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AM1 QUANTUM-CHEMICAL STUDY OF THE MECHANISM OF THE CYCLOCONDENSATION OF 4-HYDROXY-4-METHYL-2-PENTANONE WITH ETHYL CYANOACETATE

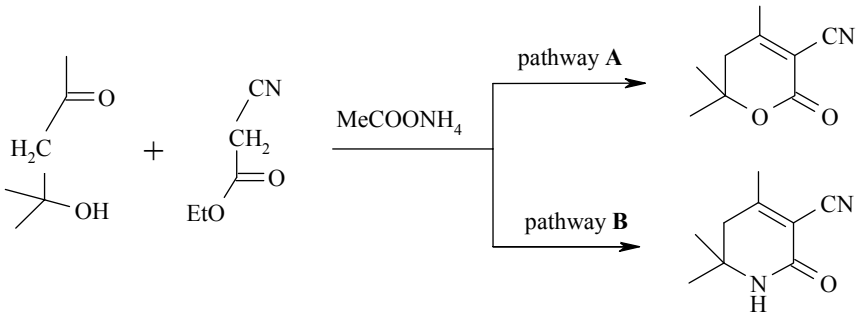
M. Fleisher, D. Jansone, and E. Lukevics

The reaction of 4-hydroxy-4-methyl-2-pentanone with ethyl cyanoacetate in the presence of ammonium acetate is a consecutive-parallel multistep domino process. The regioselectivity of the reaction is due to the direction of the electrophilic attack of the intermediate formed in the first step, namely, ethyl 2-cyano-3,5-dihydroxy-3,5-dimethylhexanoate.

Keywords: lactam, AM1, domino reaction, mechanism, cyclocondensation.

The reaction of 4-hydroxy-4-methyl-2-pentanone with ethyl cyanoacetate in the presence of ammonium acetate not only holds great practical importance but also holds considerable theoretical interest in light of the circumstance that, for example, either an oxygen-containing or nitrogen-containing heterocyclic compound may be obtained depending on the reaction conditions [1].

Scheme 1



A lactone is formed in the presence of catalytic amounts of ammonium acetate (pathway **A**). On the other hand, a lactam is obtained when the concentration of ammonium acetate is increased considerably such that it acts as a reagent (pathway **B**).

In the present work, we used the AM1 semiempirical quantum-chemical method to study the mechanism of this cyclocondensation [2]. Experience has shown that activation energies, electron affinities, and heats of deprotonation obtained by this method are in good accord with experimental data [3]. Furthermore, the AM1 method gives results for addition and cyclization reactions, which are comparable in accuracy to *ab initio* calculations [4].

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The mechanism for the activation of 4-hydroxy-4-methyl-2-pentanone was examined in our previous work [5]. Protonation of this alcohol occurs by the action of the catalyst components with an activation energy of 7.3 kcal/mol.

The nucleophilic attack in the reaction of the other reagent, ethyl cyanoacetate, with the acetate anion involves the methylene group. Deprotonation of the ethyl cyanoacetate molecule occurs as the result of the transfer of one of the hydrogen atoms in the anion. The activation energy found for this process was found to be 5.8 kcal/mol.

The reaction between the two activated species, namely, protonated 4-hydroxy-4-methyl-2-pentanone and deprotonated ethyl cyanoacetate, proceeds without a barrier and enthalpy ΔH = -140.4 kcal/mol and leads to an adduct with a C-C single bond. In the initial position selected (Fig. 1*a*), the distance between the oppositely-charged C(1) and C(2) atoms was 4.708 Å.

In the adduct obtained (Fig. 1*b*), this distance is 1.559 Å, which corresponds to the standard single bond value [6]. According to the IUPAC nomenclature rules, this adduct is the ethyl ester of 2-cyano-3,5-dihydroxy-3,5-dimethylhexanoic acid (**1**).

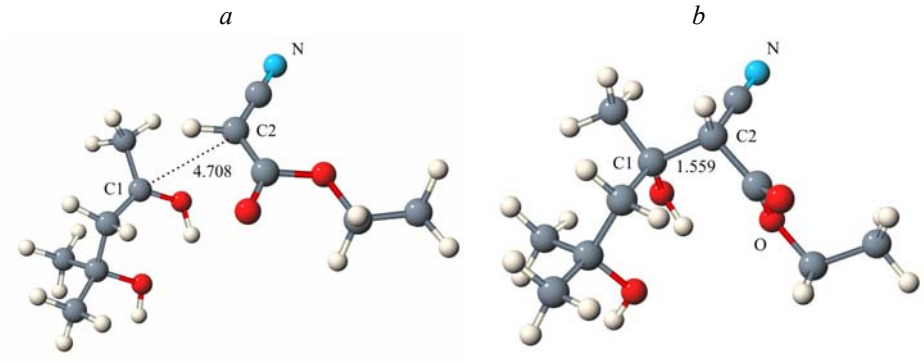


Fig. 1. Reaction between protonated 4-hydroxy-4-methyl-2-pentanone and deprotonated ethyl dicyanoacetate: *a*) initial state, *b*) reaction product, namely, ethyl 2-cyano-3,5-dihydroxy-3,5-dimethylhexanoate (the distances here as in Figs. 2-4 are given in angstroms).

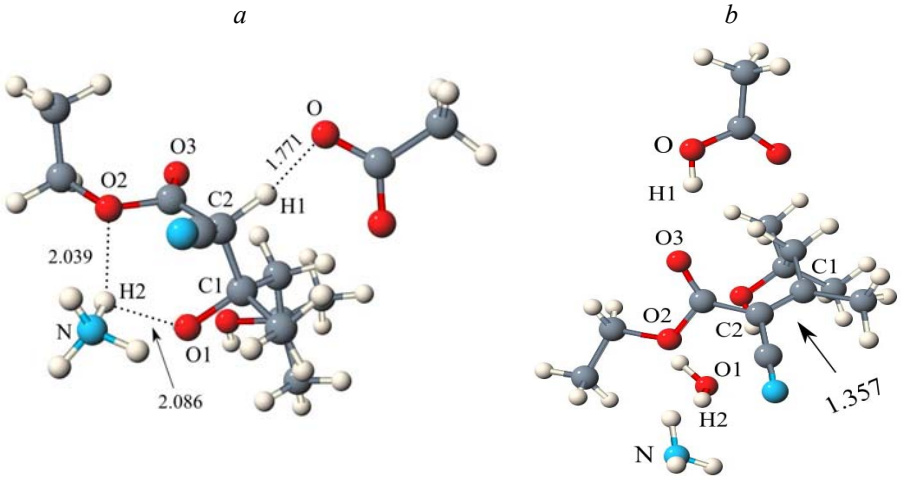


Fig. 2. Dehydration of adduct **1**: *a*) prereaction complex, *b*) reaction products: ethyl ester of (*Z*)-2-cyano-5-hydroxy-3,5-dimethyl-2-hexenoic acid, acetic acid, H_2O, and NH_3.

The reaction of adduct **1** with the catalyst components leads to formation of a prereaction complex with heat of complexation ΔH = -99.9 kcal/mol (Fig. 2*a*). Figure 1 shows that there are two most probable directions for attack of the adduct by a proton from the ammonium cation: either O(1) of the hydroxyl group at C(1) or O(2) of the ethoxy group.

The O(1)–H(2) distance was taken as the reaction coordinate. Dehydration of adduct **1** occurs after reaching the transition state system (activation energy E_a = 11.8 kcal/mol), leading to a compound with a C(1)–C(2) double bond (1.357 Å), which is the product of the Knoevenagel aldol condensation reaction, namely, the ethyl ester of (*Z*)-2-cyano-5-hydroxy-3,5-dimethyl-2-hexenoic acid (**2a**) (Fig. 2*b*). The enthalpy of this reaction ΔH = -51.7 kcal/mol.

Our calculation showed that intermediate **2a** has high electron affinity. The proton adds to the terminal O(3) atom bearing significant negative charge (-0.328) ΔH = -154.0 kcal/mol), which enhances the charge differentiation on C(3) and O(4): the positive charge on C(3) is enhanced from 0.355 to 0.465, while the negative charge on O(4) increases from -0.329 to -0.393. The free valence index of C(3) also increases from 0.172 to 0.270.

The nucleophilic attack of protonated intermediate **2a** by the acetate anion proceeds at H(3) of the hydroxyl group at the isopropylic carbon atom (Fig. 3). This reaction takes place spontaneously with ΔH = -156.8 kcal/mol.

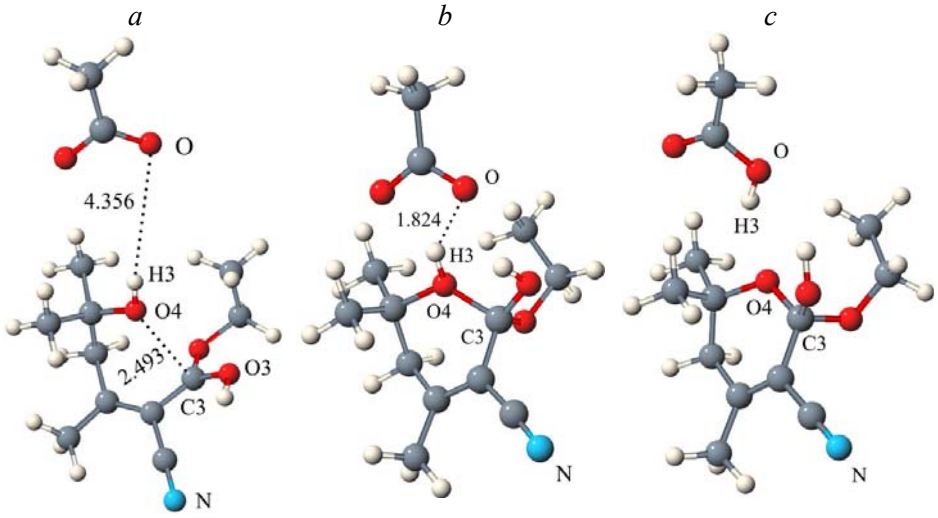


Fig. 3. Reaction of the protonated Knoevenagel reaction product **2a** and acetate anion: a) initial position, *b*) intermediate state, and *c*) reaction products: 2-ethoxy-2-hydroxy-4,6,6-trimethyl-5,6-dihydro-2H-pyran-3-carbonitrile and acetic acid.

A change in the geometry of the anion occurs as the reactive species approach each other, steadily leading to a decrease in the distance between oppositely-charged O(4) and C(3). A cyclic carbocation is formed upon closure of the bond between these atoms (Fig. 3*a*), which, after transfer of proton H(3) to the acetate anion, converts to the intermediate 2-ethoxy-2-hydroxy-4,6,6-trimethyl-5,6-dihydro-2H-pyran-3-carbonitrile (**3a**) (Fig. 3*c*).

The last step in this pathway involves the loss of ethanol. An ethanol molecule and intermediate carbocation are obtained (ΔH = -138.0 kcal/mol) after attack of the ethoxy group oxygen atom by a proton.

The subsequent reaction of the carbocation with the acetate anion occurs exothermally without an energy barrier (ΔH = -154.7 kcal/mol). Figure 4*a* shows our starting position. The final reaction product, 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile (**4**) (Fig. 4*b*), is formed after approximation of the reacting species and capture of the proton of the hydroxyl group of the carbocation by O(1) in the acetate anion.

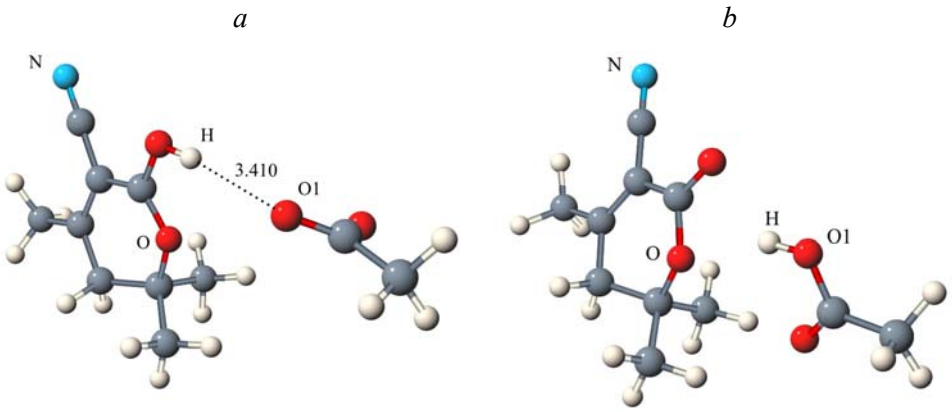


Fig. 4. Reaction of the cyclic carbocation with acetate anion: *a*) initial state, *b*) final cyclocondensation reaction product, 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile.

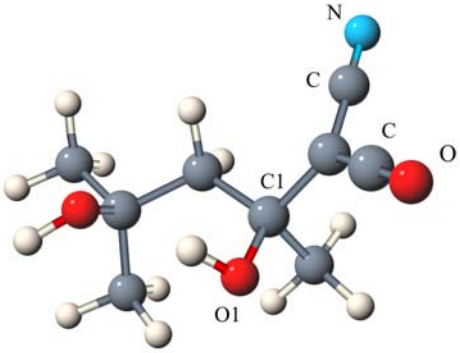


Fig. 5. Structure of intermediate **2a** optimized by AM1 calculation.

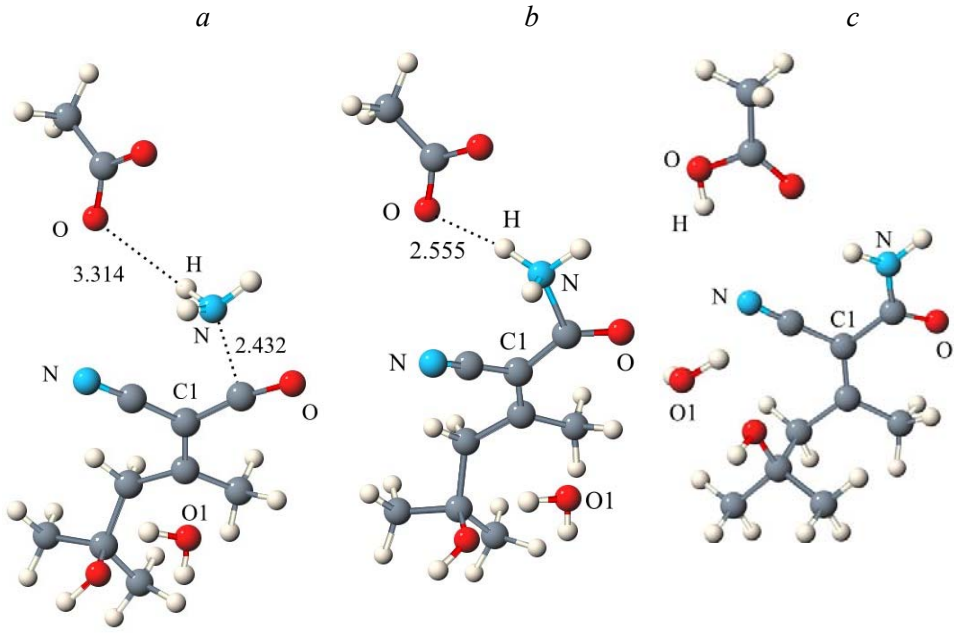


Fig. 6. Reaction of protonated complex with acetate anion: *a*) loss of H_2O molecule, *b*) addition of ammonia molecule to carbonyl group, *c*) reaction products: amide of (*E*)-2-cyano-5-hydroxy-3,5-dimethyl-2-hexenoic acid, acetic acid, and H_2O.

Now, let us examine the course of the reaction when the proton attacks O(2) of the ethoxy group (Fig. 2*a*). Our calculation shows an electrophilic bimolecular elimination reaction giving a ketene derivative, 3,5-dihydroxy-3,5-dimethyl-2-oxomethylenehexanenitrile (**2b**) (Fig. 5).

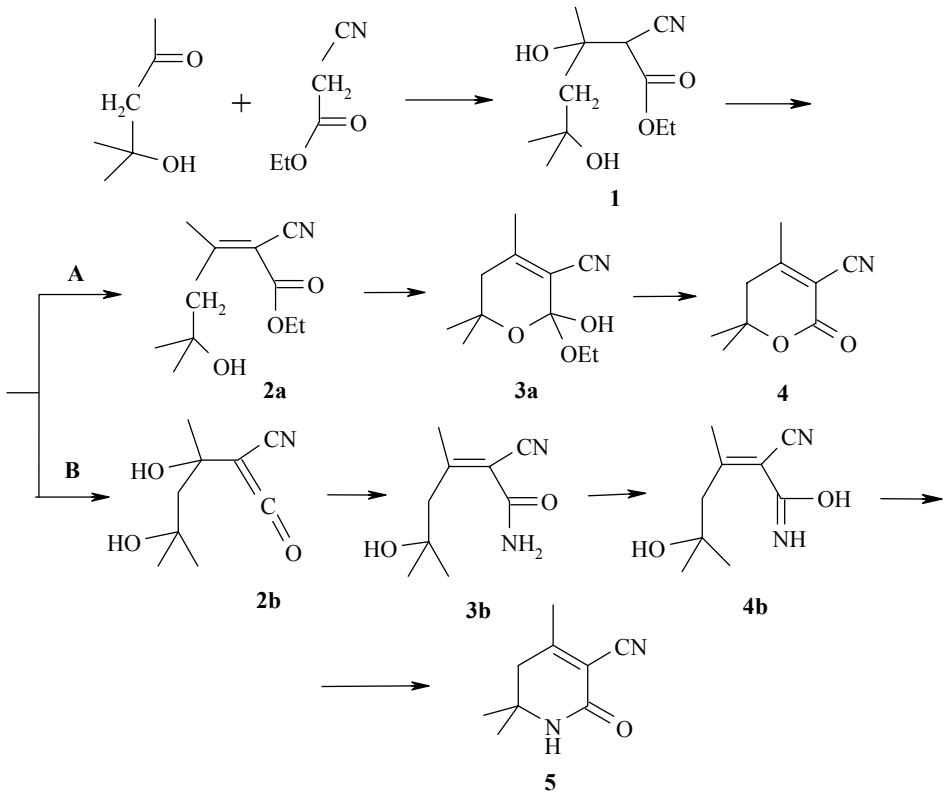
The complex consisting of intermediate **2b** and an ammonia molecule formed in the previous reaction step is activated by capture of a proton by O(1) of the hydroxyl group at C(1). Subsequent reaction of the protonated complex with acetate anion proceeds spontaneously (ΔH = -185.5 kcal/mol) (Fig. 6).

A water molecule is initially lost from C(1) (Fig 6*a*). Then, a molecule of NH_3 adds to this carbon atom (Fig. 6*b*) and capture of one of the hydrogen atoms by an acetate anion leads to the amide of (*E*)-2-cyano-5-hydroxy-3,5-dimethyl-2-hexenoic acid (**3b**) (Fig. 5*c*).

In previous work [5], we have shown that the amide form of a chemical compound readily converts to the iminol tautomer by the action of ammonium acetate. Thus, under the conditions of the reaction studied, **3b** will convert to 2-cyano-5-hydroxy-3,5-dimethyl-2-hexenimidic acid (**4b**). According to our previous work [5], **4b** will convert through intramolecular nucleophilic substitution into 4,6,6-trimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile (**5**), i.e., into the final reaction product through pathway **B** (Scheme 1).

Thus, our study has shown that the reaction of 4-hydroxy-4-methyl-2-pentanone with ethyl cyanoacetate in the presence of ammonium acetate is a consecutive-parallel multistep domino process. The regioselectivity of the reaction results from the direction of the electrophilic attack on adduct **1** formed in the first step. Upon attack by the hydroxyl group proton, the reaction proceeds through pathway **A**, which consists of consecutively formed intermediates **2a** and **3a** and, then, lactone **4** as the final product (Scheme 2).

Scheme 2



Pathway **B** occurs when the proton adds to the ethoxy group oxygen atom. Ketene **2b** is formed initially and, in the presence of excess ammonium acetate, converts to amide **3b**, whose iminol tautomer **4b** then converts to the reaction product, lactam **5**.

We should note the increasing recent interest in domino reactions due, primarily, to the search for new strategies for the synthesis of complex organic compounds. Various aspects of this subject have been discussed in many reviews and monographs
[7-12].

EXPERIMENTAL

The quantum-chemical calculations were carried out using the AM1 semiempirical method [2] in the MOPAC 6.0 program package [13]. The complete optimization of the geometrical parameters of all the structures and reaction complexes was performed with key words of the EF and PRECISE programs. Preliminary localization of the transition states was carried out using the reaction coordinate method. The subsequent search was carried out by minimization of the gradient norm (NLLSQ). Verification of the nature of the stationary points (minima and maxima) of the potential energy surface was carried out by analyzing the vibrational frequencies of the system. The computer design of the reaction systems and post processing visualization were carried using the ChemCraft [14] and Jmol programs [15].

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