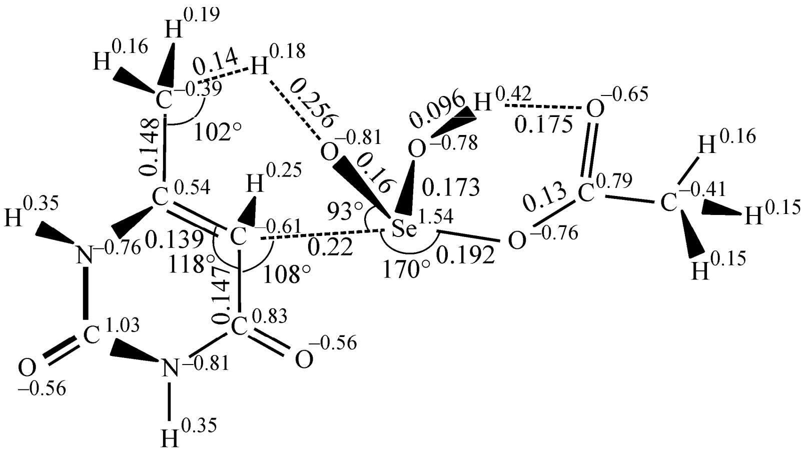


Fig. 2. The geometric and electronic structure of the transition complex at the reaction stage *1*.

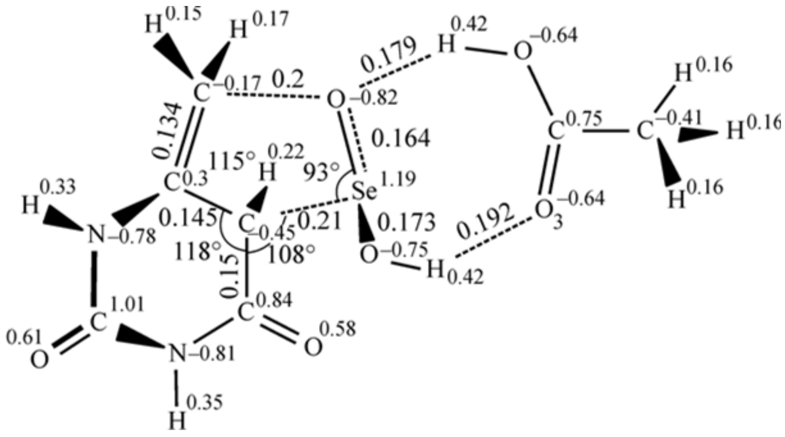


Fig. 3. The geometric and electronic structure of the transition complex at the reaction stage *2*.

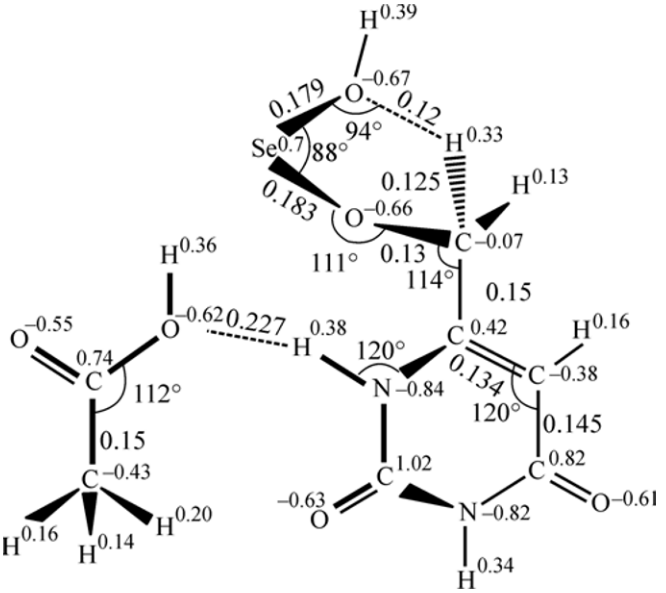


Fig. 4. The geometric and electronic structure of the transition complex at the reaction stage *3*.

passing the saddle point, at a distance of 0.19 nm between the methylene carbon and oxygen of SeO_2 the carbon–selenium bond breaks completely.

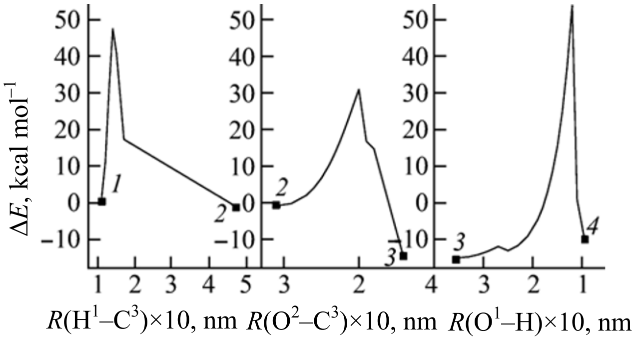


Fig. 5. The barrier for the oxidation of CH_3 group with HO(O)Se–O(O)CCH_3 molecule. $\Delta E = E_i^0 - E^0$ [$R(H^1–C^3)$ = 1.084]; (*1*–*4*) the reaction stages.

The final stage of the reaction (*c*) is characterized by a barrier of 54 kcal mol^{-1} with respect to the initial reagents. According to the electronic state of the transition complex (Fig. 4), the hydrogen atom of CH_2 group is involved into the water formation with OH group, with the simultaneous rupture of the Se–O bond to form an aldehyde group and selenium.

The total energy of the final reaction products is lower than the total energy of the initial reactants by 9.4 kcal mol^{-1}, which shifts the equilibrium toward the reaction products (Fig. 5).

Thus, the similarity of the processes of the methyl group oxidation in compound **I** with either selenium dioxide or selenious acid is the involvement part of the intermediate mixed anhydride, which has a greater reactivity. This reaction proceeds through a stage of electrophilic attack on the 5-position of pyrimidine ring followed by the formation of 6-methylene derivative and its subsequent intramolecular oxidation to form Se and orotic aldehyde.

One can also assume that the difference between the oxidation of the methyl group in compound **I** with acid **IV** consists in the fact that along with the mixed anhydride of selenious and acetic acid, in the reaction also take part selenious acid anhydride formed by the intermolecular dehydration. In addition, the released water molecules in the reaction of selenious acid with acetic acid is always in the reaction sphere due to the dipole–dipole interaction with an selenium atom and associative interactions with a molecule of orotic aldehyde, which favors the final stage in the direction of the end reaction products.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury instrument (300 MHz) in CCl_4 or $CDCl_3$ relative to internal HMDS. The IR spectra were taken on a Specord-M82 instrument (liquid film).

Synthesis of orotic aldehyde (III). A three-necked 400 ml reactor equipped with a stirrer, a thermometer and a reflux water-cooled condenser was charged with 15.9 g (0.13 mol) of 6-methyl-2,4-dioxypyrimidine **I**, and then was added 250 ml of glacial acetic acid. The mixture was kept at 50–60°C until the complete dissolution. Then 9.15 g of selenious acid was dosed. The resulting mixture was refluxed for 5 h with stirring.

The precipitated gray mass of selenium (recovered as compound **IV** [4]) was filtered off on a Schott's filter and washed thoroughly with hot acetic acid. Acetic acid was distilled off from the filtrate under vacuum (10–15 Hg mm). The resulting residue was dissolved in 300 ml of water acidified with 0.4 ml of hydrochloric acid and boiled for 15 min. After the addition of powdered charcoal (3 g) the mixture was boiled for 15 min. The solution was separated from the adsorbent by filtration. After distilling off the water in a 10–15 mm Hg vacuum to a volume of 70–80 ml, the residue was cooled. The precipitated orotic aldehyde was filtered off and washed on a filter with 20 ml of water, 20 ml of ethanol and 100 ml of diethyl ether. Orotic aldehyde was purified by sublimation in vacuum (10 Hg mm). Yield 8 g (45.5%), mp 273–275°C (decomp.), which corresponds to the published data [1, 5, 6]. In addition, after cooling the mother liquor (after washing with water and ethyl alcohol) 3 g of orotic aldehyde was obtained with the same parameters. The total yield of orotic aldehyde was 11 g (62.5%).

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