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

1. 1-METHYL-3-CARBAMIDOPYRIDINYL RADICAL AND 1-METHYL-3-CARBAMIDOPYRIDINIUM CATION

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The physicochemical properties and electronic and three-dimensional structures of the products of transformations of 1-methyl-1,4-dihydronicotinamide were calculated within the MINDO/3 approximation. The problems associated with their reactivities in reactions involving electron and hydrogen-atom transfer, as well as the problems of "hydride" transfer in chemical reactions, are discussed.

In order to interpret the reactivities of 1,4-dihydropyridines we calculated the electronic and three-dimensional structures of the 1-methyl-3-carbamidopyridinyl radical and the corresponding cation, which can be regarded as the simplest models of the coenzymes HAD and HADP [2]. As in [1], the calculations were made within the MINDO/3 approximation with complete optimization of the geometry.

Data on the equilibrium three-dimensional structure of the 1-methyl-3-carbamidopyridinyl radical (PyH$^{\bullet}$) are presented in Fig. 1. A comparison with the results of quantum-chemical calculation of 1-methyl-1,4-dihydronicotinamide (PyH$_2$) and its cation radical (PyH$_2^{+\bullet}$) [1] indicates that in PyH$^{\bullet}$ there is equalization of the lengths of the ring bonds, which constitutes evidence for an increase in the "aromaticity." However, the C$_{(3)}$–C$_{(4)}$ bond is still longer than the other heteroring bonds. The methyl and carbamido groups can undergo conjugation with the ring MO in PyH$_2$ and PyH$^{\bullet}$ to approximately the same extent, since the corresponding bond lengths in these compounds are of similar magnitude. The equilization of the ring bond lengths also corresponds to a certain degree of decrease in the μ value of PyH$^{\bullet}$ as compared with the μ value of PyH$_2$ (see Table 1).

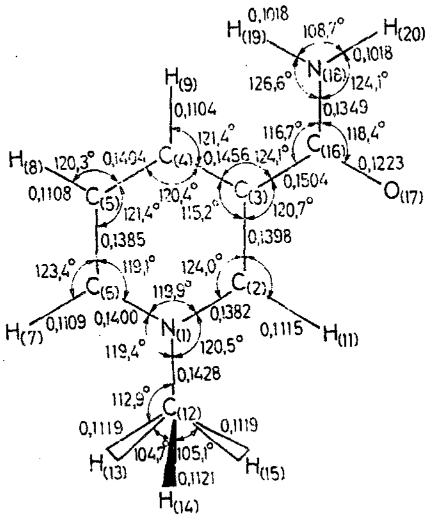

Fig. 1

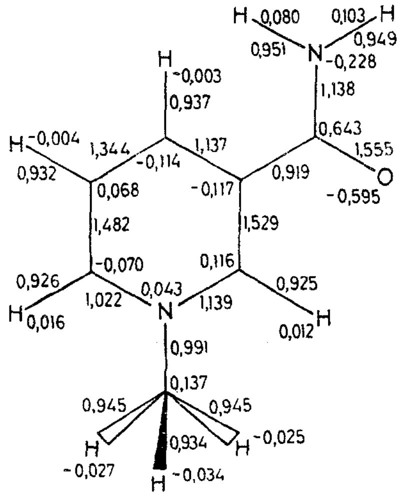

Fig. 2

Fig. 1. Three-dimensional structure of PyH$^{\bullet}$. The bond lengths are presented in nanometers.

Fig. 2. Distribution of the charges in PyH$^{\bullet}$.

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TABLE 1. Physicochemical Properties and Electronic Structures of $PyH^\cdot$ and PyH^+

Property	$PyH^\cdot$		PyH^+	
	cis	trans	cis	trans
Energy of formation, kJ/mole	5,456	−1,765	547,272	541,773
Dipole moment, μ, D	5,502	3,450	—	—
Charge				
on the heteroring atoms	−0,068	−0.075	0.382	0,385
on the H atoms of the heteroring	0,019	0,021	0,264	0.265
on the carbamido group	0.007	0,003	0.163	0,164
on the methyl group	0,042	0,051	0,191	0,186
hfs constant for the nucleus, mT				
$N_{(1)}$	1,323	0.490	—	—
$N_{(18)}$	0.020	0,020	—	—
$N_{(9)}$	1,099	1,079	—	—
Contribution to the HMO* of the BAO for the atom				
$N_{(1)}$	−0.450	−0,443	−0,484	−0,471
$C_{(2)}$	0,325	0,273	0,341	0,298
$C_{(3)}$	0,182	0.235	0.209	0,267
$C_{(4)}$	−0,578	−0.584	−0,570	−0,570
$C_{(5)}$	0,061	0.049	0,081	0.061
$C_{(6)}$	0,500	0,520	0,495	0,504

*The structure of the singly occupied molecular orbital (SOMO) is presented for $PyH^\cdot$, while the structure of the lowest vacant molecular orbital (LVMO) is presented for PyH^+.

Just as for PyH_2 [1], the conformer with a trans orientation of the carbonyl group with respect to the carbon atom in the 4 position is thermodynamically preferable, and only it is therefore examined here. The data on the energies of formation of the various conformers constitute evidence that the enthalpy of the conformational transition in $PyH^\cdot$ is close to the analogous characteristic for $PyH_2^{+\cdot}$ but lower than in PyH_2 (Table 1).

Significantly lower absolute values of the charges on the ring atoms are observed when one compares $PyH^\cdot$ (Fig. 2) with PyH_2 (see Fig. 2c [1]); the sign of the charge also differs on most of the atoms [except for $C_{(2)}$ and $C_{(3)}$]. In this connection the most likely reaction centers in reactions with "hard" electrophiles are, in addition to the $C_{(3)}$ atom, the $C_{(4)}$ and $C_{(6)}$ atoms; however, the latter is far more reactive. For $PyH^\cdot$, just as for PyH_2, reaction at the $C_{(2)}$ atom is most likely in reactions with nucleophilic reagents. Reactions associated with the radical nature of $PyH^\cdot$ were further examined.

A comparison of the data on the charge distribution in $PyH^\cdot$ and $PyH_2^{+\cdot}$ makes it possible to conclude that splitting out of a proton from the latter leads to transfer of the bulk of the electron density to the ring atoms (0.41 of the elementary charge) and the corresponding hydrogen atoms (0.25 e); the electron densities on the $C_{(4)}$ and $N_{(1)}$ atoms (0.18 and 0.15 e, respectively) undergo the greatest change. A comparison of the Wiberg indexes of the various bonds in $PyH^\cdot$ with the corresponding characteristics of other 1,4-dihydropyridine derivatives [1], like the structural data discussed above, provides evidence for equalization of the multiplicities of the ring bonds; as compared with PyH_2, the $C_{(4)}$—$C_{(5)}$ bond undergoes the maximum change.

In accordance with the structure of the boundary singly occupied MO (SOMO) in $PyH^\cdot$ (Table 1), the most likely reaction centers in the free-radical reactions of $PyH^\cdot$ are the $C_{(4)}$ and $C_{(6)}$ atoms, as well as the $N_{(1)}$ atom. The data obtained make it possible to explain the formation of primarily 4,4'-dimers from $PyH^\cdot$ as compared with 4,6'- and 6,6'-dimers by both kinetic factors (since dimerization is realized at the centers that bear the greatest spin density) and in evaluating the relative energy of interaction of the fragments from Hückel MO theory [3] in explicit form. For example, when one uses a β_{C-C} value of 1.643 eV (which corresponds to the covalent component for a single bond within the MINDO/3 approximation), the differences in the energies of formation of 4,4'-, 4,6'-, and 6,6'-dimers should be ~6 and 11 kJ/mole, respectively.

The presence of substantial spin density in the 4 and 6 positions should lead to relatively fast dimerization; this is in good agreement with the data in [4]. It is precisely the high reactivity of 1-methyl-3-carbamidopyridinyl radicals (which is not characteristic for other radicals of this type [5]) that hinders an experimental study of the properties of $PyH^\cdot$. Nevertheless, Dohlman and Becker were able to study the spectrum of the $PyH^\cdot$ radical formed in the low-temperature radiolysis of PyH_2 [6]. We made a quantum-chemical calculation of this radical by the spin-unrestricted Hartree—Fock method within the INDO-approximation [7]; the three-dimensional structure of PyH$^{\cdot}$ corresponded to that in Fig. 1. The data on the hyperfine structure (hfs) constants for the nuclei correspond to the experimental values, which are presented in parentheses: $a_{N(1)}$ = 0.486 (0.426), $a_{H(9)}$ = 1.079 (1.176). $a_{H(8)}$ = 0.447 (0.222), $a_{H(7)}$ = —0.935 (—0.855), and $a_{H(19)}$ = —0.0099 mT (—0.009 mT). The difference in the experimental and calculated a_H values is substantial only for the $H_{(11)}$ atom: —0.714 mT (—0.177 mT). One of the possible reasons for this is, in our opinion, the greater perturbing effect of the solvent molecules, which may coordinate with the adjacent carbonyl group of PyH$^{\cdot}$.

Pyridinium cations are the final product of the oxidation of 1,4-dihydropyridines. Data that characterize the equilibrium three-dimensional structure of PyH$^+$ within MINDO/3 approximation are presented in Fig. 3. Comparison of them with the results of x-ray diffraction study of the crystal hydrate of the 1-methyl-3-carbamidopyridinium ion with adenyl acetate [8] makes it possible to conclude that the lengths of virtually all of the bonds in PyH$^+$ are 0.002 nm too high as compared with the experimental values; on the whole, however, these deviations do not exceed the errors in the MINDO/3 approximation [9]. A probable reason for these deviations is also the unaccounted for effect of the gegenion and crystal-hydrate water molecules, which, according to the data in [8], have a substantial effect on the packing of the cations in the unit cell of the crystals.

The oxidation of PyH$^{\cdot}$ to PyH$^+$ leads to still greater equalization of the ring bond lengths [the $C_{(3)}$—$C_{(4)}$ bond undergoes the greatest degree of change]; however, the length of the C=O bond in the carbamido group also decreases substantially. An increase in the lengths of the $N_{(1)}$—$C_{(12)}$ and $C_{(3)}$—$C_{(16)}$ bonds should evidently lead to weakening of the degree of conjugation of the substituents with the heteroring orbitals in PyH$^+$ as compared with PyH$^{\cdot}$. On the whole, the changes in the three-dimensional structure in the oxidation of PyH$^{\cdot}$ are considerably smaller than the corresponding changes in the deprotonation of $PyH_2^{+\cdot}$.

As one should have expected, in PyH$^+$ (Fig. 4) the greatest positive charges are "located" on the $C_{(16)}$, $N_{(1)}$, $C_{(2)}$, and $C_{(4)}$ atoms. In view of the fact that the $C_{(4)}$ atom is relatively weakly shielded, it is precisely this atom that must be regarded as the most likely reaction center in reactions with "hard" nucleophiles.

A comparison of the charges on the atoms in PyH$^{\cdot}$ and PyH$^+$ provides evidence that in the one-electron reduction of the latter most of the electron density is transferred to the heteroring (1.46 e) and the hydrogen atoms (0.25 e) (see Table 1); the charges on the $C_{(4)}$, $C_{(6)}$, and $N_{(1)}$ atoms change most substantially. The Wiberg indexes presented in Fig. 4 indicate the substantially greater (than in other compounds [1]) "aromaticity" of PyH$^+$; this is also manifested in the closeness of the ring bond indexes. At the same time, the degree of conjugation of the substituents with the π system of the ring decreases appreciably (even as compared with $PyH_2^{+\cdot}$); this leads to an increase in the multiplicity of the bonds in the carbamido group.

The contributions of the AO to the lowest vacant molecular orbital (LVMO) of PyH$^+$ are presented in Table 1. This MO is localized primarily in the heteroring, while the highest occupied molecular orbital (HOMO) is localized virtually completely on the $N_{(18)}$ and $O_{(17)}$ atoms of the carbamido group; the most likely reaction centers in reactions with soft nucleophiles are the $C_{(4)}$ and $C_{(6)}$ atoms and, to a somewhat lesser extent, the $N_{(1)}$ atom. In fact, in the reaction of quaternary pyridinium salts with dithionites [10] or with cyanides [11] the addition of the nucleophilic groups takes place at the $C_{(4)}$ atom. Neither steric factors nor the substantial decrease in the degree of conjugation of the carbamide group with the 1-alkyl fragment apparently promote the possibility of the addition of nucleophilic reagents to the $C_{(2)}$ atom as compared with addition to the carbon atom in the 4 position.

One of the important reactions of PyH$^+$ is two-electron reduction (which is accompanied by protonation); from a formal point of view, this corresponds to hydride transfer:

$$PyH^+ + H^- \rightarrow PyH_2.$$

A comparison of PyH$^+$ and PyH_2 (see [1]) makes it possible to conclude that there are marked differences in their structures. Consequently, hydride-ion transfer may play a substantial role only in those cases in which very strong reducing agents — compounds that readily generate a hydride ion — are present in the system; similarly, the presence of strong oxidizing agents — hydride-ion acceptors — is necessary for the reverse reaction. Let us

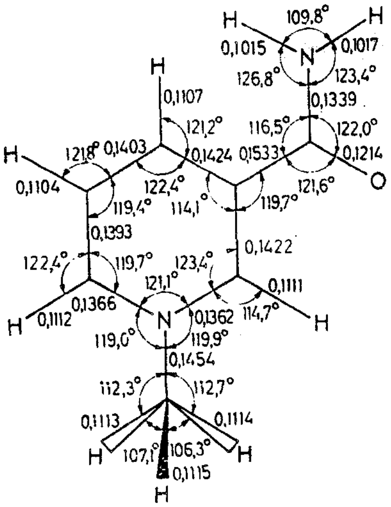

Fig. 3

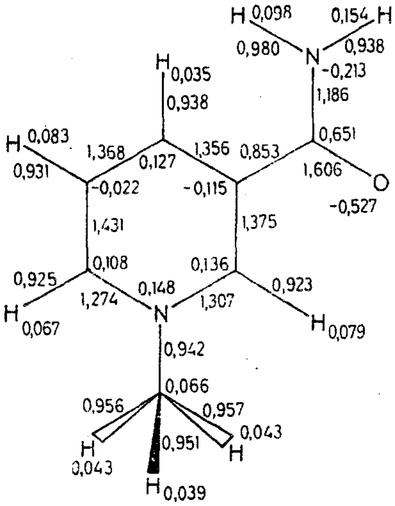

Fig. 4

Fig. 3. Three-dimensional structure of PyH^+. The bond lengths are presented in nanometers.

Fig. 4. Electronic structure of PyH^+.

note that the corresponding changes in the three-dimensional and electronic structures of derivatives of 1,4-dihydropyridines for any of the steps of the corresponding multistep "hydride-equivalent" process, for example, for the following sequence of elementary transformations

$$PyH^+ + \bar{e} \rightarrow PyH^\cdot,$$
$$PyH^\cdot + H^+ \rightarrow PyH_2^{+\cdot},$$
$$PyH_2^{+\cdot} + \bar{e} \rightarrow PyH_2,$$

are appreciably smaller; this constitutes evidence for the possibility of a "milder" pathway — through a step with relatively small potential barriers. Apparently, precisely these reactions play a major role in biochemical processes.

Specific difficulties associated with the solution of the problem of the rates and the nature of the particle or particles being transferred arise when one examines the problem of hydride transfer. First, the results of the high polarizability of the hydride ion itself ($0.0147\ nm^{-3}$ — the maximum value among anions [12]) is that, in the case of its transfer from center to center, the electron cloud is delocalized substantially between them in all stages of the process: in this connection opinions regarding "slow" electron transfer vis-à-vis "fast" hydrogen-atom transfer (or stepwise proton and electron transfer) have been expressed. Second, the relatively great rearrangements in the reagent when a hydride ion is detached, which are associated to a considerable extent with localization of the charge on a small particle, should, in conformity with Hammond's theory, correspond to a large activation barrier. In our opinion, hydride transfer therefore can be effective only in polar media, in the case of a significant difference in the redox properties of the reagents, and in the case of relative instability of the possible intermediates in multistep processes.

The theoretical examination of the problem of hydride transfer based on the results of quantum-chemical calculations also presents certain difficulties (see [13]). First, in the quantum-chemical investigation of the structure of the transition state of a reaction one most absolutely take into account the possible changes in all of the spatial and electronic coordinates. For example, even for, it would seem, a symmetrical transition state in hydride-equivalent transfer between 1,4-dihydropyridine and the corresponding pyridinium salt one must also take into account the unsymmetrical type of potential surface; this corresponds to noncoincidence of the structures for the forward and reverse reactions [14]:

$$PyH_2 + PyH^+ \rightarrow PyH_2^{+\cdot} + PyH^\cdot \rightarrow PyH^+ + (H^\cdot \ldots PyH^\cdot) \rightarrow PyH^+ + PyH_2.$$

The unsymmetrical form of the potential surface substantially complicates making accurate calculations of such complex processes, particularly in view of the need to take into account both the singlet ("pure" hydride transfer [13]) and triplet (a "diradical" pathway that includes a step involving one-electron transfer with the formation of diradical pairs) states of the system. In our opinion, therefore, the "quantum-chemical evidence" for the presence of hydride transfer obtained in a number of studies is not completely convincing.

LITERATURE CITED

1. A. M. Nesterenko, N. I. Buryak, O. M. Polumbrik, and A. A. Yasnikov, Khim. Geterosikl. Soedin. (1988, in press).
2. A. A. Yasnikov, Organic Catalysts, Coenzymes, and Enzymes [in Russian], Naukova Dumka, Kiev (1982), p. 166.
3. N. Klopman, in: Reactivities and Reaction Pathways [Russian translation], edited by H. Klopman, Mir, Moscow (1979), p. 66.
4. B. H. J. Bielski and P. C. Chan, J. Am. Chem. Soc., 102, 1713 (1980).
5. A. Kosower, in: Free Radicals in Biology [Russian translation], Vol. 2, edited by U. Prior, Mir, Moscow (1979), p. 7.
6. J. Dohlman and R. Becker, J. Magn. Reson., 27, 371 (1977).
7. J. A. Pople and D. L. Beveridge, Approximate Molecular Orbital Theory, McGraw-Hill, New York (1970).
8. D. Voet, J. Am. Chem. Soc., 95, 3673 (1973).
9. R. C. Bingham, M. J. S. Dewar and D. H. Lo, J. Am. Chem. Soc., 97, 1285 (1975).
10. A. B. Uzienko, E. K. Pavlova, and A. A. Yasnikov, Ukr. Khim. Zh., 41, 393 (1975).
11. V. Skala and J. Kuthan, Coll. Czech. Chem. Commun., 43, 3064 (1978).
12. B. V. Nekrasov, Fundamentals of General Chemistry [in Russian], Vol. 3, Khimiya, Moscow (1970), p. 95.
13. I. V. Verhoeven, Nucleic Acids, Symp. Ser., No. 14, 1 (1984).
14. P. von Eikeren, P. Kenney, and R. Tormakian, J. Am. Chem. Soc., 101, 7402 (1979).

SATURATED NITROGEN-CONTAINING HETEROCYCLES.

13.* PERHYDROACRIDINES. SYNTHESIS AND STEREOCHEMISTRY

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The configurations of the perhydroacridines formed in the catalytic hydroamination of threo-methylenedicyclohexanone and the product of its cyclization — 2-hydroxy-2,3-tetramethylenebicyclo[3.3.1]nonan-9-one — were established by means of the ^{13}C NMR spectra and alternative synthesis. It is shown that isomers with cis-anti-cis and cis-syn-cis configurations are formed as a result of the reactions. The results of x-ray diffraction analysis are presented for cis-syn-cis-N-(2-hydroxyethyl)perhydroacridine.

We have reported the synthesis of perhydroacridines by means of the catalytic reductive amination of methylenedicyclohexanone (I) and the product (II) of its cyclization [2, 3]. The present research was undertaken in order to establish the stereochemical compositions of the resulting heterocyclic bases.

It is known that a mixture of three or four isomeric perhydroacridines is formed in the hydroamination of oxo compounds I and II by means of the Leuckart reaction [4]: isomers with trans-syn-trans and trans-anti-cis configurations are obtained under the conditions of borohydride amination [5].

We have established that the catalytic reductive amination of I and II proceeds stereospecifically with the formation of heterocycles of the cis,cis type:

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*See [1] for Communication 12.

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