large strong-field increment for 2-CH_3 was observed here, and the chemical shift for this carbon atom is 14.5 ppm, whereas it was more than 19.8 ppm in all other cases. A "γ effect" in this case is clearly observed not only for $C_{(3)}$ but also for $C_{(4)}$ and $C_{(6)}$ (Table 3).

The substantial dependence of the vicinal SSCC on the solvent in isomer IIIC (Table 2) nevertheless indicates that, despite the clear preponderance of the 2a,4e,5a conformation, equilibrium 2a4e5a $\rightleftarrows$ 2e4a5e exists and is shifted to favor the diequatorial form on passing from C_6D_6 to the polar solvent $CDCl_3$.

In principle, the low barrier to inversion of the pyramidal ring nitrogen atom in N-alkylpiperidines [3] makes it possible to consider both equatorial and axial orientations of the N-methyl group as possible in all of the investigated configurational isomers. However, in no case did we obtain NMR data that would enable us to reliably establish the orientation, although, as we have previously pointed out [1], its equatorial orientation in isomers A and B finds confirmation in the ^1H chemical shifts of the protons of the piperidine ring.

EXPERIMENTAL

The ^1H NMR spectra of 5% solutions in $CDCl_3$ or C_6H_6 (with tetramethylsilane as the internal standard) were obtained with a WM-400 spectrometer (400 MHz). The method of double homonuclear resonance was used for assignment of the signals. The ^1H NMR spectra of isomer IIIB on heating to 120°C in d_6-DMSO were recorded with a WP-80 spectrometer. The ^{13}C NMR spectra of isomer IIIB were obtained at 100.6 MHz with a WM-400 spectrometer. The ^{13}C NMR spectra of the remaining compounds were recorded with a WP-80 spectrometer (20 MHz).

The authors thank I. I. Chervin for assistance in recording the NMR spectra with a WM-400 spectrometer.

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ELECTRONIC STRUCTURES AND REACTIVITIES OF DERIVATIVES OF 1,4-DIHYDROPYRIDINES.

2.* 1-METHYL-3-CARBOXYAMIDO-1,4-DIHYDROPYRIDINE AND ITS CATION RADICAL

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UDC 547.24:577.150:539.193

The three-dimensional and electronic structures of 1-methyl-1,4-dihydronicotinamide and its cation radical were calculated within the MINDO/3 approximation. The results are compared with the physicochemical properties of 1,4-dihydropyridine derivatives.

The redox transformations of the coenzymes NADH and NADPH lie at the foundation of the most important biochemical processes [1]. The corresponding 1,4-dihydropyridines are structural models of these coenzymes [2]; inasmuch as they have high physiological activity, they

*See [22] for Communication 1.

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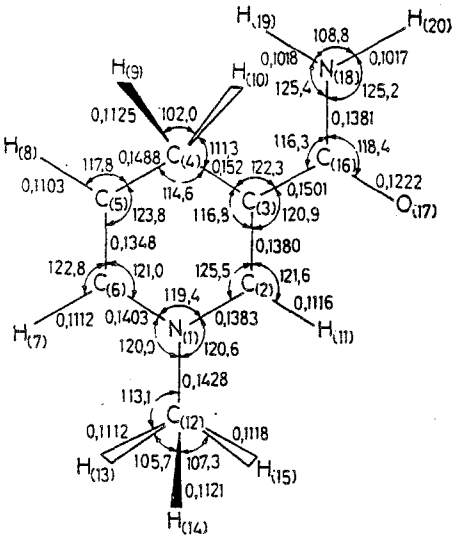


Fig. 1

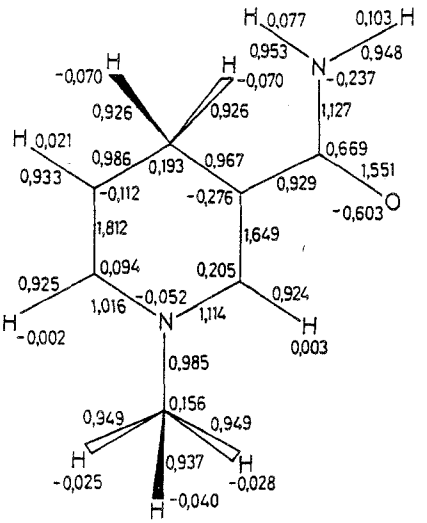


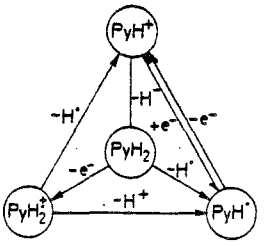
Fig. 2

Fig. 1. Three-dimensional structure and numbering of the atoms in PyH_2. The bond lengths are presented in nanometers.

Fig. 2. Charge distribution in PyH_2.

have found application as antioxidants, agents for the chemization of agriculture, and medicinal preparations [3]. Research on their properties has been systematized in reviews [2, 4, 5]; however, substantiated approaches to the interpretation of the experimental data are absent, and the conclusions based on the use of various theoretical concepts are contradictory [6, 7].

The elementary reactions involving the transfer of an electron and hydrogen and its ions that proceed without disruption of the integrity of the ring can be represented by the following scheme of interconversions of 1,4-dihydropyridine derivatives:



where PyH_2 is 1,4-dihydropyridine, $PyH_2^{+\cdot}$ is its cation radical, $PyH^{\cdot}$ is the corresponding pyridinyl radical, and PyH^+ is the pyridinium cation. Only the reversibility of the one-electron oxidation of the pyridinyl radical has been proved experimentally [8]. According to the data of Carlson and co-workers [6], the one-electron oxidation of PyH_2 is neither an equilibrium process nor a reversible process.

To evaluate the reactivities of 1,4-dihydropyridines in redox reactions we studied the electronic and three-dimensional structures of the simplest model of NADH – 1-methyl-1,4-dihydronicotinamide (subsequently indicated by PyH_2) – and its cation radical by the MINDO/3 method [9, 10] with complete optimization of the geometry. The calculations were made with a BESM-6 computer by means of the program in [11]. The starting structure of PyH_2 was selected in conformity with the results of x-ray diffraction analysis [12] and calculations of dihydropyridine derivatives [13]. The "half-electron" method was used to calculate the doublet states [14].

Data on the three-dimensional structure of PyH_2 are presented in Fig. 1. On the whole, there is satisfactory agreement between the calculated and experimental values of the bond lengths and bond angles (see [13]). The introduction of a carbamido group has little effect as compared with unsubstituted 1-methyl-1,4-dihydropyridine: only the lengths of the bonds at the $C_{(3)}$ atom and bond angle $C_{(3)}$–$C_{(4)}$–$C_{(5)}$ (from 123.1° to 114.6°) change substantially [13]. The CO bond of the carbamido group is coplanar with the plane of the ring, and the

TABLE 1. Physicochemical Properties and Electronic Structures of PyH_2 and $PyH_2^{+\cdot}$

Property	PyH_2		$PyH_2^{+\cdot}$	
	cis	trans	cis	trans
Energy of formation, kJ/mole	−75,303	−87,678	616,595	610,412
Dipole moment μ, D	6,199	4,059	—	—
Charge				
on the heteroring atoms	0,041	0,052	0,332	0,341
on the heteorring H atoms	−0,113	−0,124	0,317	0,305
on the carbamido group	0,011	0,009	0,161	0,159
on the methyl group	0,061	0,063	0,190	0,196
hfs constant, mT, for the nucleus				
$N_{(1)}$	—	—	1,086	1,081
$N_{(18)}$	—	—	0,951	0,909
$H_{(9)}$	—	—	6,275	6,364
Contribution to the Hückel MO* BAO for the atom $N_{(1)}$	0,569	0,569	0,548	0,546
$C_{(2)}$	−0,155	−0.150	−0,159	−0,154
$C_{(3)}$	−0,482	−0,494	−0,486	−0,507
$C_{(4)}$	0,111	0,093	0,118	0,096
$C_{(5)}$	−0,423	−0,420	−0,443	−0,435
$C_{(6)}$	−0,216	−0,203	−0,211	−0,193
$H_{(9)}$	0,236	0,237	0,250	0,249

*The structure of the highest occupied molecular orbital is presented for PyH_2, while the structure of the singly occupied molecular orbital is presented for $PyH_2^{+\cdot}$.

nitrogen atom is also situated in this plane; however the amino group, which has a virtually planar structure, is turned at an angle of 10.9° relative to the indicated plane.

We calculated both stable conformers of PyH_2: the conformer depicted in Fig. 1 (named the trans conformer in analogy with [13]) and the conformer corresponding to orientation of the carbonyl group near the $C_{(4)}$ atom (the cis conformer). In conformity with the data in [13], the trans conformation is the most stable conformation; however, the enthalpy of the conformational transition is relatively low (ΔH = 12.4 kJ/mole, Table 1).

The results of the calculations (Table 1) provide evidence that, on the whole, the physicochemical properties of the conformers differ only slightly, and a separate examination of the cis conformer is therefore not expedient. At the same time, the orientation of the carbamido group has a pronounced effect on the magnitude of the dipole moment of PyH_2, which is ~2 D larger for the cis conformer than for the trans conformer; this is in agreement with the results in [15] (μ_{exp} = 4.00 ± 0.05 D).

Data that characterize the charge distribution in PyH_2, as well as the Wiberg bond indexes [16], are presented in Fig. 2. The results obtained constitute evidence that PyH_2 is a highly polar compound in which the methyl and carbamido groups are relatively weakly conjugated with the heteroring, and the C—C multiple bonds are localized substantially. The formal charges on the heteroring substituents are low (Table 1); however, the close orientation of the CO group leads to appreciable polarization of the $C_{(2)}$—$C_{(3)}$ bond. The charges on the other heteroring atoms change only slightly as compared with unsubstituted 1-4-dihydropyridines [13].* At the same time, the introduction of the electron-acceptor carbamido group leads to a certain increase in the ionization potential (from 7.42 eV [13] to 7.92 eV); the result obtained is in agreement with the experimental value (8.0 eV [2]).

Data on the structures of the boundary molecular orbitals of PyH_2 are presented in Table 1. An examination of the structure of the highest occupied molecular orbital (HOMO) makes it possible to assume that the $N_{(1)}$, $C_{(5)}$, and $C_{(3)}$ atoms and the hydrogen atoms of the methylene group in the 4 position are the most likely reaction centers in reactions with soft electrophiles. In particular, the latter fact and the presence of substantial negative charge on the cited atoms constitute evidence in favor of the ease of detachment of one of them either in the form of a neutral particle or in the form of the corresponding ion. The decreased multiplicity (and, consequently, the lower strength) of the corresponding C—H bonds also favors this detachment (Fig. 2).

*In [13] there are unfortunate misprints in the data on the charge distribution in 1-methyl-1,4-dihydropyridine.

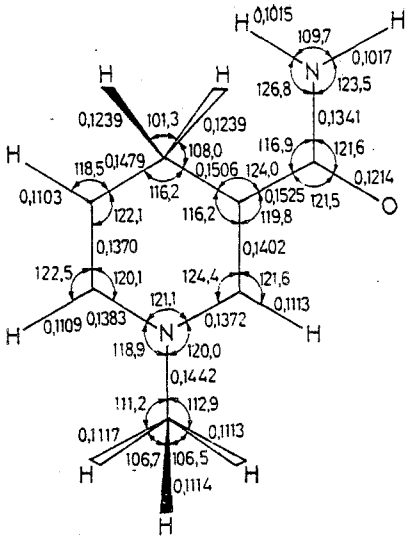


Fig. 3

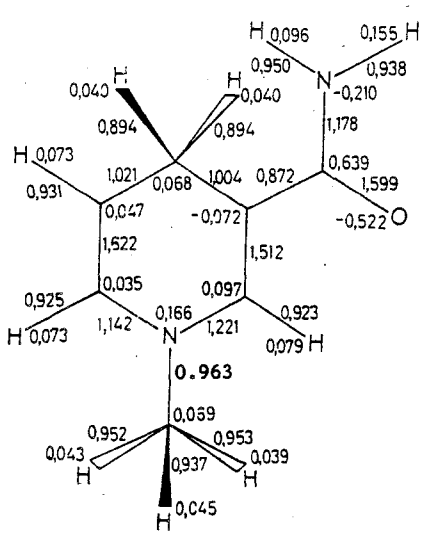


Fig. 4

Fig. 3. Three-dimensional structure of $PyH_2^{+\cdot}$. The bond lengths are presented in nanometers.

Fig. 4. Electronic structure of $PyH_2^{+\cdot}$.

The $C_{(3)}$ and $C_{(5)}$ atoms are the most likely reaction centers in the reaction of PyH_2 with hard electrophiles (for example, with a proton).* Since protonation of the $C_{(3)}$ atom should lead not only to cleavage of the $C_{(2)}=C_{(3)}$ bond but also to loss of conjugation of the carbamido group with the ring (which destabilizes the indicated intermediate), the $C_{(5)}$ atom should be the most likely reaction center in the indicated reaction. According to the results of the calculations, the $C_{(6)}$ atom in the 1,4,5-trihydronicotinamide cation (PyH_3^+) is the most likely reaction center in reactions with nucleophiles.

At the same time, in reactions with soft nucleophiles the most likely reaction center in PyH_2 is not the carbon atom of the carbamido group (the characteristic reaction center in reactions with hard nucleophiles) but rather the $C_{(2)}$ and $C_{(6)}$ atoms, which are closest to the nitrogen atom.

The results of quantum-chemical calculation of the three-dimensional structure of the 1-methyl-1,4-dihydronicotinamide cation radical ($PyH_2^{+\cdot}$) are presented in Fig. 3. It follows from a comparison of Figs. 1 and 3 that the oxidation of PyH_2 to $PyH_2^{+\cdot}$ is accompanied by substantial lengthening of the multiple bonds of the heteroring, while the remaining bonds in the heteroring become shorter. Both the methyl and carbamido groups are farther away from the heteroring and, consequently, are somewhat less inclined to undergo conjugation with the heteroring. As regards the $C_{(4)}$–$H_{(9)}[H_{(10)}]$ bonds, a substantial change in their lengths should evidently promote the detachment of a proton or a hydrogen atom from $PyH_2^{+\cdot}$.

It follows from the data on the charge distribution in $PyH_2^{+\cdot}$ presented in Fig. 4 that in the one-electron oxidation of PyH_2 [17-19] most of the electron density is transferred from the 1,4-dihydropyridine heteroring [primarily from the nitrogen atom and the $C_{(3)}$ and $C_{(5)}$ atoms] and from the hydrogen atoms in the 4 position. Changes in the overall charges on the methyl and carbamido groups evidently play a less substantial role (Table 1). Let us note that in the heteroring the Wiberg indexes of the bonds in $PyH_2^{+\cdot}$, as compared with PyH_2, change in a manner that is antibatic to the changes in the lengths of the corresponding bonds.

The detachment of an electron from PyH_2 is not accompanied by cardinal changes in the structures of the boundary MO (Table 1), and $PyH_2^{+\cdot}$ is evidently a cation radical of the π type; the greatest fraction of the spin density is located in the heteroring orbitals and on the hydrogen atoms of the methylene group; this makes the indicated atoms the most likely reaction centers in free-radical reactions. Incidently, let us note the relatively large

*Protonation of PyH_2 at the carbonyl or amino group does not lead to the formation of highly reactive products and is probably a rather fast and reversible process that has a relatively small effect on the reactivities of the heteroring atoms.

absolute values of the constants of the hyperfine structure (hfs) for the nitrogen nuclei and protons in $PyH_2^{+\cdot}$, which we calculated by the unrestricted (with respect to spin) Hartree–Fock method within the INDO approximation [20] (the three-dimensional structure of $PyH_2^{+\cdot}$ corresponded to Fig. 3). The hfs constants for the other nuclei were appreciably smaller; however, in view of the large number of nuclei with a_H values that exceed 0.1 mT, superimposition of numerous lines is possible in the EPR spectrum of the investigated cation radical, and this undoubtedly hinders its interpretation. In our opinion, the reason for the increased (as compared with other radicals) $a_{H_{(9)}}$ value is substantial weakening of the corresponding C–H bond (which follows from a comparison of the Wiberg indexes in Fig. 2 and Fig. 4); this partial "cleavage" of the bond also constitutes evidence for the relative ease of detachment of a hydrogen atom from $PyH_2^{+\cdot}$.

It follows from the data that we obtained that a change in the conformation of the carbamido group in $PyH_2^{+\cdot}$ from a trans to a cis orientation leads to substantial weakening of the $C_{(4)}$–$H_{(9)}[H_{(10)}]$ bonds and an increase in the charges on the indicated hydrogen atoms and, consequently, facilitates the detachment of a proton by base or solvent molecules. One reason for this effect of the carbamido group, in addition to the polarizing effects of the carbonyl fragment, is the development of a relatively strong hydrogen bond [$O_{(17)}$–$H_{(9)}$], the energy of the cleavage of which within the MINDO/3 approximation is ~39.5 kJ/mole; the existence of this hydrogen bond also leads to relative stabilization of the cis conformer and a decrease in the enthalpy of the conformational transition. Let us emphasize that the formation of hydrogen bonds of this type is unlikely in PyH_2 because of the like charges on the indicated atoms. The data obtained are in agreement with the assumption that the carbamido group can change its orientation in the case of oxidation of PyH_2 with strong oxidizing agents [21].

On the whole, the calculated data obtained provide evidence that $PyH_2^{+\cdot}$ should have high reactivity and disappear rapidly (for example, via deprotonation). In fact, it exists for ~1 msec in aqueous solutions [6]. The principal product of its decomposition is the $PyH^{\cdot}$ radical, which is also formed in the one-electron reduction of pyridinyl salts.

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ELECTRONIC STRUCTURES AND REACTIVITIES OF DERIVATIVES OF 1,4-DIHYDROPYRIDINES.

3.* ENTHALPIES OF ELEMENTARY PROCESSES IN THE 1,4-DIHYDRONICOTINAMIDE SERIES

A. M. Nesterenko, N. I. Buryak,
O. M. Polumbrik, and A. A. Yasnikov

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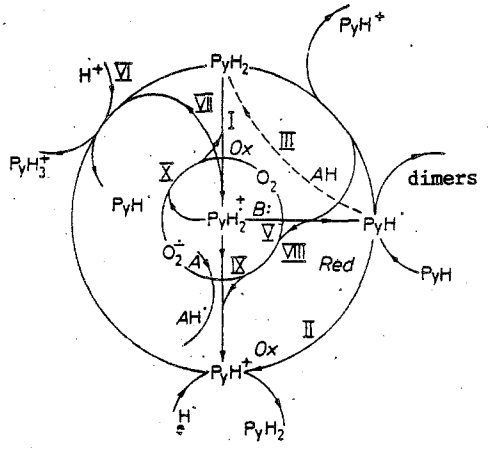
The heat effects of the elementary processes involved in electron and hydrogen transfer with the participation of 1,4-dihydropyridines were calculated by the semiempirical MINDO/3 method. The effect of a number of side and parallel processes on the kinetic principles is discussed in the case of the oxidation of 1-methyl-1,4-dihydronicotinamide. The calculated and experimental data are compared.

Additional data on the thermochemical characteristics of the corresponding elementary processes [4,5] are necessary in view of the irreversible and nonequilibrium occurrence of the fundamentally important (for biochemistry) reactions involved in the oxidation of 1,4-dihydropyridines [2, 3].

The principal processes involved in the interconversion of a series of derivatives of 1,4-dihydropyridines in the presence of oxidizing agents (Ox) or reducing agents (Red) and bases (B) or proton-donor compounds (H^+X^-), as well as hydrogen atom acceptors (A), can be represented by the scheme



where PyH_2 is 1-methyl-1,4-dihydronicotinamide, $PyH_2^{+\cdot}$ is its cation radical, PyH_3^+ is the $C_{(5)}$-protonated form of PyH_2, $PyH^\cdot$ is the corresponding pyridinyl radical, and PyH^+ is the 1-methyl-3-carbamidopyridinium cation.

On the basis of calculations of the electronic structures and physicochemical properties [1, 5] we accomplished an analysis of the energy characteristics of the most important ele-

*See [1] for Communication 2.

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