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QUANTUM-CHEMICAL INVESTIGATION OF THE MECHANISM OF CYCLOCONDENSATION OF 4-HYDROXY-4-METHYLPENTAN-2-ONE WITH CYANOACETAMIDE USING THE AM1 METHOD

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

The mechanism of formation of 4,6,6-trimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile from 4-hydroxy-4-methylpentan-2-one and cyanoacetamide in the presence of ammonium acetate has been studied by the AM1 method. It was found that, under the reaction conditions, the amide is readily converted to an iminol tautomeric form which takes part in subsequent reaction. It was shown that the reaction is a cascade process forming two intermediates. The final product 4,6,6-trimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile is formed from the product of a Knoevenagel condensation via an intramolecular nucleophilic substitution mechanism. On the basis of the activation energies obtained it can be deduced that the limiting stage is the deprotonation process of the cyanoacetiminol.

Keywords: lactam, cascade reaction, AM1 method, cyclocondensation, Knoevenagel reaction, quantum-chemical calculations.

Heterocyclic compounds are one of the most widely distributed natural classes of organic compounds and are extensively used in chemistry, medicine, biology, and technology [1, 2]. Six-membered lactams such as 4,6,6-trimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile and its derivatives are potential cardiovascular, anticancer, and neurotropic drugs [3]. The method of cyclocondensation is often used for the preparation of heterocyclic compounds including lactams but data concerning the mechanism of this type of reactions is scarce [4].

We have shown that the reaction of 4-hydroxy-4-methylpentan-2-one with cyanoacetamide in the presence of ammonium acetate gives 4,6,6-trimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile [5]:

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The investigation of the mechanism of such reactions is of great interest both from a practical and a theoretical viewpoint. The mechanism of a chemical reaction is a set of elementary stages which resulting the conversion of starting reagents to final products. Full information regarding the mechanism must include data concerning the sequence of changes in geometry and energy of each of the participants in the reaction from the point of view of the pathway leading from the starting to the final state. However, the identification of these characteristics (with rare exception) does not lend itself to direct experimental determination. Hence the finding of critical parameters of reactions demands the drawing together of theoretical approaches [4].

Theoretical methods are of special importance in cases of the absence of reliable information about the reaction course, e.g. activation energy, composition, and structure of potential intermediates, life-time etc.

We have used the semiempirical AM1 quantum-chemical method [6]. The choice of method is due to its ability to calculate activation energy, proton affinity, and deprotonation enthalpy in good agreement with experimental data [7]. Also, for addition and cyclization reactions the AM1 method gives reliable results whose degree of fit is comparable with the results of *ab initio* levels [8].

Modeling the interaction of cyanoacetamide with catalyst has shown that in the equilibrium state the mutual disposition of the ammonium cation, the cyanoamide molecule, and acetate anion can prove favourable for a tautomeric conversion of the amide group (Fig. 1a). The distance between the terminal atom O(1) of the cyanoacetamide and the nearest atom H(1) of the ammonium cation was chosen as the reaction coordinate. The presence of such a transition state is characterized by the low value of 2.9 kcal/mol for the activation energy. After overcoming the system saddle point a transfer of atom H(1) to atom O(1) occurs and the acetate anion captures atom H(2) of the amide group. As a result of such a rearrangement an iminol tautomer of the cyanoacetamide and molecules of ammonia and acetic acid are formed (Fig. 1b).

The change in enthalpy of the system counted from the transition state is -33.5 kcal/mol. Evidently the corresponding value (with a positive sign) will be the activation energy of the reverse reaction of the iminol tautomer form to the amide. The energetic profile of the tautomeric reaction converting the cyanoacetamide to the cyanoacetiminol form obtained by the method of intrinsic reaction coordinates (IRC) is shown in Fig. 2.

As a rule, an amide tautomeric form for chemical compounds is thermodinamically more stable than an iminol [9]. This trend also occurs in our case when applied to isolated tautomers. Calculation shows that the cyanoacetamide form is approximately 14.5 kcal/mol more thermodinamically stable than the cyanoacetiminol structure. However, as we observe, in the conditions of the studied reaction the iminol tautomer form predominates and takes part in subsequent reaction stages.

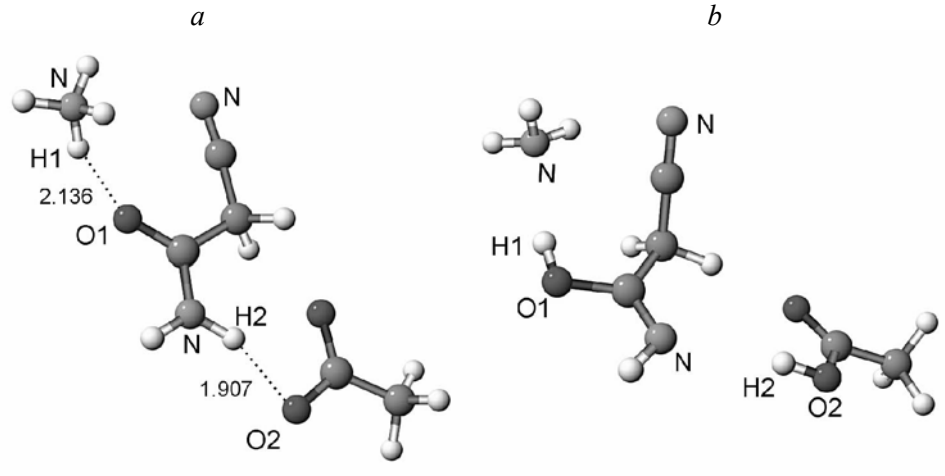


Fig. 1. Tautomeric transformation reaction of the cyanoacetamide: *a* – initial state: *b* – final system state consisting of the iminol tautomer and molecules of acetic acid and ammonia (distances give in angstroms).

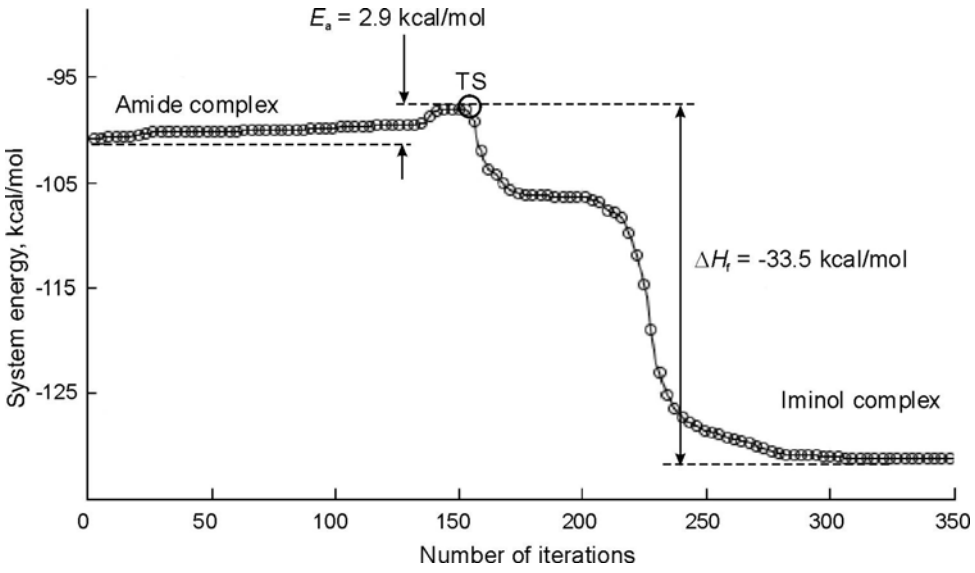


Fig. 2. Energetic profile of the tautomeric transformation of cyanoacetamide obtained by the IRC method (TS — transition state).

In our opinion the activation of the reagents can occur in the following manner. Initial interaction of the cyanoacetiminol with acetate anion forms the stable intermediate complex with an enthalpy of formation of -28.3 kcal/mol. Subsequently the methylene group of the cyanoacetiminol undergoes attack by acetate anion causing deprotonation of the cyanoacetiminol. The activation energy of this process is 12.8 kcal/mol. In the carbinol formed the greatest negative charge (-0.544) is found on the carbon atom closest to the cyano group.

At the same time there occurs in diacetone alcohol in the presence of catalyst components a marked redistribution of electron density leading to a strengthening of the nucleophilic properties of the carbonyl group oxygen atom. The negative charge on it increases from -0.325 to -0.480 which facilitates transfer of a proton from the ammonium cation to the diacetone alcohol molecule. The calculated activation energy for such process is E_a = 7.3 kcal/mol. In the cation formed the highest positive charge (0.364) is found on the carbon atom of the protonated carbonyl group.

The reaction between both activated particles (the protonated diacetone alcohol and the deprotonated cyanoacetyliminol) was further considered. In the starting state chosen by us (Fig. 3a) the distance between the oppositely charged atoms C(1) and C(2) is 3.334 Å. The reaction between them takes place spontaneously and gives an adduct with a single C–C bond (Fig. 3b).

The calculated bond length C(1)–C(2) (1.561 Å) agrees with standard experimental values [10]. The enthalpy of the reaction ΔH = -145.1 kcal/mol. According to IUPAC nomenclature rules the adduct has the designation 2-cyano-3,5-dihydroxy-3,5-dimethylhexanimidic acid.

It is seen from Fig. 3b that the hydroxyl group at C(1) and atom H(1) in the obtained adduct are mutually *trans*-related. Such a positioning favors the occurrence of a stereospecific *E*2 elimination reaction through which a proton separates from one of the neighboring carbon atoms and the nucleophile from the other to form a multiple bond between these carbon atoms [11].

Activation of the adduct is modeled by its interaction with a proton placed in a starting position at a distance of 2.817 Å from the O(1) atom of the hydroxyl group. The addition of the proton to this atom occurs spontaneously with ΔH = -142.9 kcal/mol.

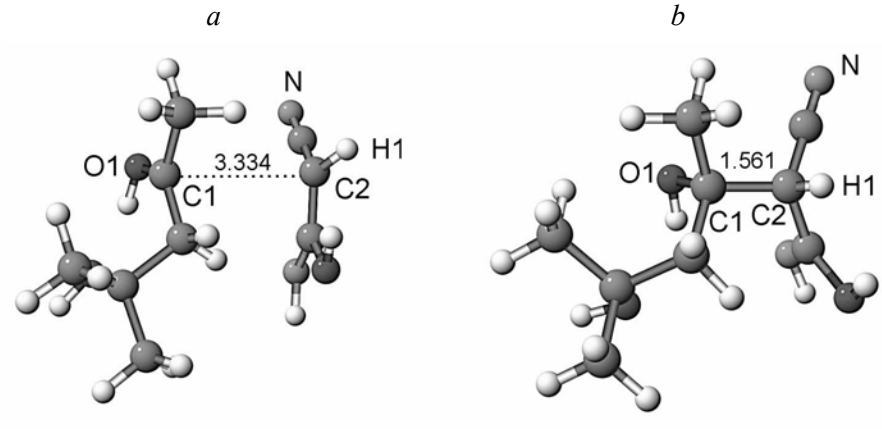


Fig. 3. Reaction between the protonated diacetone alcohol and deprotonated cyanoacetyliminol: *a* – initial state; *b* –reaction product: 2-cyano-3,5-dihydroxy-3,5-dimethylhexanimidic acid (distances given in angstroms).

The reaction of the protonated adduct with acetate anion was also considered. As a result of a barrierless approach of these particles a neutral complex is formed with a high heat of complex formation (ΔH = -107.4 kcal/mol) (Fig. 4a). The distance between the O(2) and H(1) atoms is 1.925 Å.

Following reaction of proton H(1) the transfer from the protonated adduct to the acetate anion takes place with a small activation energy E_a = 1.6 kal/mol. After crossing the system saddle point there is initially observed an addition of proton H(1) to atom O(2) of the acetate anion and then a molecule of water (leaving nucleophile) separates from atom C(1) (Fig. 4b). As a result, the bond between atoms C(1) and C(2) becomes multiple and is characterized by a length of 1.354 Å which is in agreement with a standard double bond value [10]. The enthalpy of this reaction stage is -57.1 kcal/mol. The obtained 2-cyano-5-hydroxy-3,5-dimethyl-2-hexenimidic acid intermediate is the product of an aldol Knoevenagel condensation [12].

In this compound the greatest negative charge (-0.349) is localized on the O(2) atom of the hydroxyl group at the isopropyl C(3) atom. It might be expected that this atom will undergo attack by an electrophilic particle. Fig. 5a shows the starting position for modeling of the reaction of the Knoevenagel

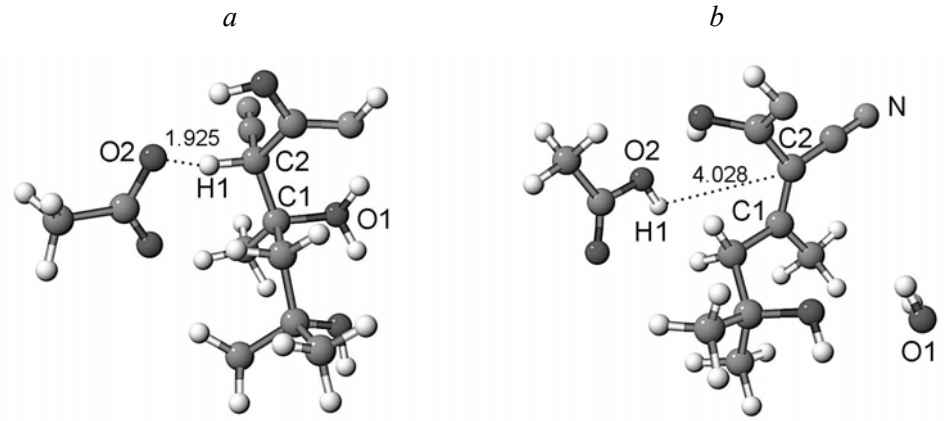


Fig. 4. Reaction between the protonated adduct and acetate anion: *a* – pre-reaction complex, *b* –reaction products: 2-cyano-5-hydroxy-3,5-dimethyl-2-hexenimidic acid, acetic acid, and water (distances given in angstroms).

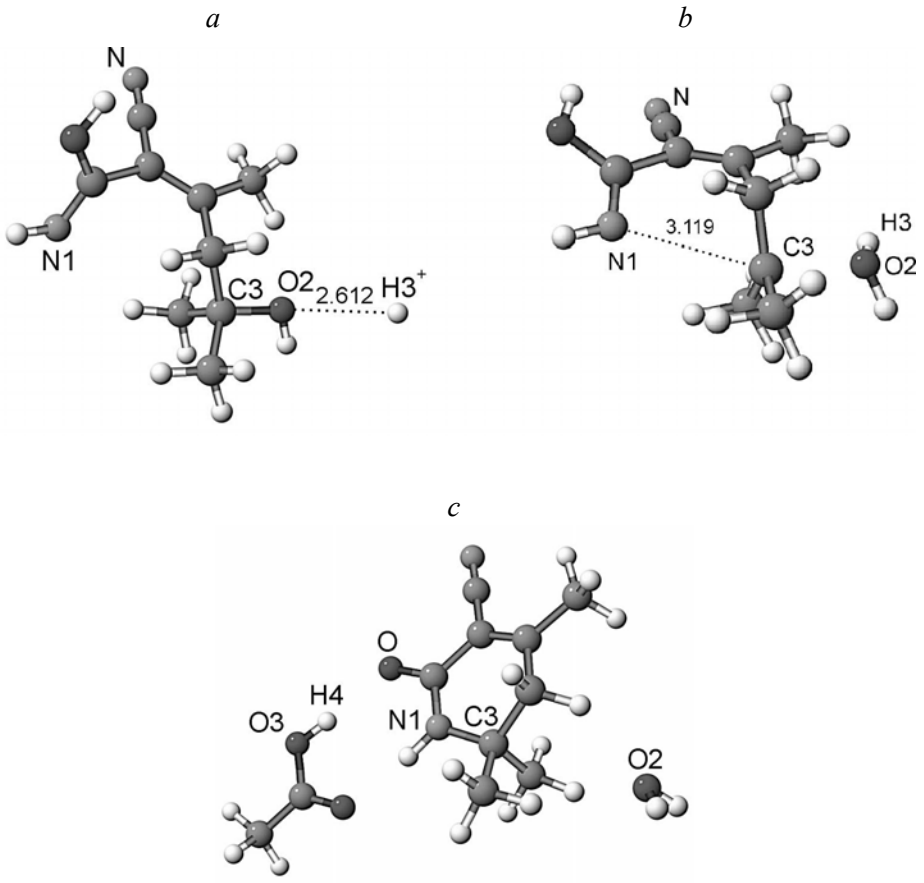


Fig. 5. Interaction of the Knoevenagel reaction product with a proton: *a* – initial state; *b* – intermediate state; *c* –reaction products: cyclic carbocation and water (distances given in angstroms).

product with a proton. The reaction occurs spontaneously. Post processing visualization shows that at the moment of addition of the proton to the hydroxyl group oxygen atom the distance between atom C(3) and atom N(1) of the iminol group is 3.932 Å.

An observed stepwise change in the geometry of the cation subsequently leads to a decrease in the distance between the negatively charged (-0.298) atom N(1) and atom C(3) carrying a positive charge (0.342). When this distance reaches 3.119 Å a separation of a water molecule of occurs from atom C(3) (Fig. 5b). Subsequent to this (after 10 cycles of optimization) the bond closes between atoms C(3) and N(1) to form the cyclic carbocation shown in Fig. 5c. The enthalpy of this reaction ΔH = -180.3 kcal/mol. Thus the given reaction stage is an intramolecular nucleophilic substitution with an asynchronous elimination-addition mechanism.

The final stage of the studied reaction is the interaction of the cyclic carbocation with acetate anion. The starting position selected by us is shown in Fig. 6a. The distance between atoms H(4) and O(3) is 4.056 Å. The reaction occurs without a barrier. After approach of the reacting components and capture of a proton of the hydroxyl group of the carbocation by the oxygen atom of the acetate anion the final heterocyclocondensation product 4,6,6-trimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile is formed (Fig. 6b). The enthalpy of this reaction stage is ΔH = -143 kcal/mol.

Hence the study we have carried out has shown that the reaction of diacetone alcohol with cyanoacetamide in the presence of ammonium acetate is a multi-stage cascade process which includes the consecutive formation of two intermediates and finishes with formation of the final 4,6,6-trimethyl-2-oxo-

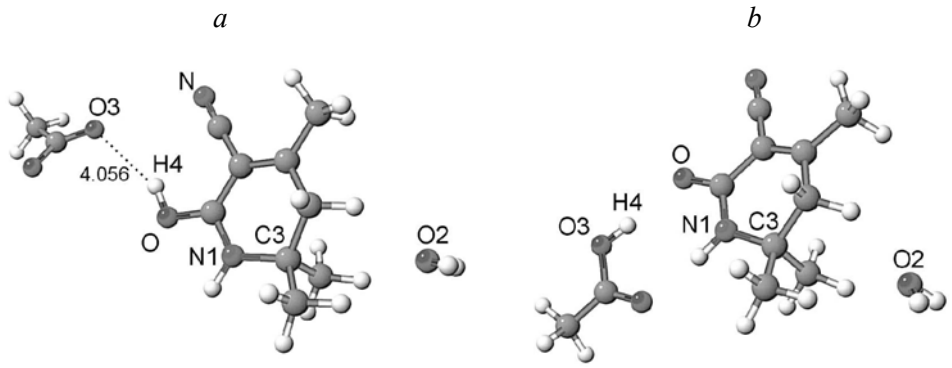
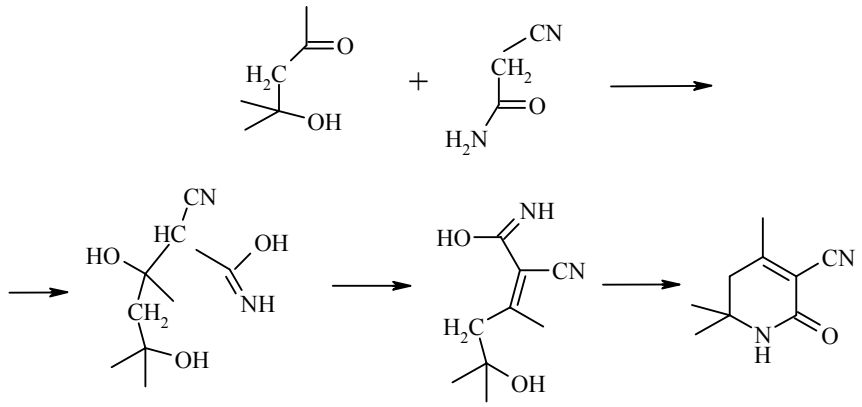


Fig. 6. Reaction of the cyclic carbocation with acetate anion: *a* – initial state; *b* – final cyclocondensation product: 4,6,6-trimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile (distances given in angstroms).

1,2,5,6-tetrahydropyridine-3-carbonitrile reaction product by an intramolecular nucleophilic substitution. Judged by the observed activation energies the limiting stage of the reaction is the deprotonation process of the cyanoacetiminol.



EXPERIMENTAL

Quantum-chemical calculations were carried out using the semiempirical AM1 method [6] as implemented in the MOPAC 6.0 program package [13]. A full optimization of the geometrical parameters for all of the structures was carried out with keyword PRECISE The reaction coordinate method was used for preliminary localization of the transition states. A further search was carried out by minimization of the gradient norm. Verification of the nature of the stationary points (minimum / transition state) of the potential energy surface was carried out by analysis of the vibrational frequencies of the system. The method of intrinsic reaction coordinates was used to obtain the energy profile of the tautomeric conversion of the cyanoacetamide. The computer design of the reaction systems and post processing visualization were achieved using the ChemCraft [14] and Jmol [15] programs.

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