

QUANTUM-CHEMICAL MODELING OF THE REACTION OF 3-PYRIDINE- CARBALDEHYDE WITH 3-CYANO- 4,5,5-TRIMETHYL-2(5H)-FURANONE

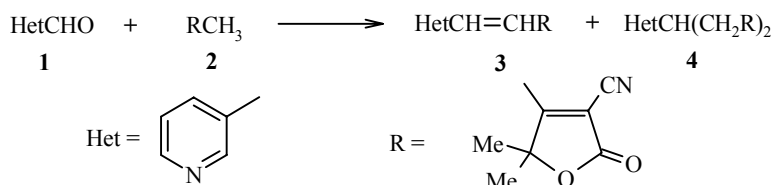
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The condensation of pyridinecarbaldehydes with 3-cyano-4,5,5-trimethyl-2(5H)-furanone and 3-cyano-4,6,6-trimethyl-5,6-dihydro-2(2H)-pyranone leads to the formation of the products of crotonic condensation and compounds of the Michael adduct type. A model investigation of the mechanism by the semiempirical AM1 quantum-chemical method for the case of the reaction of 3-pyridinecarbaldehyde with 3-cyano-4,5,5-trimethyl-2(5H)-furanone showed that the products can be formed in parallel from one and the same intermediate compound.

Keywords: 3-pyridinecarbaldehyde, 2(5H)-furanone, condensation, semiempirical AM1 method.

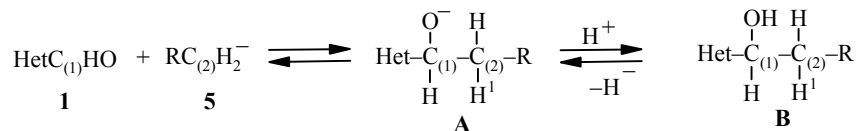
It has been reported in the literature that the condensation of 2- and 4-pyridinecarbaldehydes and 2-quinolinecarbaldehyde with acetophenone and also of 2-quinolinecarbaldehyde with acetaldehyde in the presence of an alkaline catalyst takes place by an untraditional mechanism, and compounds of the Michael adduct type are formed together with the product of crotonic condensation [1-3]. There are at present hardly data on the unusual reaction mechanism. It was suggested that the Michael adducts could be formed by aldol condensation of the aldehyde and the CH acid followed by dehydration and addition of a second molecule of the nucleophilic reagent at the double bond of the obtained olefin [1, 3].

We established a similar reaction in the interaction of 2-, 3-, and 4-pyridinecarbaldehydes with such γ - and δ -lactones as 3-cyano-4,5,5-trimethyl-2(5H)-furanone and 3-cyano-4,6,6-trimethyl-5,6-dihydro-2(2H)-pyranone [4]. In the presence of catalytic amounts of sodium hydroxide in methanol solution at 20-78°C the yield of the Michael product amounted to 25-65%. In the present work we undertook a model quantum-chemical investigation of the reaction mechanism for the case of the reaction of 3-pyridinecarbaldehyde (**1**) with 3-cyano-4,5,5-trimethyl-2(5H)-furanone (**2**), leading to the product of crotonic condensation **3** and the product of Michael addition **4**.



Latvian Institute of Organic Synthesis, Riga; e-mail: leite@osi.lanet.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 748-754, June, 2001. Original article submitted May 23, 2000.

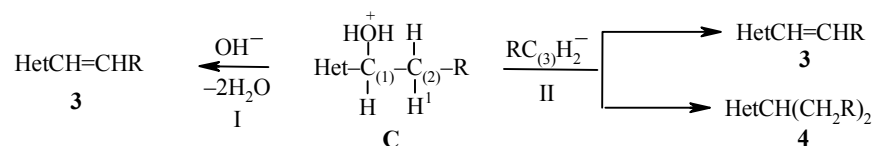
Starting from the general scheme of the mechanism proposed for the condensation of aldehydes with CH acids in the presence of an alkaline catalyst [5] it can be assumed that attack on the aldehyde by the RCH_2^- anion **5**, formed in the presence of the alkaline catalyst, leads to the intermediate **A**, which is converted by adding a proton into the intermediate **B**. The unsaturated product **3** is formed as a result of the elimination of water from the intermediate **B**.



In order to assess the probability of the individual postulated stages of condensation and one or the other path to the formation of the reaction products we undertook a quantum-chemical investigation of the energetics of the processes in the reaction of the reagents and the transformation of the supposed intermediates by the semiempirical AM1 method. Calculation of the potential energy surface (PES) of the reaction system, consisting of the trimethylfuranone **2** and the OH^- ion, shows that the formation of the anion **5** takes place without a barrier. The heat of reaction amounts to -378.9 kJ/mole.

During investigation of the interaction of the molecule of the aldehyde **1** with the anion **5** it was established that for the formation of the intermediate **A** the reacting system must pass through a transition state, overcoming an energy barrier of 90.8 kJ/mole. The heat of formation of the intermediate **A** is -3.3 kJ/mole. Analysis of the frequencies of the normal vibrations shows that they are only positive for the intermediate **A**, and this structure consequently corresponds to a minimum on the PES of the system. The anion **A** is characterized by a C(1)–C(2) bond length of 1.631 Å and high proton affinity (1257.7 kJ/mole). It follows from the nature of the variation of the heat of reaction during the transformation of the anion **A** into the intermediate **B** that proton capture is realized spontaneously.

As shown by the calculations, the source of the proton in this case may be complexes representing hydrated sodium ions: $[\text{H}_2\text{O}\cdots\text{Na}]^+$. After addition of the proton the C(1)–C(2) bond becomes stronger, and its length in the intermediate **B** amounts to 1.538 Å, which corresponds to the experimentally determined value for a single C–C bond [6].



The intermediate **B** is also characterized by fairly high proton affinity (520.0 kJ/mole). Protonation takes place without a barrier and contribute to a further decrease in the length of the C(1)–C(2) bond in the intermediate **C** to 1.508 Å. The heat of protonation is -280.5 kJ/mole. The subsequent transformation of the intermediate **C** depends on the nature of the attacking nucleophile. During attack by the hydroxyl group the unsaturated product (**3**) is formed (path I).

Figure 1 shows the structure of the reaction system consisting of the intermediate **C** and the OH^- anion (a), the intermediate complex in which the OH^- anion is connected with the H^1 atom by a hydrogen bond (b), and the reaction products in the form of compound **3** and two molecules of water (c). Visualization of the process shows that the removal of the first water molecule takes place when the distance from H^1 to the O of the OH^- group amounts to 3.856 Å. With the approach of the hydroxyl group to a distance of 1.239 Å a bridge structure is formed through hydrogen bonds H^1-O and $\text{H}^1-\text{C}(2)$ (Fig. 1, b). The $\text{H}^1-\text{C}(2)$ bond is then broken, a second

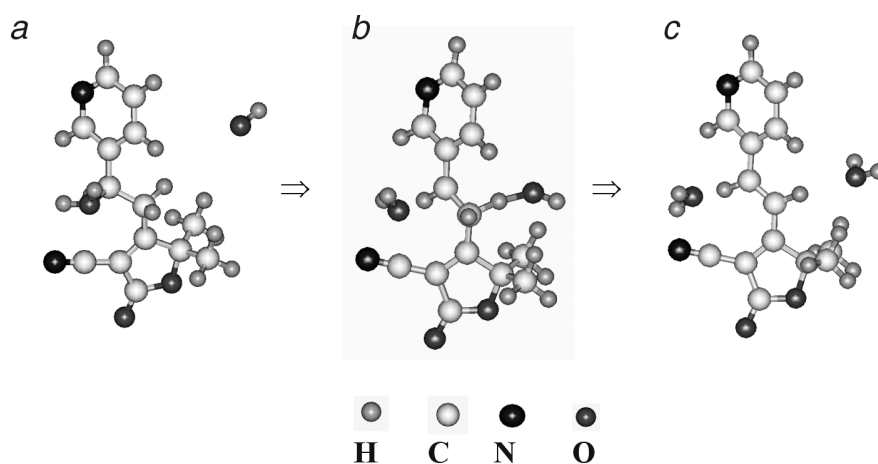


Fig. 1. The transformations of the protonated intermediate **C** in the reaction with the OH^- group (according to the data from the semiempirical AM1 method): a) Reaction system consisting of the protonate intermediate **C** and the OH^- group; b) intermediate complex with the $\text{H}^1\text{-O-H}$ bridging bond; c) reaction products – compound **3** and two water molecules.

water molecule leaves, and compound **3** is formed (Fig. 1, c). The calculated length of the double bond (1.348 \AA) agrees with the experimental value [6]. The predicted heat of formation of the crotonic condensation product **3** in this path amounts to -973.0 kJ/mole .

The reaction of the anion **5** with the intermediate **C** (path II) proceed regioselectively and cause the formation of the two reaction products **3** and **4** depending on the direction of attack. During attack by the anion on the H atom [starting distance $\text{C}(3)\text{-H}^1$ 3.725 \AA , angle $\text{C}(1)\text{-C}(2)\text{-C}(3)$ 105°] after approach of the reagents to a distance of 3.671 \AA between the $\text{C}(2)$ and $\text{C}(3)$ atoms dehydration occurs. With approach of the $\text{RC}(3)\text{H}_2^-$ anion to the $\text{C}(2)$ atom to a distance of 2.806 \AA an intermediate complex is initially formed through a hydrogen bond $\text{C}(2)\text{-H}^1\text{-C}(3)$. The $\text{C}(2)\text{-H}^1$ bond is then broken, and the product **3** and the initial methylfuranone **2** appear. In this case the heat of formation of the pyridylvinylactone **3** amounts to -605.4 kJ/mole .

Consequently, path I to the formation of this product, according to prediction, is preferred on account of the alignment of the proton affinity values of the anions OH^- and **5** (1505.9 and 378.9 kJ/mole respectively). Attack by the anion **5** on the other reaction center of the intermediate **C**, i.e., the $\text{C}(1)$ atom [starting distance between $\text{C}(1)$ and $\text{C}(3)$ 3.348 \AA , angle $\text{C}(3)\text{-C}(1)\text{-C}(2)$ 89.9°], gives rise to departure of a water molecule on approach of the reagents to a distance of 3.068 \AA and the subsequent formation of a compound of the Michael adduct type **4**. The heats of formation of the products **3** and **4** in this case are comparable (-605.4 and -656.1 kJ/mole respectively), and their appearance must therefore be equally probable from the thermodynamic standpoint.

Thus, on the whole (with regard to both paths) the formation of compound **3** is more probable than the formation of compound **4**. In fact, at room temperature the yield of the crotonic condensation product **3** is higher than the yield of the product **4** (Table 1).

If the temperature is increased to 78°C only compound **3** is formed. If the transformation of the protonated intermediate **C** along paths I and II is regarded as elimination and substitution, it should be noted that the above-mentioned experimental fact agrees with the idea existing in the literature that the elimination reaction should predominate with increase of temperature [5, 7].

TABLE 1. The Effect of Temperature and the Amount of Catalyst on the Direction of Condensation Reaction*

Aldehyde:NaOH molar ratio	Reaction Temperature, °C	Time, h	Yield of product, %	
			crotonic condensation	Michael type adduct
1 : 0.06	20	2.5	45.0	33.8
1 : 0.06	78	2.5	39.7	—
1 : 0.3	20	2.5	27.0	—
—	20	2.5	<1%	<1%
—	20	14.0	18.4	56.3

*Ratio of aldehyde **1** and furanone **2** 1:1.

On the other hand only product **3** is formed if the concentration of the catalyst in the reaction zone is increased to an aldehyde:NaOH ratio of 1:0.3, since (as expected) the rate of the transformation along path I is increased considerably. At the same time path II becomes more favorable in the absence of the catalyst, and the main product is compound **4**. Thus, the obtained experimental material favors the proposed model of condensation of the aldehyde **1** with the lactone **2**.

The formation of compound **4** is accompanied by inversion of the configuration of the tetrahedral carbon atom (Walden inversion), indicating that the reaction takes place by an S_N2 mechanism of bimolecular nucleophilic substitution [7]. Figure 2 shows the molecular structure of compound **4**, optimized by the AM1 method. According to the calculations, the angle between the planes of the furan rings amounts to 60°, and the angles between the latter and the plane of the pyridine ring amount to 161.9 and 121.6°.

The nature of the dependence of the heat of formation of the product **3** from the complex **C** and the OH⁻ anion on the number of iteration steps (*n*) during optimization indicates the absence of an activation barrier at this stage of the reaction (Fig. 3). According to the presented curve, the energy of the system changes most abruptly (by ~419 kJ/mole) at the moment of formation of the hydrogen bond and elimination of the water molecule. (The arrow corresponds to the structure shown in Fig. 1b.)

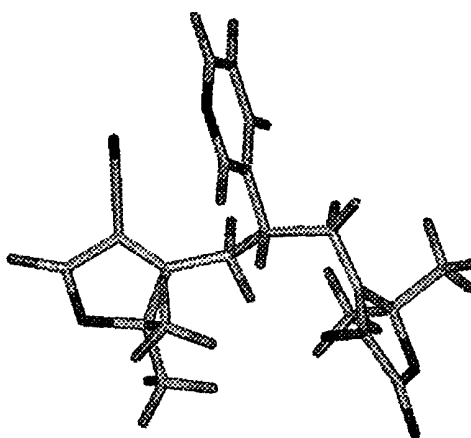


Fig. 2. The three-dimensional structure of the molecule of 4,4'-[2-(3-pyridyl)-1,3-propanediyl]bis[5,5-dimethyl-2-oxo-2(5H)-furan-3-carbonitrile] **4** according to data from the semiempirical AM1 method.

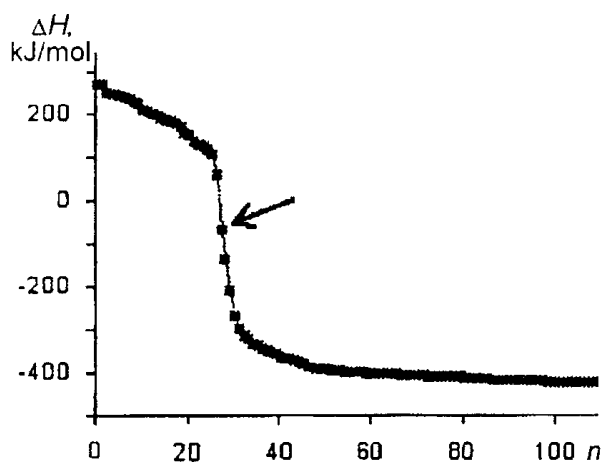


Fig. 3. The change of the heat of formation of the system of the protonated intermediate C–OH⁺ group during the optimization leading to the product **3**. (The arrow corresponds to structure b in Fig. 1.)

In our opinion, the low probability proposed in the literature for the formation of compound **4** by addition of a second molecule of methylfuranone at the double bond of the crotonic condensation product **3** is also favored by the following. According to the calculated data, compound **3** is fairly strongly polarized (dipole moment 5.5 D), but the olefinic carbon atoms most likely have an excess of electron density (their calculated charges are -0.062 and -0.156), which is unfavorable for the addition of a second anion **5** to the nucleophilic olefin **3**. According to the results of thin-layer chromatography, both products are formed almost simultaneously under the reaction conditions.

Thus, quantum-chemical analysis of the mechanism of the condensation of 3-pyridinecarbaldehyde with trimethylfuranone shows that the parallel formation of the two reaction products is possible from one and the same intermediate compound, representing the protonated product of the aldol condensation of 3-pyridinecarbaldehyde with 3-cyano-4,5,5-trimethyl-2(5H)-furanone. The reaction of the intermediate product with the hydroxyl group followed by dehydration leads to the pyridylvinylfuranone. At the same time the reaction of this intermediate with the trimethylfuranone anion takes place regiospecifically and can lead to the formation of both the crotonic condensation product and the compound of the Michael adduct type.

EXPERIMENTAL

The yields of the reaction products were determined by HPLC on a Nova-Pak Silica column (3.9×150 mm). The eluent consumption was 1 ml/min (2% methanol + 98% chloroform). The detector was spectrophotometric ($\lambda = 254$ nm). The ¹H NMR spectrum was recorded on a Mercury 200B instrument (200 MHz) in DMSO-d₆ with TMS as internal standard.

4,4'-[2-(3-Pyridyl)-1,3-propanediyl]bis(5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carbonitrile) (4). A solution of 3-pyridinecarbaldehyde (0.35 g, 3.23 mmol), 3-cyano-4,5,5-trimethyl-2(5H)-furanone (0.98 g, 6.47 mmol), and sodium hydroxide (0.00735 g, 0.18 mmol) in ethanol (3.5 ml) was stirred at room temperature for 6 h. The precipitate was filtered off and recrystallized from alcohol. We obtained 0.58 g (1.48 mmol, 45.7%) of compound **4**; mp 154-156°C (decomp.). ¹H NMR spectrum (DMSO-d₆), δ , ppm, *J* (Hz): 1.32 and 1.55 (6H and 6H, s and s, 4 gem-CH₃); 3.14-3.39 (4H, m, CH₂); 3.88 (1H, m, CH); 7.39 (1H, m, *J* = 8.0 and 4.6, 5-H_{Het}); 7.91 (1H, m, *J* = 8.0 and 2.0, 4-H_{Het}); 8.50 (1H, m, *J* = 4.6 and 1.4, 6-H_{Het}). Found %: C 67.55; H 5.37; N 10.68. C₂₂H₂₁N₃O₄. Calculated %: C 67.51; H 5.41; N 10.74.

The synthesis of compound **3** and its physicochemical characteristics were presented in [4].

The quantum-chemical calculations were carried out by the AM1 method using the MOPAC 5.0 software [8] with full optimization of the geometry of the reagents, reaction products, and reaction systems in the BFGS regime [9]. The transition state of the condensation reaction of pyridinecarbaldehyde with the furanone anion was first localized in the reaction coordinate, taken as the distance between the C(1) and C(2) atoms of the reacting molecules. Further refinement of the transition state was realized by minimization of the gradient norm (the NLLSQ version). The proton affinity was calculated as the difference between the total energies of the molecule and its protonated form. In view of the absence of 5.0 corresponding parameters in the MOPAC program the sodium atom was modeled in the calculations by quasi-particle "sparkle." Computer design of the reaction system was realized by means of the LabVision software package [11].

Additional information on the Cartesian coordinates of the intermediate complex **A** and also on the changes of the geometry in the course of the reactions, taking place by paths I and II with the formation of compound **4**, can be obtained from the authors on request (e-mail: misha@osi.lv). The XYZ format of the data is suitable for the molecular visualization and animation programs ReView (Jeffrey J. Gosper, Chemistry Department, Brunel University, Uxbridge, Middx, UK, 1996) and XMol Version 1.3.1 (Minnesota Supercomputer Center, Inc., Minneapolis, MN, 1993).

The work was carried out with financial support from the Latvian Science Council (Program "Development of modern methods of organic chemistry with the aim of establishing the industrial production of new medicinal products in Latvia").

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