Oxidative ammonolysis of 3,4-dimethylpyridine on the vanadium oxide catalysts

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Abstract: Oxidative ammonolysis of 3,4-dimethylpyridine on an individual vanadium oxide (V_2O_5) catalyst and binary vanadium oxide catalysts, modified by additions of SnO_2 and ZrO_2, has been studied. A connection between CH-acidity of the methyl groups of the substrate in the gaseous phase and in the chemosorbed state and the sequence of their transformation into a cyano group has been established. It has been shown that nucleophilicity of vanadyl oxygen, calculated by the Density Functional Theory method, increases with V_2O_5 modification by SnO_2 and ZrO_2 additions. Herewith, an increasing yield of 3-methyl-4-cyanopyridine and imide of pyridine-3,4-dicarboxylic acid was observed. A proposed mechanism of the imide of pyridine-3,4-dicarboxylic acid formation has been discussed

Keywords: quantum-chemical method; imide of pyridine-3,4-dicarboxylic acid; mechanism; V_2O_5; SnO_2; ZrO_2.

INTRODUCTION

Mono- and dicyanopyridines have become very important in the recent years since they form the starting materials for a number of valuable intermediates of medicines, animal feed additives, food additives and other commodities.[1–3]

Oxidative ammonolysis of mono- and dimethylpyridines is the most rational method for obtaining mono- and dicyanopyridines.[4,5]

Oxidative ammonolysis of dialkylpyridines of the unsymmetrical structure showed that alkyl groups at positions 2 and 4 are more reactive than in positions 3 and 5.[6] Therefore, the primary product of the conversion of 2,3-dimethylpyridine on the V–Sn–Fe oxide catalyst is 2-cyano-3-methylpyridine.

In the oxidative ammonolysis of 2,5-dimethyl- and 2-methyl-5-ethylpyridines, the methyl group in position 2 reacts first to form 2-cyano-5-methyl- and 2-cyano-5-ethylpyridine, respectively. It was established[7] that the interaction of

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the pyridine base and the acid site on the catalyst surface causes increase in the activity at the 2-position in all stages of the oxidative transformation of 2-methyl--5-ethylpyridine.

Oxidative ammonolysis of 2,5-lutidine was studied on a series of vanadium oxide catalysts (V_2O_5–Al_2O_3, V_2O_5–K_2O–Al_2O_3, V_2O_5-pumice stone, V_2O_5––MoO_3-pumice stone, V_2O_5–Cr_2O_3-pumice stone). It was established that a methyl group in position 2 is oxidized into 2-cyano-5-methylpyridine, which then transforms into 2,5-dicyanopyridine.[8] Okada *et al.*[9] have studied oxidative ammonolysis of isomeric dimethylpyridines on the catalyst 5 % Cr_2O_3–9 % *γ*-Al_2O_3 at 360 °C. It was established that the activity of methyl groups in positions 2-(6-) or 4- is higher than that in position 3-(5-). In the case of 3,4-dimethylpyridine a methyl group in 4-position is oxidized by formation of monocyano-methylpyridine. Selectivity of the formation of 3-methyl-4-cyanopyridine makes up 92 %. Methyl groups of 2,4-dimethylpyridine showed a close reactivity: 2-methyl-4-cyanopyridine and 4-methyl-2-cyanopyridine were obtained with the same selectivity (42 %). The reasons of the observed regularities are not discussed in the article, but they are undoubtedly related to the structural features of the initial compounds and the nature of their interaction with the catalyst.

Earlier we had carried out modeling of chemosorption of dialkylpyridines on the surface of vanadium oxide catalyst with the participation of active centers of different nature. It was shown that the sequence of transformation of methyl substituents of dialkylpyridines into cyano group was determined by the enthalpy value of their deprotonation.[6]

The main goal of this work was an experimental and quantum chemical study of the reactivity of methyl groups of 3,4-dimethylpyridine in oxidative ammonolysis. The tasks of the work included studying the effect of oxide-promoters, SnO_2 and ZrO_2, on the activity of binary vanadium oxide catalysts.

<div align="center">EXPERIMENTAL</div>

Materials

Initial 3,4-dimethylpyridine was purchased from Sigma-Aldrich (583-58-4) and used without further purification.

An individual vanadium oxide (V_2O_5) catalyst and binary catalysts $V_2O_5 \cdot 4MeO_2$ (Me: Sn or Zr) were obtained by mixing the initial oxides of analytical grade in the required mole ratio. Further, the obtained mixture was pressed into tablets and calcined at 650 °C in the air flow for 3 h. The catalysts were ground into grains with the size of 1–2 mm.

Synthesis experiments

Catalytic testing was carried out on a flow-type microreactor with the length of 200 and diameter of 20 mm with the fixed layer of catalyst (0.01 L) at atmospheric pressure. 3,4--Dimethylpyridine and a vaporization zone at 250 °C, mixed with air oxygen and ammonia and finally fed into the microreactor.

The feeding rate of 3,4-dimethylpyridine made up 40 g per 1 L of catalyst per hour. The mole ratio of the reagents was 3,4-dimethylpyridine: O_2:NH_3:H_2O = 1:16:(6–22.5):32. Oxi-

dative ammonolysis was carried out at the temperature interval from 270 to 370 °C. The reaction products were caught up in the air-lift type scrubbers irrigated by water.

Analysis of 3,4-dimethylpyridine ammoxidation products

3-Methyl-4-cyanopyridine after recrystallization from chloroform melted at 46 °C.

Imide of pyridine-3,4-dicarboxylic acid after recrystallization from ethanol melted at 224 °C (with subliming).

Elemental analysis was performed by means of CE440 elemental analyzer.

The IR spectra were recorded on a Nicolet 5700 (Thermo Elecrtron Corporation) spectrophotometer and the wavenumbers are given in cm^{-1}. The NMR spectra were recorded on a JNM-ECA Jeol 400 in dimethyl sulfoxide-d_6 and the chemical shifts (δ) are expressed in ppm values downfield from TMS.

The characterization data for 3-methyl-4-cyanopyridine and imide of pyridine-3,4-dicarboxylic acid are given in the Supplementary material to this paper.

The reaction products were determined by a gas chromatographic method with a flame-ionization detector. The products of deep oxidation were analyzed by a gas chromatographic method with a thermal conductivity detector.[10]

Computing details of quantum-chemical modeling

The description of quantum chemical calculations is given in the previous article.[10]

Optimization of the geometry of the organic molecules and carbanions in the gaseous phase was carried out by the ab initio method (HF/6-31G*). Modeling of chemisorption was carried by the density functional theory method,[11] using a two-exponent basic set LanL2DZ with an effective core potential.

At non-empirical calculations of energy and optimization of geometry of molecules Born–Oppenheimer approximation that considers the movement of the nucleus, and just assumes that they are not strongly coupled with the changes in the electronic states, was used. For the elimination of possible errors in a definition of the total energy of molecule and taking account of the effect of molecular translation, rotation and vibration, the frequency calculations for initial chemical compounds and their complexes with the optimized geometry's clusters were carried out (*ab initio* method with a different basis sets and DFT method (B3LYP/Lanl2DZ Freq test, temperature = 603.15 K), respectively. For obtaining the exact value of the total energy of a system at zero degrees Kelvin, zero-point energy (*ZPE*, Eq. (1)) must be added to the received E_{tot}. Similarly, for obtaining the exact value of the total energy of the complex at the reaction temperature thermal energy (E_{therm}) of complexes (Eq. (2)) must be added to the received E_{tot}:[12]

$$DE = 2625.5[(E_{anion} + ZPE_{anion}) - (E_{molecule} + ZPE_{molecule})] \qquad (1)$$

$$DE = 2625.5[(E_{anion/cluster} + E_{therm.anion/cluster}) - (E_{molecule/cluster} + E_{therm.molecule/cluster})] \quad (2)$$

The energy of heterolytic cleavage of C−H bond (E_{C-H}) and the enthalpy of deprotonation of the methyl group with proton transfer to vanadyl oxygen (*DE*) and value of proton affinity ($PA_{V=O}$) of vanadyl oxygen was calculated by formulas (3) and (4), respectively:

$$E_{C-H}, DE = 2625.5(E_{ads.carbanion} - E_{ads.mol}) \qquad (3)$$

$$PA_{V=O} = 2625.5(E_{init.} - E_{final}) \qquad (4)$$

The calculations carried out by the GAUSSIAN 09W program, version D.01.[13]

RESULTS AND DISCUSSION

The experimental data of oxidative ammonolysis of 3,4-dimethylpyridine on the V_2O_5, $V_2O_5·4SnO_2$ and $V_2O_5·4ZrO_2$ catalyst are presented in Fig. 1. As seen, at 250–330 °C the main product is 3-methyl-4-cyanopyridine. With a further rise of temperature an increase of initial substance conversion (A), a decrease in the yield of 3-methyl-4-cyanopyridine (B) and the formation of imide of pyridine-3,4-dicarboxylic acid, the product of intramolecular cyclization (C), is observed. Among the reaction products 3-cyano- and 4-cyanopyridines, pyridine and CO_2 are found, the yield of which depends on the reaction conditions and the catalyst used. It has been noted that 3,4-dicyanopyridine is not formed.
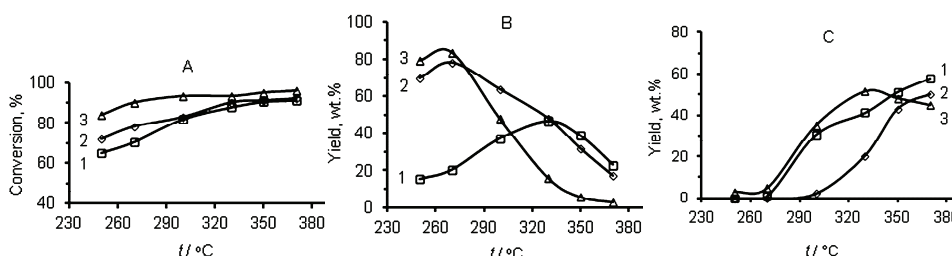

Fig. 1. The effect of temperature and composition of the catalyst on the conversion of 3,4-dimethylpyridine (A), yield of 3-methyl-4-cyanopyridine (B) and imide of pyridine-3,4-dicarboxylic acid (C): 1 – V_2O_5, 2 – $V_2O_5·4SnO_2$, 3 – $V_2O_5·4ZrO_2$.

The yield of 3-methyl-4-cyanopyridine and catalytic activity, estimated by the conversion of 3,4-dimethylpyridine, increases in the order:

$$V_2O_5 < V_2O_5·4SnO_2 < V_2O_5·4ZrO_2$$

It was found that an increase of the mole ratio of NH_3 to 3,4-dimethylpyridine promotes a rise in the yield and selectivity of the 3-methyl-4-cyanopyridine formation on $V_2O_5·4SnO_2$ at 300 °C (Fig. 2). The competing adsorption of 3,4-dimethylpyridine and ammonia on the same acid sites on the catalyst surface leads to decrease the conversion of the initial 3,4-dimethylpyridine.
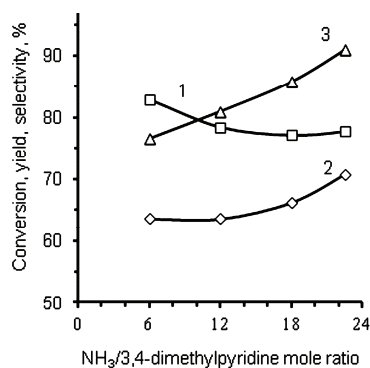

Fig. 2. The effect of NH_3/3,4-dimethylpyridine mole ratio on the conversion (1) of 3,4-dimethylpyridine, and yield (2) and selectivity (3) of 3-methyl-4-cyanopyridine.

Upon interpretation of the experimental data on a relative reactivity of the methyl groups of 3,4-dimethylpyridine it is necessary to take into account that methylpyridines represent weak CH-acids. Under the effect of a strong base they can lose a proton from the methyl group and form a carbanion.[14] In a catalytic reaction a role of a proton acceptor can be played by nucleophilic oxygen of the surface. It is evident that reactivity of the methyl groups is influenced by their CH-acidity.

The experimental data of CH-acidity in the gaseous phase are known only for monomethylpyridines, and at present, these characteristics are not available for dimethylpyridines. That is why with the help of an ab-initio quantum-chemical method (HF/6-31G*) we have calculated deprotonation enthalpy (*DE*), which is an analogue of CH-acidity of the methyl groups of the molecule of the initial compound, coming from the values of total energy of the initial molecule and the corresponding carbanions:

$$PyCH_3 \leftrightarrows PyCH_2^- + H^+ - DE$$
$$DE = E_{tot}(PyCH_2^-) - E_{tot}(PyCH_3) \tag{5}$$
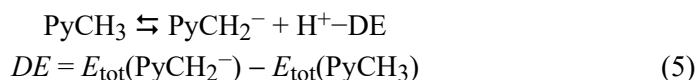
where E_{tot} – total energy of the corresponding compound.

An non-bonding electron pair of carbanion is situated at the highest occupied molecular orbital (HOMO).[15] Stabilization of the intermediate carbanions is a consequence of an interaction of an non-bonding electron pair of carbanion with π-electron system of the pyridine ring. This is favored by the aromatic nature of the analyzed position and the possibility of extensive anion delocalization. Stability of carbanions may be characterized by an energy value of the highest occupied molecular orbitals (E_{HOMO}). A methyl substituent in position 4 has a lower value of *DE* due to the conjugation effect, a higher extent of delocalization of an nonbonding electron pair of the formed carbanion, and the total energy (E_{tot}) of the latter is lower than that of the carbanion in position 3. The results of the ab initio quantum-chemical calculations, presented in Table 1, are in accordance with the notions of classic organic chemistry and experimental data on the sequence of entering of the substituents of 3,4-dimethylpyridine into the reaction (Fig. 1).

Table I shows the results of the quantum-chemical calculations for the isolated molecules of 3,4-dimethylpyridine and its aromatic analogue with the ortho-located methyl substituents – *o*-xylene. The data on the primary products of their transformation, 3-methyl-4-cyanopyridine and o-tolunitrile (o-methylbenzonitrile, *o*-cyanotoluene), are also provided here.

The non-empirical method correctly describes the experimental regularity according to which the methyl group in the 4-position of 3,4-dimethylpyridine has a more mobile proton. So, oxidative transformations of the substrate under mild conditions proceed only with this substituent.

TABLE I. Total energies of molecules of 3,4-dimethylpyridine, *o*-xylene, mononitriles and corresponding anions (E_{tot}), enthalpy of proton detachment from the methyl groups in the gaseous phase (*DE*), energies of the highest occupied molecular orbitals of anions (E_{HOMO}), calculated by the *ab initio* method (HF/6-311+G**)

Initial molecule	$-E_{tot}$(molecule) u	$-E_{tot}$(anion) u	*DE* kJ·mol⁻¹	$-E_{HOMO}$ kJ·mol⁻¹
3,4-Dimethylpyridine	324.84460	324.21140 (3)	1662.4 (3)	90.3 (3)
		324.22261 (4)	1633.0 (4)	144.5 (4)
o-Xylene	308.84755	308.20785	1679.5	77.8
3-Methyl-4-cyanopyridine	377.54978	376.95097 (3)	1572.2 (3)	186.8 (3)
o-Tolunitrile	361.55825	360.94967	1597.8	166.0

Similar results were obtained in modeling the chemisorption of 3,4-dimethylpyridine on the surface of a vanadium oxide catalyst (Fig. 3). Energy of heterolytic cleavage of C−H (E_{C-H}) bond of the methyl groups of the substrate in positions 3 and 4 is rather high and is less for the substituent in position 4 (1178.2 and 1070.6 kJ·mol⁻¹, respectively, Table II). Upon transfer of the proton, detached from the methyl group, to vanadyl oxygen a new O−H bond is formed. Herewith,
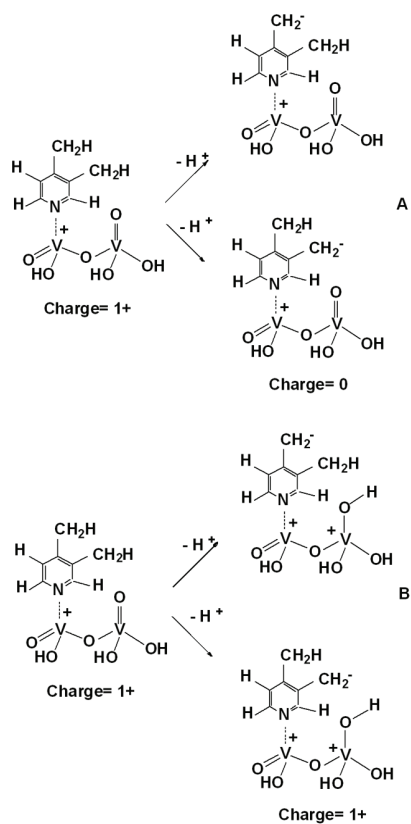

Fig. 3. Heterolytic cleavage of C−H bond without proton transfer to vanadyl oxygen (A) and with it (B).

energy is released which compensates the expenditures for deprotonation of the methyl groups. As a result, deprotonation enthalpy (*DE*) of the methyl groups in positions 3 and 4 has considerable lesser values (238.2 and 157.1 kJ·mol^{-1}, respectively). The substituent in position 4, possessing the least *DE* value, should enter into the reaction first. Thus, the results of the calculations for a molecule of 3,4-dimethylpyridine in the gaseous phase and in the adsorbed state correlate with the experimental data on the sequence of transformation of the methyl substituents of 3,4-dimethylpyridine into a cyano group.

TABLE II. Total energies of the connected with the Lewis acidic center molecule of 3,4-dimethylpyridine and carbanions (E_{tot}), energy of heterolytic cleavage of C−H bond of the methyl groups of the adsorbed substrate (E_{C-H}), deprotonation enthalpy (*DE*) of the methyl groups, calculated by the DFT method (B3LYP/LanL2DZ)

Structure	$-E_{tot}$ / u		E_{C-H} / kJ·mol^{-1}
	Adsorbed molecule	Adsorbed carbanion	
Cleavage of C−H bond (Fig. 3A)	922.81280	922.40501 (4-position)	1070.6 (4-position)
		922.36405 (3-position)	1178.2 (3-position)
Heterolytic cleavage of C−H bond with carry of a proton on vanadyl oxygen (Fig. 3B)	922.81280	922.75297 (4-position)	157.1 (4-position)
		922.72206 (3-position)	238.2 (3-position)

The energies of the initial compounds and their complexes with clusters with optimized geometry were determined (Tables III and IV), using the Born–Oppenheimer approximation and taking into account the effects of molecular translation, rotation and vibration.

TABLE III. Total energies (E_{tot}), zero-point energy (*ZPE*) of the 3,4-dimethylpyridine and carbanions in gaseous phase and enthalpy deprotonation of substitutions, calculated by *ab initio* method (HF/6-311+G** Freq test)

Structure	$-E_{tot}$ / u	*ZPE* / u	*DE* / kJ·mol^{-1}
3,4-dimethylpyridine	324.84460	0.15266	–
3-Carbanion	324.21140	0.13647	1620
4-Carbanion	324.22261	0.13709	1592.1

An effect of activated adsorption of the substrate upon a relative reactivity of the methyl substituents in the pyridine ring has been studied. We have carried out modeling of the adsorption of 3,4-dimethylpyridine by nitrogen's heteroatom of the pyridine ring on the acidic Lewis center of vanadium oxide catalyst (vanadium cation) at a temperature of reaction 603.15 K (Table IV).

Thus, we have established that calculations using the Born–Oppenheimer approximation correctly describe the relative reactivity of methyl groups in the 3,4-dimethylpyridine molecule both in the gaseous phase and in the cluster––bound state.

TABLE IV. Total energies (E_{tot}) and thermal energy (E_{therm}) of the 3,4-dimethylpyridine and carbanions on cluster, enthalpy deprotonation of substitutions (*DE*), calculated by DFT method (B3LYP/Lanl2DZ)

Structure	$-E_{tot}$ / u	E_{therm} / u	*DE* / kJ·mol^{-1}
3,4-Dimethyl-pyridine/cluster	922.81280	0.26333	–
3-Carbanion/cluster	922.72206	0.26141	233.2
4-Carbanion/cluster	922.75297	0.26192	153.4

The difference in the behavior of 3,4-dimethylpyridine and *o*-xylene in oxidative ammonolysis on V–O-catalysts was shown through experiments with 3,4--dimethylpyridine in which we have not detected a corresponding dinitrile (3,4--dicyanopyridine). The cause of this might be for the following reasons. The methyl group in the molecule of 3-methyl-4-cyanopyridine, more reactive than that in the molecule of *o*-tolunitrile, enters into reaction of intramolecular cyclization earlier, than a second cyano group is formed thereof. Our quantum-chemical calculations (Table I) testify to a greater mobility of the protons of the methyl substituent of 3-methyl-4-cyanopyridine in comparison with the protons of the methyl group of *o*-tolunitrile.
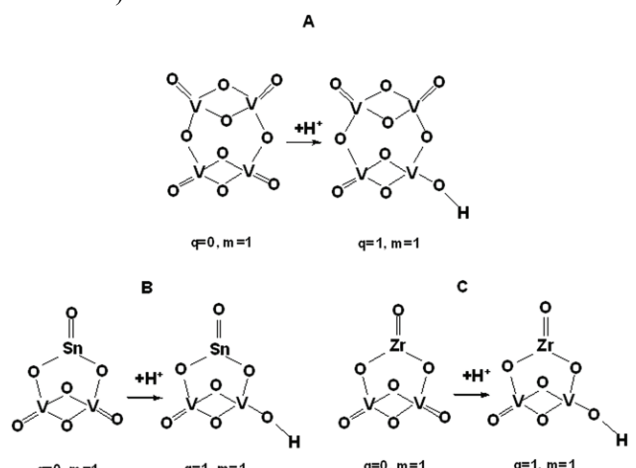
We have established that upon oxidative ammonolysis of 3,4-dimethylpyridine the promotion of vanadium pentoxide by the additions of SnO_2 and ZrO_2 results in a marked increase in the yield of 3-methyl-4-cyanopyridine and shifting of its maximum to the field of lower temperatures (Fig. 1B). It is considered,[16] that activity and selectivity of vanadium oxide catalysts of hydrocarbons oxidation are connected with the existence of different forms of active oxygen at the catalyst surface. An important role is played here by a double bond oxygen of the lattice (V=O). An intermediate action of SnO_2 and ZrO_2 upon the activity of the vanadium oxide catalysts, studied by us, may be stipulated by their effect upon the reactivity of V=O bond. Indeed, the calculations have shown (Table V), that upon the transfer from V_2O_5 to binary catalysts a value of proton affinity of vanadyl oxygen increases. These results confirm that the mechanism of the promoting effect of SnO_2 and ZrO_2 additives to V_2O_5 is to activate both the chemisorbed substrate (Table II) and the vanadyl oxygen responsible for the deprotonation of the oxidizing methyl group at the initial stages of the process.

It has been established that additions of the above-mentioned oxides to V_2O_5 increase nucleophilicity of vanadium oxygen (*PA*, Table V), the conversion of substrate and the yield of the primary reaction product, 3-methyl-4-cyanopyridine (Fig. 1A and B).

The mechanism of formation of an imide cycle in oxidative ammonolysis of *o*-xylene and 3,4-dimethylpyridine is of the interest. By its ability to intramolecular cyclization 3,4-dimethylpyridine is similar to *o*-xylene. The authors[17] have assumed that the transformation of *o*-xylene into phthalimide proceeds through the stages of formation of *o*-tolunitrile, oxidation of a methyl substituent of the

latter and interaction of its oxidized forms with a triple bond of a nitrile group, as a result of which isoimide of phthalic acid is formed. The unstable isoimide is easily transformed into phthalimide at a high temperature.

TABLE V. The total energies of the vanadium-containing clusters and their protonated forms (E_{tot}), proton affinity of oxygen bound to the vanadium ion (PA), calculated by the DFT method (B3LYP/LanL2DZ)

Reaction	$-E_{tot}$ / u		PA / kJ·mol⁻¹
	Initial state	kJ·mol⁻¹	
A	1038.17019	1038.45849	756.9
B	672.90766	673.20234	773.7
C	716.26601	716.58135	827.9

Accounting for the above-stated and the analogous structure of *o*-xylene and 3,4-dimethylpyridine, the following Scheme 1 of the formation of imide of pyridine-3,4-dicarboxylic acid from 3,4-dimethylpyridine can be proposed.
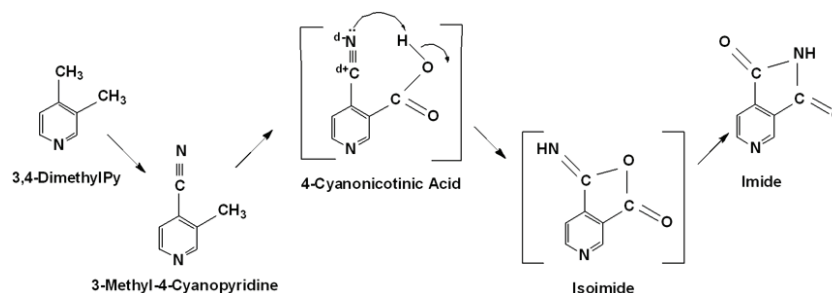
Scheme 1. Formation of imide of pyridine-3,4-dicarboxylic acid from 3,4-dimethylpyridine.

The scheme includes 4-cyanonicotinic acid and isoimide of pyridine-3,4--dicarboxylic acid as hypothetic intermediate products. One must suppose that

the transformation of 3-methyl-4-cyanopyridine into imide includes the superficial stages of oxidation of the methyl group in position 3 and an electrophilic attack of a proton at a nitrogen atom of the nitrile group.

In the scheme the proton belongs to the carboxylic group, however, protons as potential hydrogen donors, present in the reaction mixture (ammonia, water vapors), may induce heterocyclic cleavage of N−H or O−H bonds under the effect of a catalyst. The results of our ab initio quantum-chemical calculations (HF/6-31G*) testify in favor of this hypothesis of the imide formation mechanism. An isolated molecule of 3-methyl-4-cyanopyridine is characterized by the pronounced polarization of a triple bond in the nitrile group, as a result of which a carbon atom carries a positive charge (δ_C = +0.274), and a nitrogen atom carries a negative charge (δ_N = -0.447). This favors the electrophilic attack of the proton at the nitrogen atom with the formation of isoimide. The total energy level of isoimide (E_{tot} = -526.039 u) is higher than that of imide (E_{tot} = −526.067 u) by 73.5 kJ·mol^{-1}. This indicates a possibility of transformation of the thermodynamically less stable isoimide into imide of pyridine-3,4-dicarboxylic acid.

CONCLUSION

The correlation between the position of methyl substituents in pyridine cycle and their reactivity in oxidative ammonolysis of 3,4-dimethylpyridine on modified vanadium oxide catalysts has been found.

It was found that due to the high CH-acidity in the gas phase and in conditions modelling chemisorption on the Lewis acid sites of the catalyst surface, methyl substituent at 4-position has higher reactivity and the first reacts obtaining 3-methyl-4-cyanopyridine. The temperature increase favors intramolecular cyclization with the formation of imide of pyridine-3,4-dicarboxylic acid. A possible mechanism of 3,4-dimethylpyridine transformation into imide of pyridine-3,4--dicarboxylic acid has been proposed. The main stages of the mechanism were confirmed by physicochemical methods and quantum chemical calculations.

It was established that the modification of V_2O_5 by additions of SnO_2 and ZrO_2 increases the nucleophilicity of vanadyl oxygen and promotes the yield of 3-methyl-4-cyanopyridine, the primary reaction product.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

И З В О Д

ОКСИДАТИВНА АМИНОЛИЗА 3,4-ДИМЕТИЛПИРИДИНА НА
ВАНАДИЈУМ-ОКСИДНИМ КАТАЛИЗАТОРИМА

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Испитивана је оксидативна аминолиза 3,4-диметилпиридина на V_2O_5 и бинарним ванадијум-оксидним катализаторима, модификованим додавањем SnO_2 и ZrO_2. Утврђена је повезаност CH-киселости метил-група супстрата у гасовитој фази, стања хемисорпције и корака њихове трансформације у циано-групу. Показано је да нуклеофилност ванадил-кисеоника, израчуната методом теорије функционала густине (*Density Functional Theory, DFT*), расте приликом модификације услед додавања SnO_2 и ZrO_2 и утиче на повећавање приноса у добијању 3-метил-4-цијанопиридина и имида пиридин-3,4-дикарбоксилне киселине. Размотрен је предложени механизам реакције формирања имида пиридин-3,4-дикарбоксилне киселине.

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