CONTRIBUTION TO QUANTUM-CHEMICAL INTERPRETATION OF 3-AMINOCARBONYLPYRIDINIUM CATION REACTIVITY*

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Received October 22nd, 1975

Reactivity characteristics of 1-methyl-3-aminocarbonylpyridinium cation (*I*) have been studied on the basis of HMO, SCF-MO, EHT and CNDO/2 methods with special respect to attack by nucleophilic and free-radical reagents. It has been demonstrated that biological reducibility of nicotinamideadenine dinucleotide (NAD^+) (modelled by the ion *I*) to dihydronicotinamide-adenine dinucleotide (NADH) can be interpreted in the terms of the isolated molecule approximation most easily as a nucleophilic attack by a reduced biological substrate having properties of very "soft" nucleophile. In this context LUMO symmetry in all theoretical models of the ion *I* is considered important. In connection with the choice of the appropriate EHT and CNDO/2 wave functions some aspects of geometry of the ion *I* have been discussed with respect to recent experimental facts.

Action of nicotinamideadenine dinucleotide (NAD^+) in biochemical oxidation of a given substrate consists in formal transport of hydride ion to 4-position of the quarternary salt *I* (R = adenosino(di)phosphateribosyl) giving the respective reduced form *II*, *i.e.* 1,4-dihydronicotinami-deadenine dinucleotide (NADH). So far, however, it was impossible to decide unambiguously whether the transport has one or two steps[1-4].

Quantum chemistry can contribute to solution of this problem by interpretation of reactivity of a suitable model of the ion *I*. An extensive experiment in this direction was carried out on the basis of simple HMO method[5-7]. Sorry to say that the calculated characteristics were interpreted with the presumption that 4-position of the ion *I* must be the most reactive one to nucleophilic attack. However, this presumption was made doubtful by the further development in the field of dihydropyridines, especially so after introduction of complex hydrides in syntheses of these compounds[8-12]. Borohydride reductions of the ions type *I* give 1,6-dihydropyridine derivative *III* as the main reaction product in a number of cases[13], and, in accord with that, also NAD^+ gives, on action with sodium borohydride, probably the 1,6-dihydro analogue of NADH (ref.[14]) which is little active enzymatically. Therefore, the arguments of HMO studies[5-7] cannot be considered sufficient for unambiguous support of nucleophilic character of the biochemical reduction with NAD^+.

* Part V in the series On Calculations of Biologically Important Compounds; Part IV: This Journal *41*, 3282 (1976).

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In this work we tried to show that within the HMO method it is possible to come to a better understanding of the reactivity of ion *I* (below always R = CH_3) by applying the Klopman–Hudson concept[15,16] of "soft" and "hard" reagents and by appropriate choice of the chemical reactivity indices. By introduction of SCF procedure in the π-approximation as well as EHT and CNDO/2 we tried to verify the extent of the influence of the extremely approximative character of HMO procedure itself on the conclusions obtained.

CALCULATIONS

The calculations of π-electron density were carried out by the HMO method[17] using the empirical parameters $h_{CH_3} = 2{\cdot}0$; $h_{N^+} = 0{\cdot}0$ to $2{\cdot}5$; $h_N = 1{\cdot}5$; $h_O = 1{\cdot}0$; $k_{N-CH_3} = 0{\cdot}7$; $k_{C-N^+} = 1{\cdot}0$; $k_{C-N} = 0{\cdot}8$; $k_{C=O} = 1{\cdot}0$ and by SCF procedure according to the Pople version[18]. The used values of ionization potentials IP, electron affinities EA, and exchange integrals β are summarized in Table I. The calculations on the level of all valence electrons were carried out by EHT and CNDO/2 procedures[20,21]. In contrast to former EHT calculations[22] of the cation *I*, where the diagonal elements of **H**-matrix were approximated by the VOIP values according to Hinze and Jaffé[23], in the present work we have used the values published by Skinner and Pritchard[24]. For the Slater exponent of hydrogen we have used the value 1·3 which, according to our view and in accord with the work[25], gives somewhat more realistic course of the dependence of energy *vs* the rotation angle α in the region $\alpha = 90°$. The IP values are summarized in Table II along with the corresponding Slater exponents. The necessary geometrical data were taken from X-ray analysis results of the quarternary salt *I* (R = CH_3) with 9-adenyl acetate obtained by Voet[26]. The same geometry was

TABLE I

The Parameters Used in SCF MO LCAO Calculations

Atom	IP[a] eV	EA[a] eV	Bond	k^b	r Å
C	11·22	0·69	C=C	1·0	1·40
N^+	13·65	2·53	C—C	0·9	1·52
N	25·00	10·00	C—N^+	1·0	1·40
O	16·00	2·00	C—N	1·0	1·22
			C=O	1·0	1·34

[a] See ref.[19]; [b] in the units $\beta = -2{\cdot}388$ eV.

used in CNDO/2 calculations with the parameters according to the original procedure[21] which are given in Table II.

Static reactivity indices of the cation *I* were the charges Q_i of individual centres obtained from the respective electron densities q_i and HMO free valence F_i, the dynamic ones were HMO and SCF localization energies L_n, L_r, and L_e computed according to Wheland[27] and corresponding to the attacks by nucleophilic, radical, and electrophilic reagents, respectively. For analogous reaction types the respective nucleophilic, radical, and electrophilic superdelocalizabilities S_n, S_r, and S_e were calculated according to Fukui[28]. Electron distribution data at the level of the EHT method were obtained on the basis of the Mulliken population analysis[29]. Besides static distribution of the valence electrons in the ion *I* we tried to obtain information about electron-acceptor affinities of the individual centres with the help of the corresponding valence-inactive parts of electron population in the lowest unoccupied molecular orbital LUMO defined by the relation (*1*)[30]:

$$p_i^{\mathrm{LUMO}} = 2\sum_{\mu}^{i}(c_\mu^{\mathrm{LUMO}})^2 , \qquad (1)$$

where c_μ^{LUMO} stands for the expansion coefficient of the μ-th AO in LUMO, and the summation is carried out over all the AO's at a given centre *i*. In the given case LUMO has π-character, and only $2p_z$ atomic orbitals contribute to the resulting value of the valence-inactive population.

The Klopman–Hudson equation[15,16] obtained on the basis of general polyelectronic perturbation theory allows to obtain the energy contributions corresponding to electrostatic and covalent interactions of the donor–acceptor pair of particles. In this procedure the character of the reagent used can be taken into account, too.

TABLE II
The Parameters Used in Calculations by EHT and CNDO/2 Methods

Atom	IP_s eV	IP_p eV	$\frac{1}{2}(IP + EA)_s$ eV	$\frac{1}{2}(IP + EA)_p$ eV	Slater exponent	β^a eV
H	−13·6	—	− 7·176	—	1·3[a]	−9·0
C	−21·4	−11·4	−14·051	−5·572	1·625	−21·0
N	−26·0	−13·4	−19·316	−7·275	1·950	−25·0
O	−32·3	−14·8	−25·390	−9·111	2·275	−31·0

[a] EHT; in CNDO/2 calculations the value 1·2 was used.

The procedure was applied to HMO wave function, and using Eq. (2) we evaluated the extent of covalent interactions of the individual positions of the ion *I* with nucleophiles of various polarizabilities.

$$\Delta E_{da}^{cov.} = \sum_{m}^{occ.} \sum_{n}^{unocc.} \frac{(c_d^m c_a^n \Delta\beta_{da})^2}{\varepsilon_m^* - \varepsilon_n^*} \qquad (2)$$

where $\Delta E_{da}^{cov.}$ is the change of covalent energetic contribution due to formation of the bond between orbitals of atoms of donor *d* and acceptor *a*, $\Delta\beta_{da}$ is the change of resonance integral between the interacting orbitals of the donor and acceptor atoms, c_d^m and c_a^n are the expansion coefficients of the atomic orbitals of donor and acceptor in molecular orbitals *m*, *n* with the energies ε_m^* and ε_n^*, respectively. Besides that the used symbol c_{-1}^i corresponds to the expansion coefficient of the *i*-th AO in the lowest unoccupied molecular orbital (LUMO).

RESULTS AND DISCUSSION

Formation of NADH during oxidation of a given substrate by action of NAD^+ can be mechanistically represented[2] as a one-step transformation (*A*) or two two-step processes (*B*) and (*C*) for X = H:

$$I + H^{(-)} \rightarrow II \qquad (A)$$

$$I \xrightarrow{e} IV \xrightarrow{H^\bullet} II \qquad (B)$$

$$I \xrightarrow{2e} V \xrightarrow{H^{(+)}} II \qquad (C)$$

HMO Basis in approximation of isolated molecule. Pullman and Pullman[5-7] evaluated the chemical reactivity indices in the ion *I* and intermediates *IV* and *V* and came to the conclusion that the mechanism (*A*) is the most probable. Their argumentation is supported by the finding that the electron density *q* and the localization energy L_n for the ion *I* result in the prediction of the relative reactivities of positions $4 > 2 > 6$, whereas the indices *F*, L_r, and L_e for the intermediates *IV* and *V* prefer the positions 2 and 6. We carried out a series of HMO calculations for the models *I*, *IV* and *V* with variable parametrization of the influence of heteroatoms in the molecule and came to the conclusion that the mentioned position reactivity order in the ion *I* with respect to the indices L_n and *q* would make itself felt only in the case of introduction of so called "auxiliary inductive parameter" $h_C = 0{\cdot}3$ for the both atomic centres in the positions 2 and 6. In all cases not considering this additional parameter, be it with the use of the parameters from the monograph[7] or of the generally recommended parametrization[17,31], the 4-position is not the most

reactive one theoretically. Besides that the calculations have shown that relative values of the investigated HMO reactivity indices are most dependent on the parameter of the coulombic integral of the heterocyclic nitrogen atom h_{N^+} and almost independent of the variation of parametrization of the atoms of amide group. If it is taken into account that, according to the present experience[7,17,31], the relation $h_{N^+} > 1$ can

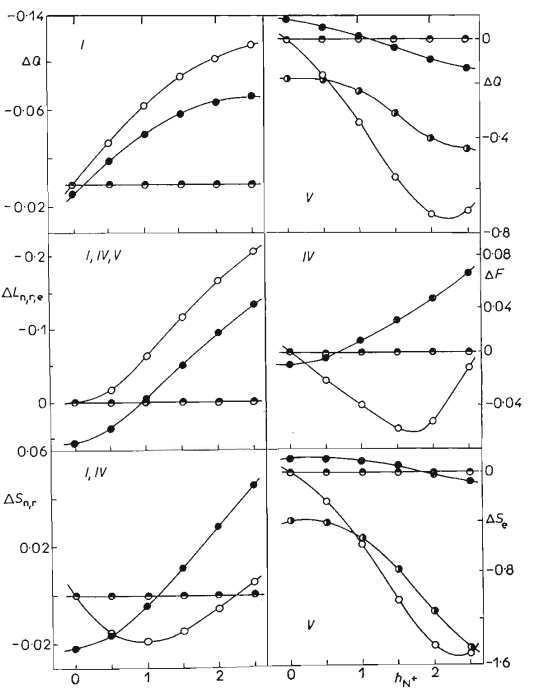
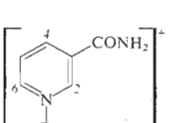


FIG. 1

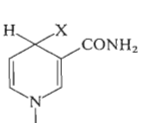
Dependence of Relative Values of HMO Reactivity Indices of Nicotinamide Part of NAD^+ Related to Index for 4-Position on Parameter of Coulombic Integral h_{N^+} of Heterocyclic Nitrogen Centre

Roman numerals denote the type of the nicotinamide fragment. ○ 2-position, ◓ 4-position, ◑ 5-position, ● 6-position.

always be considered for the quarternary pyridine nitrogen centres, the prognosis of the highest reactivity to nucleophilic attack at the 4-position (based on Q, L_n, and S_n indices) can be entirely excluded (Fig. 1). Here it is worth-while mentioning that the superdelocalizability S_n, which was formerly proved suitable for estimation of nucleophilic attack of pyridinium compounds (refs[32–35]), predicts the reactivity preference at 6-position of the ion *I* in accord with the course of borohydride reductions[13] going most probably by the mechanism type (*A*). In addition to it from Table III it is obvious that this prognosis by means of the index S_n does not change even when the auxiliary inductive parameter h_C is used for the positions 2 and 6.



I



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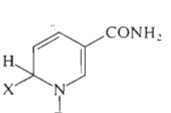

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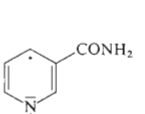
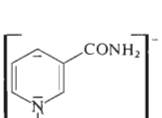
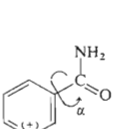


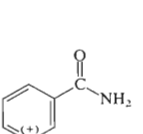
IV



V



Ia ($\alpha = 180°$)



Ib ($\alpha = 0°$)

Relative values of the indices in individual cases (and not their absolute values) are decisive for judging the relative reactivity of the atomic centres in the ions *I* and *V* and radical *IV*. From the definition relations for localization energies[27] it can easily be seen that ΔL_n for *I* is equal to ΔL_r for *IV* which, in turn, is equal to ΔL_e for *V*, the coulombic integral of the investigated position being constant, so that the same

curves of the dependence on h_{N+} parameter belong to the individual positions (Fig. 1). Therefore, we suppose that HMO localization energies cannot be used for differentiation of the courses (*A*), (*B*), and (*C*), because this differentiation depends exclusively on the introduction of the "auxiliary inductive parameter" for some of the positions. In the case of superdelocalizabilities it is impossible to differentiate the cases (*A*) and (*B*), because ΔS_n for *I* equals ΔS_r for *IV* and, in addition to it, free valences *F* for the intermediate *IV* give identical prognosis of the relative reactivity (Fig. 1), *i.e.* the order $6 > 2, 4$ for $h_{N+} > 1$. As also the indices *Q* and S_e predict analogous relative reactivity of the positions in the intermediate anion *V*, possibility of the course (*C*) cannot be excluded *a priori*, too. Hence this analysis of properties of the reactivity indices and parameters indicates that it is hardly possible to draw reliable conclusions in favour of one of the versions (*A*) to (*C*) of biochemical NAD^+ reduction from simple HMO method in the isolated molecule approximation, which Pullman and Pullman[7] tried to do.

HMO Basis of the Klopman and Hudson concept of "hard" and "soft" reagents. It was proved earlier[36] that reactivity of pyridine and its N-oxide to various substitution reagents can be explained satisfactorily by explicit considering the reagent polarizability which, in HMO formalism, makes itself felt in the competition of so called coulombic and covalent interactions. We have applied this approach[36] for the ion *I* attacked by a nucleophile. Fig. 2 gives the interaction π-electron energies ΔE_n calculated in this way for the positions 2, 4, 6 as a function of the approximated orbital energy ε_d^* of the attacking nucleophile. It is obvious that in the region of the easily polarizable *i.e.* "soft" reagents the 4-position is the most reactive one (for ε_d^* within $-0{\cdot}4$ and $-0{\cdot}1\beta$). With decreasing polarizability of the reagents (so called "hard" reagents[37]) the most reactive centre of the ion *I* shifts in the favour of 6-position and at last at 2-position. This conclusion can be interpreted in accord with

TABLE III

Comparison of Chemical Reactivity Indices of HMO Model of the Ion *I* with Respect to Use of "Auxiliary Inductive Parameter" for 2 and 6 Positions

Position	q^a	q^b	S_n^a	S_n^b	L_n^a	L_n^b
2	0·688	0·803	1·837	2·238	1·703	1·912
4	0·792	0·776	1·834	2·294	1·865	1·780
6	0·726	0·842	1·873	2·360	1·768	1·989

[a] Calculated according to the parameters[7] without "auxiliary inductive parameter"; [b] parameter $h_C = 0{\cdot}3$ was used for the positions 2 and 6.

a number of the abovegiven reactions, where especially the organic substrates oxidized by NAD^+ and ions of the type $S_2O_4H^-$ can be classified as "soft" reagents, which can account for their preferential interaction with 4-position. Recently it was suggested[38] that the primary attack of the ion *I* by $Na_2S_2O_4$ could take place also at 6-position. In that case a similar reactive zone (Fig. 2) could be considered as that in the case of BH_4^- ion. Hence BH_4^- ion as well as neutral diethylamine[39] appear to be medium "hard" reagents attacking preferentially the 6-position. Now it remains to explain why the ions *I* are not attacked at 2-position by "hard" reducing reagents (for $\varepsilon_d^* > 0{\cdot}1$). We suppose that the reason must be looked for in the participation of steric effects which is not involved in the Klopman index. The positions 2 and 4 are partially hindered by the amide group, the 2-position being additionally affected by steric effect of the substituent R at the nitrogen atom. This interpretation is supported by the experimental finding[40,41] that introduction of methyl groups in 4 and 6 positions of the ion *I* results in obtaining the mixtures of the corresponding 1,2- and 1,6-dihydro derivatives on borohydride reduction. In connection with that, however, it must be noted that the reason for the cyanide anion CN^- reacting with the ions type *I* to give exclusively the 4-substituted products (see *e.g.* ref.[42]) is due to the thermodynamically controlled formation of the 1,4-dihydro derivative *II* (X = CN). These derivatives can be secondary products of an equilibrium reaction of the primary 1,6-dihydro isomers type *III* (X = CN), which was shown by Lyle and coworkers[43,44].

EHT Method. The calculation of electron distribution in the ion *I* (R = CH_3) was carried out to investigate the influence of explicit considering of σ-skeleton and overlap on the reactivity prognosis.

The conformation found by X-ray diffraction[45,26] for the fragment *I* in dehydrolactase and in quarternary salt of cation *I* with 9-adenyl acetate corresponds to the almost plane structure *Ia*. This fact is noteworthy, because nicotinamide itself in crystalline

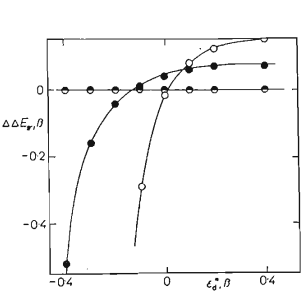


FIG. 2

Dependence of the Klopman Reactivity Index for HMO Model of the Ion *I* (h_{N^+} = = 2·0) on the Approximated Energy of Nucleophilic Reagent ε_d^*

Relative data with respect to 4-position. Description of the points see in Fig. 1.

state shows the conformation *Ib* which is deviated from the plane by $\alpha = 24°$ (see ref.[46]). Therefore, we have investigated the changes of total electron energy E_{tot} with the torsion angle α. From Fig. 2 it is obvious that the curve $E_{tot} = f(\alpha)$ has two energy minima, the second deeper one at $\alpha = 170°$ being in satisfactory accordance with the experimental value[26] $\alpha = 174{\cdot}3°$. However, we have found that this result of the EHT method is largely dependent on respecting all the experimentally found[26] bond lengths and bond angles. Choice of a less accurate geometry of the EHT model for the ion *I* (*e.g.* geometry of the nicotinamide itself) results in the first minimum at the curve $E_{tot} = f(\alpha)$ being deeper so that the EHT calculation gives[22] a geometry closer to the conformation *Ib* (Fig. 3). However, the electron distribution depends but very little on the precision of choice of the starting geometry of the ion *I*.

The EHT reactivity prognosis based on the total charge Q_{tot} in the Mulliken atomic population is connected obviously with the coulombic type interactions with the substrate, and it leads to the preference of the positions 6 and 2 as in the HMO procedure (Table IV). On the contrary, the prognosis based on "valence-inactive population" in the lowest unoccupied MO (LUMO) (see Calculations) and, hence, also covalent interaction with the substrate prefers the positions 4 and 6 to the position 2, not regarding magnitude of the torsion angle α (Fig. 4). Thus the conclusions on the EHT level agree satisfactorily with the application of the Klopman and Hudson concept, as the change Q_{tot} expresses rather the behaviour of the ion *I* to "hard" nucleophiles, whereas the second EHT index expresses its behaviour to the "soft" ones.

SCF Procedures. π-Electron charges *Q* for the ion *I* in the Pople SCF-π-MO method are again connected with the attack by a "hard" nucleophile and, according

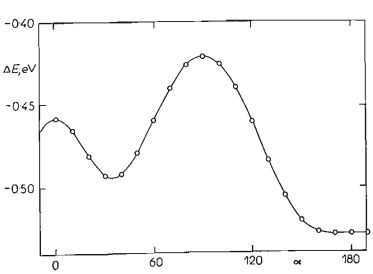


FIG. 3

Dependence of Total Electronic Energy of EHT Model of the Ion *I* ($R = CH_3$) on Torsion Angle α

to what was expected, they predict higher reactivity at 2- and 6-positions than at 4-position with the both plane conformations *Ia* and *Ib* (Table IV). On the contrary, the atomic localization energy L_n (Table V) prefers unambiguously the 4-position to 2- and 6-positions, and its behaviour is different from that of the HMO localization energy (Table III, Fig. 1). We presume that SCF index expresses better the behaviour of the ion *I* towards "soft" nucleophiles, because structure of the Wheland activated complexes could be taken as an expression of extremely strong covalent interaction substrate-reagent.

When considering explicitly the influence of all valence electrons we investigated the total charges Q_{tot} at the studied atomic centres of *Ia* conformation calculated

TABLE IV

Calculated Electric Charges at Atomic Centres in Various Quantum-Chemical Models of the Ion *I*

Position	HMO[a]	SCF[b]	EHT[b]	CNDO/2[b]
1	−0·620	−0·213	−0·013	0·075
2	0·313	0·132	0·314	0·145
3	−0·034	−0·027	−0·013	−0·035
4	0·207	0·044	0·089	0·105
5	−0·015	−0·015	−0·052	−0·002
6	0·275	0·109	0·330	0·136
C[c]	0·338	0·177	1·070	0·366
N[c]	−0·613	−0·414	−0·402	−0·257
O[c]	0·149	0·207	−1·223	−0·310

[a] For $h_{N^+} = 2{\cdot}0$; [b] for the conformation *Ia*; [c] atoms of amide group.

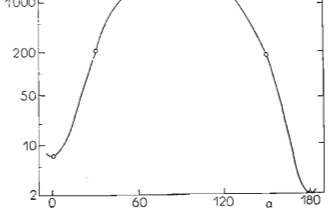


FIG. 4

Dependence of "Valence-Inactive Population" Values for EHT Model of the Ion *I* (R = CH_3) on Torsion Angle α

For description of the points see Fig. 1.

by the CNDO/2 method.* From the data of Table IV is is obvious that "hard" nucleophiles will attack the 2- and 6-positions rather than the 4-position.

Properties of LUMO. The abovementioned findings made us to consider the biological substrates and some other "soft" nucleophiles (as *e.g.* $S_2O_4^{2-}$ or $S_2O_4H^-$ ions) as being able of polarization to such an extent that they can form with NAD^+ an activated complex or an intermediate which can decompose to the oxidation product and the enzymatically active 1,4-dihydroisomer of NADH. In the Klopman–Hudson concept this complex is characterized by that the energy of covalent interaction makes the predominant contribution to the corresponding activation energy. It can be supposed that, in analogy to the description of this interaction by the HMO method (see Calculations), the character of the model of substrate – NAD^+ complex will generally be affected mostly by the expansion coefficients of AO's and by energy of the frontier orbital, *i.e.* with respect to the nucleophilicity of the substrate LUMO. In the case of the plane conformations *Ia* and *Ib* it is unambiguously of the π-type, *i.e.* it shows antisymmetrical behaviour with respect to the plane of the heterocyclic ring. From Fig. 5 it can be seen that character of LUMO with respect to the wave function symmetry in the region of atomic centres is identical in all the used versions of semiempirical calculations. In addition to it, the highest expansion coefficient in the LCAO expansion belongs always to $2p_z$ AO of the carbon atom at 4-position, *i.e.* to the place to which, in the course of the electron flow from the substrate to NAD^+, the nucleus of hydrogen atom is transferred, too. Strictly speaking, this

TABLE V
SCF Atomic Localization Energies for Nucleophilic Attack of the Ions *Ia* and *Ib*[a]

Ion	Position		
	2	4	6
Ia	11·419	11·406	11·461
Ib	11·466	11·391	11·450

[a] The values are given in eV.

* The curve $E_{tot} = f(\alpha)$ has no realistic energy minima[22] and, therefore, the geometrical aspects were not investigated in this case.

interpretation agrees best with the two-step mechanism* (*B*) in which, at first, one electron of the substrate is transferred into the LUMO of the ion *I*, being immediately followed by attachment of the radical $H^{\bullet}$ at the place of the highest π-spin density at the atomic centre 4. The determining factor for 1,4-dihydropyridine structure of the enzymatically active NADH could thus be in the high reactivity of the intermediates at 4-position caused by the existence of π-electron septet. Formation of this π-electron configuration was used before[48] for explanation of the increased reactivity of the 4-position in the pyridine itself towards some reagents, and this interpretation can seem, at the first sight, alternative to the Klopman and Hudson concept[15,16]. However, in our opinion the approach[48] expresses the situation with an extremely "soft" nucleophile transferring (due to its easy polarization) the both electrons to the substrate gradually in kinetically enough distinguished steps, so that, during the reaction, a certain concentration can be maintained of reactive intermediates having the electronic structure with π-septet. In this context we can point at some not yet quite well understood reasons of EPR signals found[49-51] with some NAD^+–NADH systems and at the presumptions made by some authors[3] about the role of radicals.

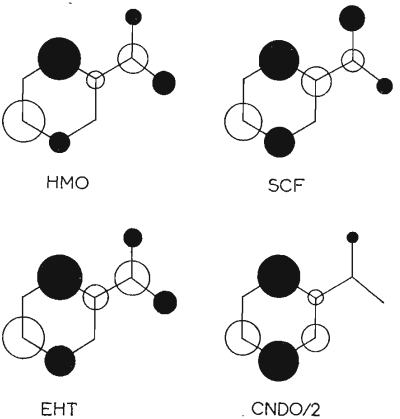


FIG. 5

Schematic Representation of LUMO in Quantum-Chemical Models of the Ion *I*

Radii of the circles are proportional to the magnitude of the extension coefficient of AO, dark and light colour denote the sense of wave function.

* The alternative mechanism (*C*) is significantly disproved by the fact that no proton interchange with the medium[47] takes place in the process of biochemical oxidation with NAD^+.

Identification of the particles *IV* thus remains the key problem in decision between the one-step (*A*) and the two-step (*B*) mechanisms. For the abovementioned reasons, neither the concept of "soft" and "hard" nucleophiles nor the theoretical calculations limited to the approximation of the isolated molecule can contribute to differentiation between (*A*) and (*B*). At unusually great concentration of the particles *IV* their dimerization can predominate as a competitive process. It was proved[52] that the ions *I* do give dimers with ring connection at the 6-position when treated with some metals. In Fig. 6 a high spin density at all of these positions can be seen. In our opinion, linking of them is due especially to their sterical accessibility as compared with the alternative positions 4 and 2.

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Translated by J. Panchartek.