ab initio MO-SCF STUDY OF PROTOTROPIC TRANSFORMATIONS OF NON-SUBSTITUTED DIHYDROPYRIDINES*

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The equilibrium systems formed by ionization of all the isomeric dihydropyridines *I*, *II*, *III*, *IV*, and *V* with the particles H_3O^+, H_2O and OH^- have been characterized on the basis of the total energy changes calculated with the use of the STO-3G and 4-31G basis sets. Relative thermodynamic stabilities of the corresponding dihydropyridine forms are discussed.

Simple dihydropyridines are remarkable first for their relation to a number of important chemical and biochemical processes, next for obvious lability of their molecules as compared with pyridine molecule. Using the semi-empirically calculated[1] heats of formation and non-empirically calculated molecular energies[2] it was predicted that the molecules of 6π-electron isomers *I* and *II* would be more stable thermodynamically than the 4π-electron isomers *III*, *IV*, and *V*. A presumption was also proposed[2] that tautomerisms $II \rightleftharpoons IV$ and $III \rightleftharpoons I \rightleftharpoons IV$ could be significant in real systems, especially so under conditions of suitable prototropic catalysis. With the aim of elucidation of probability of such equilibria, we decided to examine the systems involving ionized or non-ionized water molecules as the proton carriers. Bodor and Pearlman characterized[1] the formerly known molecular particles $I - V$ by their heats of formation and atomic charges calculated by the MINDO/3 method. This paper brings our results obtained by means of non-empirical MO calculations using the STO-3G and 4-31G basis sets.

CALCULATIONS

The *ab initio* MO calculations of the ions *Ia* – *Va*, *Ib*, *IIb*, H_3O^+, OH^- and water molecule were carried out in the STO-3G and 4-31G bases using the standard Gaussian 76 program. The starting molecular geometries were taken from refs[3,4]. The calculated molecular energies are given in Table I. Due to incomplete description of geometry of the compound *IVa* in ref.[1], the structure of *IVa* was submitted to full optimization on the basis of the MINDO/3 wave function. The complete geometry parameters are given in Table II. The optimized structure *IVa* appears to be a better approximation from the point of view of non-empirical total energy as compared with ref.[1].

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RESULTS AND DISCUSSION

The equilibrium constants $K_A - K_D$ characterizing acid protonation (*A*), neutral protonation (*B*), neutral deprotonation (*C*), and basic deprotonation (*D*) can be considered to be theoretical measure of prototropic stability and acid-base properties of the dihydropyridines *I* – *V* in contact with humidity in gas phase.

$$\mathrm{DHP} + \mathrm{H_3O^+} \xrightleftharpoons{K_A} \mathrm{DHPH^+} + \mathrm{H_2O}\,, \tag{A}$$

$$\mathrm{DHP} + \mathrm{H_2O} \xrightleftharpoons{K_B} \mathrm{DHPH^+} + \mathrm{OH^-}\,, \tag{B}$$

$$\mathrm{DHP} + \mathrm{H_2O} \xrightleftharpoons{K_C} \mathrm{DP^-} + \mathrm{H_3O^+}\,, \tag{C}$$

$$\mathrm{DHP} + \mathrm{OH^-} \xrightleftharpoons{K_D} \mathrm{DP^-} + \mathrm{H_2O}\,, \tag{D}$$

where the symbol DHP corresponds to some of the dihydropyridines *I* – *V*, and the symbols $\mathrm{DHPH^+}$ and $\mathrm{DP^-}$ to some of the ionized forms *Ia* – *Va* and *Ib* or *IIb*,

TABLE I

Total energy *E* of the structures studied

Compound	STO-3G[a]	4-31G[a]
I	−244·76245	−247·44860
II	−244·76533	−247·45287
III	−244·77812	−247·44144
IV	−244·77998	−247·44169
V	−244·78165	−247·44595
Ia	−245·15085	−247·76658
IIa	−245·14856	−247·76742
IIIa	−245·16039	−247·77882
IVa	−245·22658	−247·83353
Va	−245·14772	−247·77138
Ib	−244·01406	−246·81142
IIb	−244·01638	−246·81478
H_2O	− 74·95892	− 75·90014
H_3O^+	− 75·32687	− 76·19348
OH^-	− 75·05757	− 75·22965

[a] The *E* values are given in non-dimensional units defined as: $E = E_{tot}/k$, where $k = 2\,625{\cdot}5\ \mathrm{kJ\,.\,mol^{-1}}$.

TABLE II

Geometry of the *IVa* molecule optimized with respect to all degrees of freedom on the basis of the MINDO/3 wave function

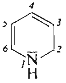
Bond	Length (pm)	Valence angle	Magnitude (°)	Torsion angle	Magnitude (°)
N(1)—C(2)	129·21	C(4)—C(3)—C(2)	115·7	C(4)—C(3)—C(2)—N(1)	1·4
C(2)—C(3)	149·55	C(5)—C(4)—C(3)—	115·0	C(5)—C(4)—C(3)—C(2)	−4·5
C(3)—C(4)	153·95	C(6)—C(5)—C(4)	123·6	C(6)—C(5)—C(4)—C(3)	4·3
C(4)—C(5)	149·52	N(1)—C(6)—C(5)	118·4	N(1)—C(6)—C(5)—C(4)	−0·5
C(5)—C(6)	134·82	C(2)—N(1)—C(6)	125·5	C(2)—N(1)—C(6)—C(5)	−3·3
C(6)—N(1)	141·32	C(3)—C(2) N(1)	121·5	C(3)—C(2)—N(1)—C(6)	2·7
H(1)—N(1)	102·85	H(1)—N(1)—C(6)	114·9	H(1)—N(1)—C(6)—C(5)	176·4
H(2)—C(2)	111·45	H(2)—C(2)—C(3)	119·8	H(2)—C(2)—C(3)—C(4)	−177·3
H(3)^a—C(3)	111·65	H(3)^a—C(3)—C(2)	106·8	H(3)^a—C(3)—C(2)—N(1)	−123·8
H(3)^a—C(3)	111·75	H(3)^b—C(3)—C(2)	106·7	H(3)^b—C(3)—C(2)—N(1)	126·8
H(4)^a—C(4)	111·59	H(4)^a—C(4)—C(3)	109·8	H(4)^a—C(4)—C(3)—C(2)	−128·5
H(4)^b—C(4)	111·54	H(4)^b—C(4)—C(3)	109·7	H(4)^b—C(4)—C(3)—C(2)	118·7
H(5)—C(5)	110·34	H(5)—C(5)—C(4)	117·7	H(5)—C(5)—C(4)—C(3)	−176·0
H(6)—C(6)	110·67	H(6)—C(6)—N(1)	114·7	H(6)—C(6)—N(1)—C(2)	175·2

[a,b] The symbol *a* and *b* denotes the hydrogen atoms situated above and below the plane of the heterocyclic ring, respectively.

respectively. With respect to definition of the Gibbs free energy change $\Delta G = -RT \, . \ln K$, the equilibria $(A)-(D)$ will be shifted to the right, if the $\Delta G_{\mathrm{A-D}}$ values are negative at the given temperature. Further we introduce a simplifying presumption that (within semi-quantitative considerations of the examined series of species *I* – *V*, *Ia* – *Va*, *Ib*, *IIb*) the order of $K_{\mathrm{A}} - K_{\mathrm{D}}$ will not be changed by correction to zero point and – to a certain extent – by contribution of correlation energy. In this way the Gibbs energies $\Delta G_{\mathrm{A-D}}$ can be acceptably approximated by the energy differences $\Delta E_{\mathrm{A-D}}$ defined by Eq. (*1*)

$$\Delta E = - \sum_{\text{reactants}} E_{\text{tot}} + \sum_{\text{products}} E_{\text{tot}} \,, \tag{I}$$

where the symbol E_{tot} corresponds to total molecular energy (calculated by the *ab initio* MO method – see Table I). On the basis of this reasoning it is thus possible to consider high positive values of these energies (*i.e.* $\Delta E_{\mathrm{A-D}} \gg 0$) to be prediction of non-probability of the corresponding processes $(A)-(D)$, whereas the value $\Delta E_{\mathrm{A-D}} \ll 0$ indicate these processes to be highly effective.



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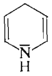

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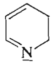

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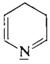

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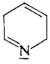
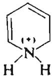
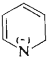


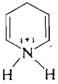
V



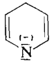
Ia



Ib



IIa



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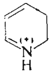
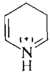
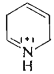


IIIa



IVa



Va

With respect to the fact that application of the STO-3G and 4-31G basis sets leads to markedly underestimated calculated energies of negative ions (*i.e.* DP^- and OH^- in our case), comparison of the ΔE values given in Table III for various processes $(A)-(D)$ may seems not to be well-founded. It is obvious that only the ΔE_{A} values can be considered quite acceptable, energies of neutral and positive particles being only involved in their calculation. In the case of the (B) process it is obvious that especially the calculation accuracy of hydroxyl ion energy should affect the absolute values of ΔE_{B} only and not their order. If the used energies of OH^- and H_2O particles were calculated in the extended[5] AOs basis sets or with involvement of the correlation energy contribution[6,7], then the obtained ΔE_{B} values were higher by 10·5 kJ mol^{-1} or lower by 213·4 kJ mol^{-1}, respectively, than those obtained with the use of mere 4-31G basis set. These corrections indicate the distinct role of the correlation energy for OH^- and H_2O particles, but they do not markedly change the relation between the ΔE_A and ΔE_B values, the former remaining negative, and the latter remaining positive with higher absolute value. As no similar correlation could be carried out for the structurally more complex DP^- ions, the interpretations of ΔE_C and ΔE_D values must be considered uncertain and suitable for qualitative conclusions only.

Table III summarizes the energy data calculated from Eq. (*1*) and indicating that application of STO-3G and 4-31G basis sets leads mostly to qualitatively identical interpretation conclusions. From the quantitative point of view, the 4-31G energies are preferred, and the subsequent discussion is based entirely on their interpretation.

TABLE III

The calculated energies of the processes (*A*)—(*D*)

Process	Type	STO-3G[a]	4-31G[a]
I→*Ia*	(*A*)	−53·69	−327·26
I→*IIIa*	(*A*)	−78·72	−96·84
I→*Va*	(*A*)	−45·47	−77·32
III→*IIIa*	(*A*)	−11·33	−115·70
V→*Va*	(*A*)	4·96	−84·27
II→*IIa*	(*A*)	−40·10	−55·70
II→*IVa*	(*A*)	−245·00	−229·27
IV→*IVa*	(*A*)	−206·49	−258·62
I→*Ia*	(*B*)	1 346·74	924·59
I→*IIIa*	(*B*)	1 321·70	893·37
I→*Va*	(*B*)	1 354·95	912·89
III→*IIIa*	(*B*)	1 362·84	874·51
V→*Va*	(*B*)	1 405·37	905·94
II→*IIa*	(*B*)	1 360·31	934·49
III→*IVa*	(*B*)	1 155·47	760·94
IV→*IVa*	(*B*)	1 193·94	731·59
I→*Ib*	(*C*)	998·82	902·76
III→*Ib*	(*C*)	1 039·95	883·89
V→*Ib*	(*C*)	1 048·98	895·81
II→*IIb*	(*C*)	1 000·30	905·13
IV→*IIb*	(*C*)	1 038·78	875·79
I→*Ib*	(*D*)	−401·60	−87·45
III→*Ib*	(*D*)	−360·46	−106·30
V→*Ib*	(*D*)	−351·18	−94·40
II→*IIb*	(*D*)	−400·11	−85·08
IV→*IIb*	(*D*)	−361·64	−114·42

[a] The energy values are given in kJ mol^{-1}.

From Table III it is seen that all the calculated ΔE_B and ΔE_C values are strongly positive, hence ionization of the dihydropyridines *I*–*V* on contact with a water molecule can be considered negligible. Negative values of ΔE_A for 1,2-dihydropyridine (*I*) indicate a possible protonation of the substrate at 1, 3 and 5 positions, the relative amounts of the protonated forms being *Ia* > *IIIa* > *Va*, which differs from the prediction based on the heats of formation and the electron distribution obtained[1] by the MINDO/3 calculation. According to the ΔE_A values, the 1,4-dihydropyridine (*II*) should be spontaneously transformed (on action of H_3O^+) into *IVa* and *IIa* forms, the C-protonated form *IVa* being obviously dominant in accordance with the mentioned[1] approach based on MINDO/3, which agrees in predicting an easier protonation at 3 position than at 1 position. A similar ability of ionization is predicted from negative ΔE_A values for 2,3- (*III*) and 2,5-dihydropyridines (*V*) which give exclusively the 1-ionized forms *IIIa* and *Va*, respectively. Negative ΔE_A value of 3,4-dihydropyridine (*IV*) predicts an efficient formation of the N-protonated form *IVa*.

As already mentioned, the given conclusions do not differ qualitatively from the prediction of protonation[1] based on the semi-empirical MINDO/3 method, even though the authors cited did not use a purely thermodynamic criterion. Acceptability of our thermodynamic approach is seen in the common chemical experience *viz.* that prototropic transformations are so fast that kinetic effect is practically insignificant for composition of the reaction mixtures.

TABLE IV

Prediction of tautomerism for the dihydropyridines *I*–*V*

Tautomerism	Ionization scheme	Process	Catalyst	Spontaneous course[a]
$III \rightleftharpoons I \rightleftharpoons V$	$III \rightarrow IIIa \leftarrow I$	(*A*)	H_3O^+	+
	↓			
	$V \rightarrow Va$	(*B*)	H_2O	—
	$I \rightarrow Ib \leftarrow III$	(*C*)	H_2O	— (?)
	$V \nearrow$	(*D*)	OH^-	+ (?)
$II \rightleftharpoons IV$	$II \rightarrow IVa \leftarrow IV$	(*A*)	H_3O^+	+
		(*B*)	H_2O	—
	$II \rightarrow IIb \leftarrow IV$	(*C*)	H_2O	— (?)
		(*D*)	OH^-	+ (?)

[a] + means likely, — means unlikely.

Prototropic dihydropyridine tautomerism: Character of the calculated ΔE_{A-D} values given in Table II enables – to a certain extent – to assess the effect of the presence of H_2O, H_3O^+ or OH^- particles on the previously considered[2] tautomeric processes $III \rightleftharpoons I \rightleftharpoons V$ and $II \rightleftharpoons IV$. It can be expected that ionization will be able to evoke spontaneous course of these processes, if the energy change of the elementary reaction steps defined by Eq. (*1*) is negative. In the opposite case no favourable effect of the given type of ionization on establishing of the tautomeric equilibrium can be expected. In Table IV and attempt is made to predict qualitatively the effect of the ionization equilibria (*A*)–(*D*) on the said tautomerism. Obviously, the interaction with water molecules should not be favourable, because the ΔE_B values are always positive (Table III). On the contrary, 1,2- (*I*) and 1,4-dihydropyridines (*II*) should exhibit tautomerism on interaction with H_3O^+ ions in accordance with the corresponding ΔE_A values.

Basic properties of the dihydropyridines I–V: Comparison of the theoretically calculated energy requirements for the processes (*A*), (*B*) makes it possible to suggest basicity order of the individual isomeric dihydropyridines *I* – *V* with respect to the interacting type of the particle, the protonation being possible both at nitrogen and at carbon (N- and C-basicity, respectively). For the protonation (*A*) the N-basicity order is: $I > IV > III > V > II$. In comparison of the C-basicities, 1,4-dihydropyridine (*II*) is considerably preferred to 1,2-dihydropyridine (*I*). If the basicity type is not taken into account, the order is: $I > IV > II > III > V$, *i.e.* the 1,2-dihydro derivative *I* is the most basic one. Similar reasoning for the process (*B*) results in the N-basicity order: $IV > III > V > I > II$, which is different from the process (*A*), the C-basicity order being identical for (*A*) and (*B*). With respect to total basicity, the most substantial difference is that in basicity of 1,2-dihydropyridine (*I*) in the order: $IV > II > III > I > V$.

Charge distribution: Comparison of the charge distribution (Table V) obtained by the Mulliken population analysis on the basis of semi-empirical and non-empirical wave functions exhibits qualitatively different features for calculation of cations and anions.

If the population derived from the non-empirical 4-31G wave function is considered most reliable, then comparison of the both non-empirical populations leads to qualitatively identical conclusions. Some insignificant deviations are encountered with the cations *Ia* – *Va* for those populations only which are close to zero, and thus STO-3G (with respect to lower charge localization) gives a population differing in sign. For the *Ib* and *IIb* anions the STO-3G basis set (similar to the valence MINDO/3 base) provides probably non-realistic negative populations at all hydrogen atoms.

Of course, far more serious differences can be observed when comparing the MINDO/3 charge populations[1] with the 4-31G charge distribution. In the case

TABLE V

Comparison of the calculated charge densities for ionized forms of the dihydropyridines *I*—*V*

Calculation	N(1)	C(2)	C(3)	C(4)	C(5)	C(6)	H(1)[a]	H(2)[a]	H(3)[a]	H(4)[a]	H(5)[a]	H(6)
						1-Hydrogen-1,2-dihydropyridinium (*Ia*)						
MINDO/3[b]	0·259	0·096	—0·010	0·011	0·097	—0·069	0·106 0·107	0·039 0·038	0·079	0·074	0·078	0·095
STO-3G	—0·287	—0·032	—0·017	—0·057	0·002	0·030	0·306 0·306	0·134 0·134	0·110	0·113	0·133	0·123
4-31G	—0·964	—0·176	—0·141	—0·183	—0·151	0·068	0·457 0·457	0·272 0·272	0·258	0·264	0·281	0·286
						1-Hydrogen-1,4-dihydropyridinium (*IIa*)						
MINDO/3[b]	0·316	—0·073	0·077	0·047	—0·075	0·076	0·098 0·099	0·098	0·078	0·042 0·042	0·083	0·093
STO-3G	—0·293	0·035	0·016	—0·137	0·007	0·010	0·304 0·304	0·126	0·136	0·127 0·237	0·123	0·115
4-31G	—1·003	0·090	—0·102	—0·464	—0·101	0·032	0·454 0·454	0·285	0·279	0·266 0·266	0·265	0·280
						3-Hydrogen-1,2-dihydropyridinium (*IIIa*)						
MINDO/3[b]	0·078	0·115	0·011	0·140	—0·110	0·269	0·123	0·030 0·031	0·044 0·045	0·068	0·092	0·062
STO-3G	—0·249	—0·004	—0·132	0·054	—0·083	0·205	0·288	0·108 0·129	0·126 0·127	0·142	0·123	0·167
4-31G	—0·805	—0·105	—0·467	—0·022	—0·294	0·321	0·443	0·240 0·269	0·269 0·269	0·287	0·277	0·317

3-Hydrogen-1,4-dihydropyridinium (*IVa*)											
MINDO/3	0·178	0·194	0·025	0·050	0·049	−0·027	0·114	0·072	0·052 0·050	0·036 0·033	0·080	0·096
STO-3G	−0·243	0·225	−0·112	−0·107	0·003	0·031	0·306	0·171	0·127 0·126	0·110 0·109	0·127	0·127
4-31G	−0·830	0·348	−0·442	−0·369	−0·143	0·094	0·459	0·313	0·267 0·266	0·244 0·243	0·266	0·287
5-Hydrogen-1,2-dihydropyridinium (*Va*)											
MINDO/3[b]	0·120	0·129	−0·036	0·005	0·034	0·228	0·114	0·035 0·036	0·083	0·074	0·054 0·055	0·072
STO-3G	−0·242	−0·012	−0·035	−0·030	−0·137	0·227	0·288	0·129 0·129	0·118	0·118	0·140 0·140	0·169
4-31G	−0·786	−0·149	−0·168	−0·120	−0·515	0·355	0·442	0·268 0·268	0·264	0·264	0·281 0·281	0·314
2-Hydridopyridyl anion (*Ib*)											
MINDO/3[b]	−0·414	0·377	−0·287	0·181	−0·379	0·279	—	−0·202 −0·203	−0·054	−0·122	−0·040	−0·135
STO-3G	−0·409	0·012	−0·173	−0·057	−0·243	0·044	—	−0·039 −0·040	−0·030	−0·011	−0·037	−0·016
4-31G	−0·717	−0·024	−0·299	−0·106	−0·412	0·149	—	0·045 0·045	0·073	0·093	0·070	0·086

TABLE V
(*Continued*)

Calculation	N(1)	C(2)	C(3)	C(4)	C(5)	C(6)	H(1)[a]	H(2)[a]	H(3)[a]	H(4)[a]	H(5)[a]	H(6)
4-Hydridopyridyl anion (*IIb*)												
MINDO/3[b]	−0·426	0·237	−0·316	0·326	−0·290	0·217	—	−0·129	−0·052	−0·192 −0·192	−0·066	−0·117
STO-3G	−0·448	0·019	−0·174	−0·072	−0·175	0·021	—	−0·009	−0·034	−0·045 −0·038	−0·029	−0·015
4-31G	−0·785	0·018	−0·301	−0·246	−0·295	0·107	—	0·097	0·065	0·043 0·047	0·073	0·088

[a] The upper and the lower values belong to the hydrogen atoms above and below the plane of the heterocyclic ring, respectively. [b] Taken from ref.[1].

of anions the hydrogen populations are overestimated on the one hand, and on the other hand the populations at the sp^3 carbon centres are considerably underestimated. The other populations show at least approximative qualitative agreement. In the case of calculation of cations. of course, the MINDO/3 charge distribution[1] leads to entirely different qualitative conclusions both for C- and for N-protonations.

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