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OXIDATION MECHANISM OF 6-METHYL-2,4-DIOXOPYRIMIDINE WITH SELENIUM OXIDE AND SELENOUS ACID

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*Analysis of the oxidation mechanism of 6-methyl-2,4-dioxopyrimidine with selenium oxide and selenous acid with the formation of orotic aldehyde has been carried out by the ab initio quantum-chemical method on the 6-31G** basis. The mixed anhydride of acetic and selenous acids is formed with a gain of energy. It possesses high activity and steric accessibility in electrophilic attack on position 5 of the pyrimidine ring. The three-stage mechanism of the oxidation of the methyl group in 6-methyluracil by the mixed anhydride of selenous and acetic acids has been analyzed.*

Keywords: selenium dioxide, 6-methyluracil, orotic aldehyde, selenous acid.

A quantum-chemical investigation has been carried out in the present work of the mechanism of oxidation of 6-methyl-2,4-dioxopyrimidine (6-methyluracil) with selenium oxide and selenous acid in acetic acid with the formation of orotic aldehyde. The calculations were carried out by the *ab initio* method on the 6-31G** basis [1].

As we established previously [2], the oxidation of 6-methyluracil with selenous acid in a medium of acetic acid, unlike the use of selenium oxide under the same conditions, permits a significant reduction in the amount of acetic acid and an increase in the yield of orotic aldehyde. In both cases the reaction proceeds according to the same mechanism, i.e. through the stage of forming a mixed anhydride of acetic and selenous acids [3], which is also in agreement with the results of [4], in which the intermediate formation of selenous acid in the process of oxidation of 6-methyluracil with selenium dioxide was proposed.

On analysis of the process of forming a mixed anhydride of acetic and selenous acid as one of the stages of the oxidation of 6-methyl-2,4-dioxopyrimidine with selenium oxide and selenous acid in acetic acid, it turned out that for SeO_2 the gain in energy was 5.5 kcal/mol, but for H_2SeO_3 it was about 1 kcal/mol. The resulting mixed anhydride (Fig. 1) is more reactive than SeO_2 and H_2SeO_3.

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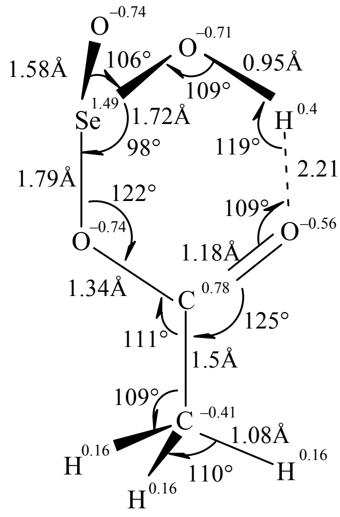

Fig. 1. Electronic and geometric structure of the mixed anhydride of selenous and acetic acids (total energy $E_0 = -347994.4$ kcal/mol). Here, and in Figs 3-5 numbers in the upper index are charges on atoms.

The charge on the selenium atom at 1.23 in selenium dioxide and 1.46 in selenous acid is increased in the anhydride to 1.49. In addition, unlike selenium oxide and selenous acid, the selenium atom in the anhydride possesses a larger spatial accessibility on electrophilic attack at position 5 of the pyrimidine ring. Analysis of the reaction pathway of the anhydride with 6-methyluracil revealed the subsequent stages of the oxidation process of the methyl group of 6-methyluracil given in Fig. 2.

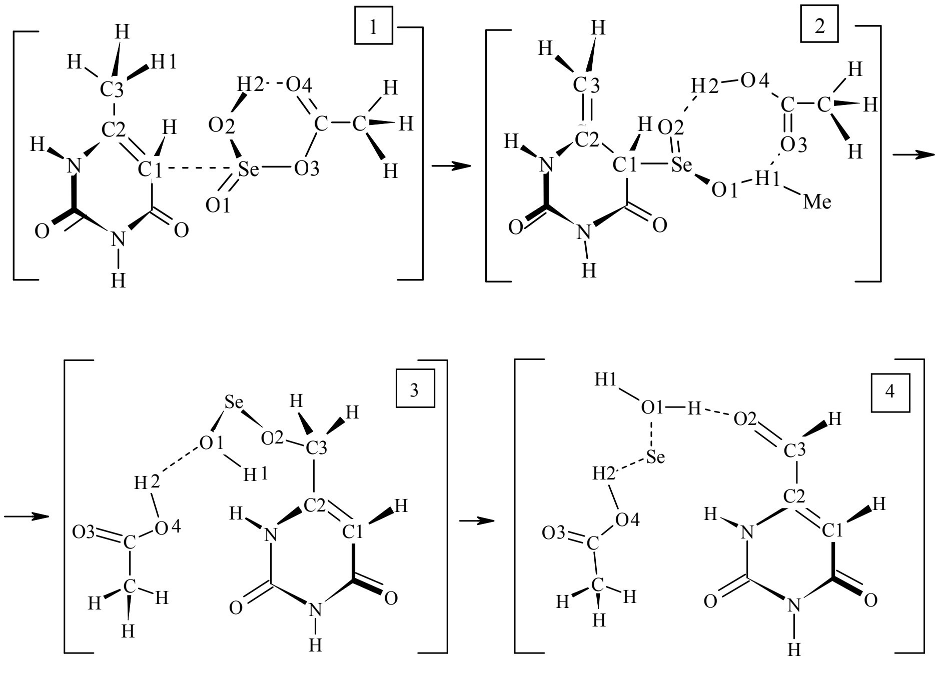

Fig. 2. Reaction scheme for the oxidation of the Me group by the HO(O)Se–O(O)CMe molecule.

1. Stage of forming the 6-methylene derivative (Fig. 3). A molecule of selenous anhydride (selenium atom) approaches the electrophilic carbon atom of the pyrimidine base, and at a distance of 2.2 Å a barrier point arises with an activation energy of 47.5 kcal/mol. The charge on the oxygen atom becomes even more negative (-0.615), and on the selenium atom the positive charge is 1.541. Simultaneously transfer of a hydrogen atom of the methyl group to the oxygen of the Se=O group in the anhydride is observed with the synchronous transfer of a hydrogen atom from the Se–OH group to the acyl radical. Subsequently elimination of acetic acid occurs with the formation of the intermediate 6-methylene-5-pyrimidineselenous acid.

2. In the second stage, which proceeds with an energy of activation of about 31.8 kcal/mol, attack by the oxygen atom of the selenous acid residue occurs, directed at the carbon atom of the methylene group with the formation of an intermediate structure (Fig. 4). After passing the critical point, at a distance of 1.9 Å between the carbon atom of the CH_2 group and the oxygen atom of the SeO_2 group, complete rupture of the carbon–selenium bond occurs.

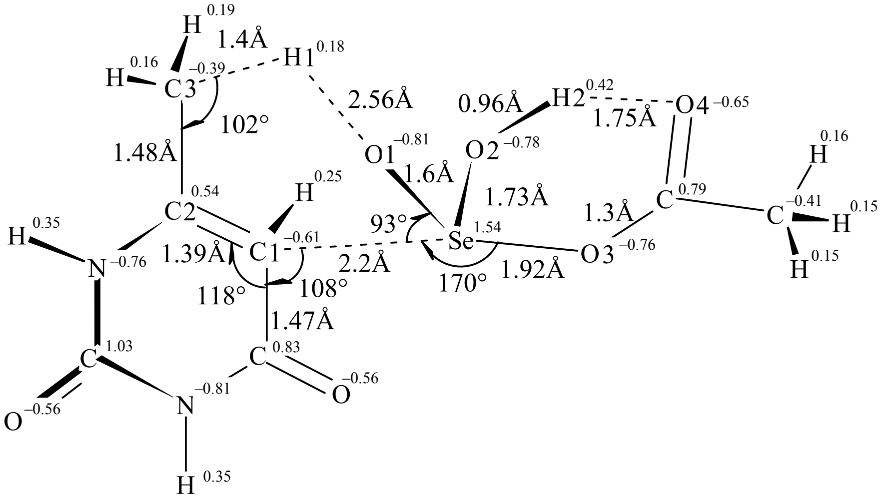

Fig. 3. Geometric and electronic structure of the transition complex at the first stage of the reaction.

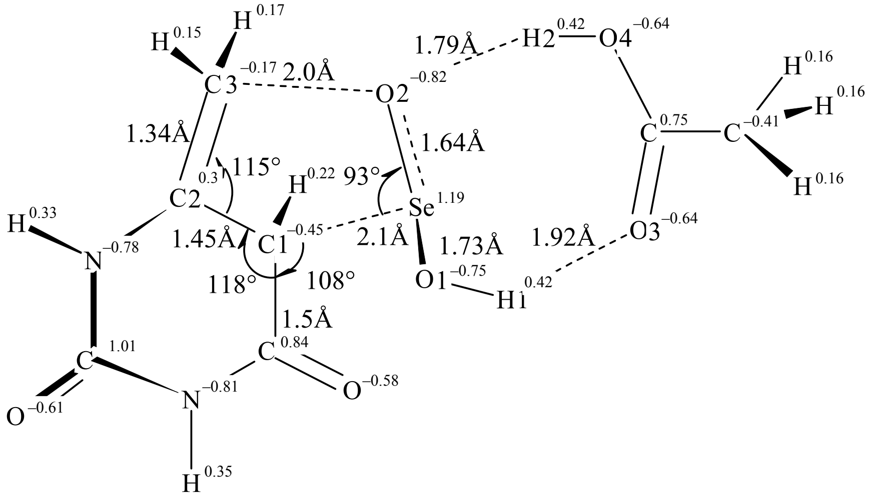

Fig. 4. Geometric and electronic structure of the transition complex at the second stage of the reaction.

3. The closing stage of the reaction is characterized by a barrier of 54 kcal/mol relative to the initial reactants. The structure of the transition complex provides approach of the CH_2 group to the OH group with the formation of water, simultaneous rupture of the Se–O bond and with the formation of the carbonyl (aldehyde) group. The eliminated water molecule, as a result of dipole–dipole interactions with the eliminated selenium atom formed as a result of the reaction, and the associated interaction with a molecule of orotic aldehyde, assists this stage to proceed to the final reaction products (Fig. 5).

The total energy of the final reaction products is less than the sum of the energies of the initial reactants by 9.4 kcal/mol, which assists displacement of the equilibrium towards the reaction products (Fig. 6).

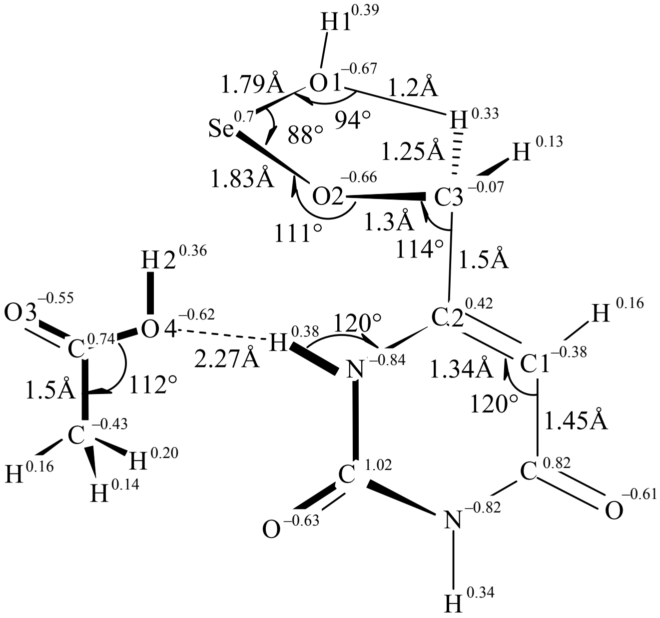

Fig. 5. Geometric and electronic structure of the transition complex at the 3rd stage of the reaction.

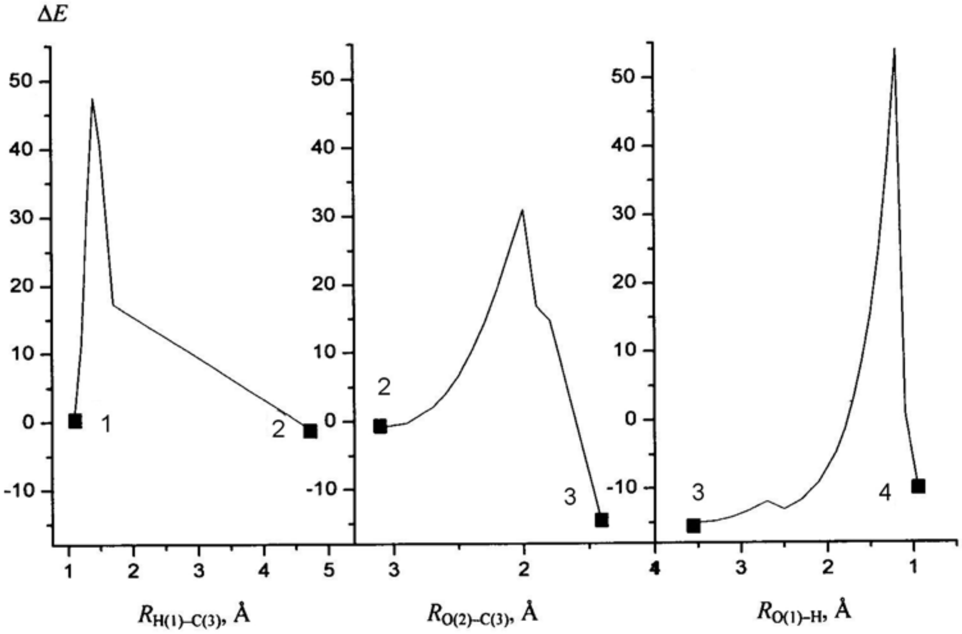

Fig. 6. Reaction barrier in the oxidation of the methyl group by the HO(O)Se–O(O)CMe molecule, $\Delta E = E_0(\mathrm{i}) - E_0$ ($R_{H(1)\text{-}C(3)} = 1.084$), kcal/mol.

Oxidation of 6-methyluracil into orotic aldehyde by selenium dioxide and selenous acid in a medium of acetic acid therefore proceeds by the most probable mechanism, comprising the formation of the intermediate anhydride of acetic and selenous acids possessing higher reactivity. This reaction proceeds through the stage of electrophilic attack at position 5 of the pyrimidine ring with subsequent formation of the 6-methylene derivative, then its further intramolecular oxidation with the formation of Se, orotic aldehyde, and water, assists the separation of the final reaction products.

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