22. A. M. Nesterenko, N. I. Buryak, O. M. Polumbrik, and A. A. Yasnikov, Khim. Geterotsikl. Soedin., No. 12, 1640-1644 (1987).

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

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

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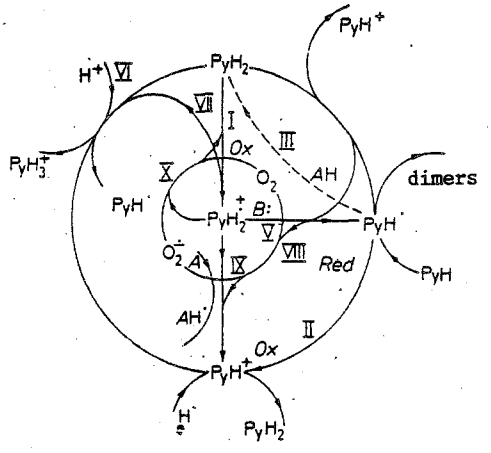
The heat effects of the elementary processes involved in electron and hydrogen transfer with the participation of 1,4-dihydropyridines were calculated by the semiempirical MINDO/3 method. The effect of a number of side and parallel processes on the kinetic principles is discussed in the case of the oxidation 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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TABLE 1. Physicochemical Characteristics of the Most Stable Conformers of 1-Methyl-1,4-dihydronicotinamide Derivatives

Property	PyH_2	$PyH_2^{+\cdot}$	PyH_3^+	$PyH^\cdot$	PYH^+
Energy of formation, kJ/mole	−87,68	610,41	518,37	−1,77	541,77
Ionization potential, eV*	7,89	13,17	13,68	6,39	13,83
Electron affinity, eV	−0,61	6,62	5,13	−0,62	4,94
ΔH_{ox}, eV	7,24	—	—	5,64	—
ΔH_{conf}, kJ/mole	12.37	6.18	—	7,22	5,50

*1 eV corresponds to 96.487 kJ/mole.

mentary processes presented in the scheme. A number of principles follow from data on the energies of formation, the "vertical" [6] ionization potentials, and the electron affinities, as well as the enthalpies of the conformational transitions of the investigated compounds in vacuo (Table 1).

First, a relatively large difference between the ionization potentials of the electrically neutral systems and the electron affinities of the corresponding cations is observed; this constitutes evidence for the existence of nonequilibrium character of processes involving one-electron oxidation (reduction) of the corresponding derivatives of 1,4-dihydropyridines (processes I and II in the scheme). The differences in the indicated calculated energy characteristics are much smaller for processes, the reversibility of which has been established experimentally or is assumed (see [6, 7]). At the same time, the half sums of the ionization potentials and the electron affinities are close to the enthalpies of the corresponding processes determined from the differences in the energies of formation of the starting compounds and the reaction products.

Second, the ionization potential of $PyH^\cdot$ is appreciably smaller than that of PyH_2, whereas the difference in the electron affinities of these compounds are insignificant. Further, it follows from the energies of formation of $PyH^\cdot$ and PyH_2 presented in Table 1 that the pyridinyl radical, which has a very low affinity for the hydrogen atom ($\Delta H = -85.9$ kJ/mole), cannot effectively dehydrogenate even compounds in which the C–H bond is weakened substantially (process III).

According to the data obtained, $PyH_2^{+\cdot}$ should readily split out a hydrogen atom ($\Delta H = -68.6$ kJ/mole, process IV). In fact, a study of the mass spectra of PyH_2 showed [8] that the $PyH_2^{+\cdot}$ formed in its ionization readily loses a hydrogen atom to give the thermodynamically stable PyH^+ cation.

The question of the tendency for $PyH_2^{+\cdot}$ to split out a proton is important for an understanding of the peculiarities of the reactivities of 1,4-dihydropyridines in their one-electron oxidation. Since this process is not reversible and is not an equilibrium process, the experimental results regarding the strength of $PyH_2^{+\cdot}$ as a C–H acid permit different interpretations that lead to contradictory data ($pK_a = -3.5$ [9] and $pK_a = 3.5$ [10]). The results presented in Table 1 make it possible to estimate the proton affinity of $PyH^\cdot$ in the gas phase as being $\Delta H = -919.2$ kJ/mole (process V). This value undoubtedly has qualitative character, and one must use extreme caution in comparing it with the data for condensed systems [11]; however, a comparison of it with the calculated characteristics of other compounds (see [12, 13]), particularly vinylamine [14] and its derivatives [15], makes it possible to assume that $pK_a = 3.5$ is the more correct value.

One of the possible pathways for the decomposition of $PyH_2^{+\cdot}$ in the absence of bases – proton acceptors – is its reaction with PyH_2, which leads to protonation of the latter (process VI). Since the difference in the energies of formation of PyH_3^+ and PyH_2 corresponds to proton affinity $\Delta H = -935.3$ kJ/mole, according to our data, the heat effect of the indicated isodesmic reaction is $\Delta H = 6.1$ kJ/mole. Consequently, in the absence of bases $PyH_2^{+\cdot}$ can protonate PyH_2 (process VII); this has a substantial effect on the kinetics of oxidation of 1,4-dihydropyridines in that it changes both the reaction order and the apparent rate constant of the reaction.

Another effective pathway for the destruction of $PyH_2^{+\cdot}$ cation radicals is their reaction as an oxidizing agent with the $PyH^\cdot$ pyridinyl radical formed during its deprotonation

(process VIII). The data presented in Table 1 make it possible to estimate the change in enthalpy in this reaction as being $\Delta H = -154.6$ kJ/mole.

Data that characterize their redox potentials $E_{1/2}$ are also valuable for an understanding of the peculiarities of the reactions of 1,4-dihydropyridines in an aqueous medium (and primarily for interpretation of the mechanisms of reactions with the participation of the coenzymes NADH and NADPH). In a number of cases the indicated potentials can be sufficiently accurately estimated on the basis of empirical relationships between $E_{1/2}$ and the ionization potentials (or electron affinities) [16]. When we used the relationships proposed in [16] and the thermochemical values of the ionization potentials and electron affinities (Table 1), we obtained the following characteristics (for solutions of 1-methyl-1,4-dihydronicotinamide in acetonitrile with respect to a saturated calomel electrode): $E^{red}_{1/2} = -1.92$ V, $E^{ox}_{1/2} = 0.96$ V. The experimentally determined $E^{ox}_{1/2}$ value for 1-benzyl-1,4-dihyronicotinamide in aqueous solutions with respect to a saturated calomel electrode is ~0.81 V [9]; this is in good agreement with the calculated value. Incidently, the "vertical" ionization potential of PyH_2 is also in good agreement with the experimental data (see [1]).

In conformity with the data presented in Table 1 for PyH$^{\bullet}$ with the use of the same empirical relationships [16] we obtained the following redox potentials: $E^{red}_{1/2} = -1.93$ V, $E^{ox}_{1/2} = -0.127$ V.

Since the oxidation potential of oxygen in water at an oxygen pressure of 101 kPa is 0.28-0.32 V with respect to a standard hydrogen electrode [17], its potential with respect to a saturated calomel electrode is 0.04-0.08 V. Oxygen therefore is not inclined to oxidize PyH_2 in aqueous solutions but can readily oxidize the corresponding PyH$^{\bullet}$ pyridinyl radical, the oxidation potential of which is appreciably lower (−0.127 V) (process IX). On the other hand, complication of the occurrence of the primary oxidation of PyH_2 by side processes is possible when oxygen is present in the 1,4-dihydropyridine–water–strong oxidizing agent system. In particular, the high oxidation potential of PyH_2^+, which is 0.96 V, can lead to the result that the superoxide radical $O_2^{\bullet-}$ formed in the oxidation of pyridinyl radicals can be oxidized by both a strong oxidizing agent and by $PyH_2^{+\bullet}$ (process X); the indicated reaction evidently corresponds qualitatively to inhibition of the principal process of oxidation of PyH_2. Let us note that inhibition by oxygen has also been established experimentally for this reaction [18].

The occurrence of redox reactions with the participation of 1,4-dihydropyridines evidently plays a substantial role in their high biological activity. For example, 1,4-dihydropyridines affect the effectiveness of transport of Ca^{2+} ions through membranes [19]. It may be assumed that the mechanism of this effect is due to the possibility of complexing at the carbamido group of 1,4-dihydronicotinamide, which promotes transport through the membrane; the oxidation of 1,4-dihydronicotinamide in the diffused complex evidently leads to its decomposition and the release of Ca^{2+} ions.

LITERATURE CITED

1. A. M. Nesterenko, N. I. Buryak, O. M. Polumbrik, and A. A. Yasnikov, Khim. Geterotsikl. Soedin., No. 1, 58 (1988).
2. O. Yu. Okhlobystin, Electron Transfer in Organic Reactions [in Russian], Izd. Rost. Univ., Rostov-on-Don (1974), p. 53.
3. G.-É. Ya. Dubur, "1,4-Dihydropyridines – their reactivities and biological properties," Author's Doctoral Dissertation Abstract, Riga (1979).
4. J. Grodkowski, P. Neta, B. W. Carlson, and L. Miller, J. Phys. Chem., 87, 3135 (1983).
5. A. M. Nesterenko, N. I. Buryak, O. M. Polumbrik, and A. A. Yasnikov, Khim. Geterotsikl. Soedin., No. 12, 1640 (1987).
6. M. Dewar, Molecular Orbital Theory in Organic Chemistry [Russian translation], Mir, Moscow (1972), p. 346.
7. A. M. Nesterenko, O. M Polumbrik, I. G. Ryabokon', and L. N. Markovskii, Zh. Obshch. Khim., 54, 1330 (1984).
8. B. J. S. Wang and E. R. Tornton, J. Am. Chem. Soc., 90, 1216 (1968).
9. B. W. Carlson, L. L. Miller, P. Neta, and J. Grodkowski, J. Am. Chem. Soc., 106, 7233 (1984).
10. Sh. Fukuzumi, Yu. Kondo, and T. Tanaka, J. Chem. Soc., Perkin 2, No. 3, 673 (1984).
11. M. I. Kabachnik, Usp. Khim., 48, 1523 (1979).
12. I. A. Koppel' and U. Kh. Mel'der, Reakts. Sposobn. Org. Soedin., 20, 3 (1983).

13. J. Catalan, O. Mo, P. Perez, and M. Yanez, J. Am. Chem. Soc., 101, 6520 (1979).
14. R. A. Eades, D. A. Weil, M. R. Ellenberger, W. E. Farneth, D. A. Dixon, and C. H. Douglass, J. Am. Chem. Soc., 103, 5372 (1981).
15. D. D. Perin, Dissociation Constants of Organic Bases in Aqueous Solution, Butterworths, London (1965).
16. G. Briegleb, Angew. Chem., 76, 326 (1964).
17. I. B. Afanas'ev, Usp. Khim., 48, 977 (1979).
18. M. F. Powell, J. C. Wu, and T. C. Bruice, J. Am. Chem. Soc., 106, 3850 (1984).
19. P. G. Kostyuk, Calcium and Cell Excitability [in Russian], Nauka, Moscow (1986).

FLUORESCENCE OF 3,5-DIETHOXYCARBONYL-1,4-DIHYDROPYRIDINE DERIVATIVES AND THEIR ANIONS

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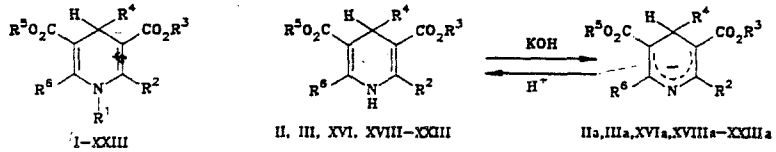
The fluorescence spectra of a group of 3,5-diethoxycarbonyl-1,4-dihydropyridine (1,4-DHP) derivatives were investigated. The introduction of electron-acceptor N-substituents and 2,6-methyl groups decreases Q markedly. The fluorescence spectra of 1,4-DHP anions are shifted bathofluorically, and the Q values are higher than for the corresponding 1,4-DHP. The fluorescence spectra have large Stokesian shifts, which are decreased for 1,4-DHP anions. A good correlation exists between the λ_{max} values of the fluorescence bands of 1,4-DHP anions and the Hammett σ_p^+ constants of the 4-R-aryl substituents.

The literature contains a wealth of information on the electronic absorption spectra of 1,4-dihydropyridines (1,4-DHP) [1, 2] and only a small amount of qualitative data on the fluorescence spectra [3, 4]. The quantitative determination of the fluorescence characteristics of 1,4-DHP derivatives in organic solvents and biological probes is of interest, and systematic studies of the fluorescence spectra of a number of 1,4-DHP derivatives were therefore made.



I–XXIII II, III, XVI, XVIII–XXIII IIa,IIIa,XVIa,XVIIIa–XXIIIa

I—III, XI, XII, XV, XVI, XVIII—XXIII R^1=H, IV, V, XIII, XIV, XVII R^1=CH_3, VI R^1=*iso*-C_3H_7, VII R^1=$CH_2COOC_2H_5$, VIII R^1=CH_2COOH, IX R^1=$COOC_2H_5$, X R^1=SO_2CH_3; I—XIV R^2=H, XV—XXIII R^2=CH_3; I—X, XV—XXIII R^3=R^5=C_2H_5, XI, XIII R^3=R^5=H, XII, XIV R^3=H, R^5=C_2H_5; I, XV R^4=H, II, IV, VI—XIV, XVI, XVII R^4=C_6H_5, III, V, XVIII R^4=4-$CH_3OC_6H_4$, XIX R^4=3-pyridyl, XX R^4=4-ClC_6H_4, XXI R^4=4-HOC_6H_4, XXII R^4=4-$CH_3C_6H_4$, XXIII R^4=4-$NO_2C_6H_4$

The spectral parameters of 1,4-DHP derivatives (I-XXIII) and their anionic forms (IIa, IIIa, XVIa, XVIIIa-XXIIIa), which are formed in the deprotonation of the nitrogen atom of the DHP ring (R^1 = H), are presented in Tables 1 and 2.

3,5-Diethoxycarbonyl-1,4-DHP (I) in ethanol solution has blue luminescence (λ_{max} 461 nm) with relative quantum yield Q = 0.59. The introduction of a 4-phenyl (II) or 4-(4'-methoxyphenyl) (III) substituent shifts the fluorescence spectrum hypsofluorically by 21-23 nm. N-Alkyl substitution (IV, VI) has little effect on the fluorescence spectra ($\Delta\lambda$ = 4 nm), in contrast to the excitation spectra, in which a bathochromic shift of 13 nm is observed when the nitrogen atom of the 1,4-DHP ring is methylated (II and IV). This can be explained in part by the asymmetry of the fluorescence band. Thus a poorly expressed vibrational

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