

EHT STUDY OF 1-METHYL-1,4-DIHYDRONICOTINAMIDE*

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Application of the simple EHT method is shown to predict the same conformation of the amide group in the investigated amide *I*, as the studies based on CNDO and PCILO procedures. The sole difference exhibited consists in the fact, that the EHT approach prefers a slightly non-planar conformation of the dihydropyridine ring. Some characteristics describing the electron distribution as well as the nature of HOMO are discussed with respect to the reducing abilities of NADH.

1-Methyl-1,4-dihydronicotinamide (*I*), which is usually considered to represent the simplest model of the pyridine section in NADH, has been thoroughly investigated at the level of all valence electrons by the PCILO (ref.¹) and CNDO (ref.²) methods. In both these cases the planar conformation *Ib* characterized by the torsion angle $\alpha = 180^\circ$, the value of which compares favourably with the experimental value 176° obtained³ on X-ray analysis of the 1-benzyl derivative *II*, was calculated to be the energetically most advantageous one. In the course of the CNDO treatment some attention was given to certain out of plane deviations of the dihydropyridine ring conformation and these were found² to lead to an enlargement of the computed electronic energy of the CNDO/2 model of the compound *I*. In the present communication we report the results of the analogous investigation based on the EHT procedure. This study was stimulated by the success of this semiempirical method in the investigation of the similar nicotinic acid derivatives^{2,4-6}. In this way we complete and extend the partial preliminary results reported elsewhere⁷.

CALCULATIONS

EHT calculations were executed on Tesla 270 computer with the models of the compound *I* localized in the cartesian space in the same way as in the previous report⁴. Non-diagonal matrix elements were approximated by the relation⁸ $H_{ij} = 0.5K(H_{ii} + H_{jj}) S_{ij}$, with the chosen value⁹

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of $K = 1.75$. Interatomic distances were taken equal to the data obtained on X-ray analysis of the 1-benzyl analogue *II* (ref.³), with exception of the substituent in the position 1. In the latter case the values of 1.44 and 1.09 Å were chosen for the respective N—C and C—H bond lengths. Residual empirical parameters of the EHT procedure were equal to those used in ref.⁴. Mulliken population analysis¹⁰ was utilized to characterize the calculated valence electron distributions.

EXPERIMENTAL

1-Methyl-1,4-dihydronicotinamide (*I*) was prepared on reducing 1-methyl-3-aminocarbonylpyridinium iodide (5 g) with sodium dithionite in the presence of sodium carbonate¹¹. The chloroform extract of the crude reaction mixture was, after drying over magnesium sulphate, concentrated to about 30 ml and chromatographically purified on a column of 340 g of aluminium oxide of the activity II (Brockmann). On combining the yellow-coloured fractions 1.83 g of crystalline compound *I*, m.p. 76–77°C (Boetius block), was obtained. Reported m.p.¹¹: 84°C (sealed tube). ¹H NMR spectrum (100 MHz) of the product (Table I) agrees well with the earlier reported 40 MHz spectrum¹² of the compound *I*. This compound undergoes a slow decomposition, when stored at laboratory temperature, especially at the access of air. Dioxane solutions of the freshly prepared amide *I* were immediately subjected to measurements of dielectric constants and densities at 25°C. Dipole moment computed from these data amounts to 4.00 ± 0.05 D ($P_A = 5\% P_E$), this value being comparable to a dipole moment of the 1-benzyl derivative *II* (in benzene), reported¹³ as 3.89 D.

RESULTS AND DISCUSSION

Electronic energy: In the course of examining the influence of the molecular geometry of the amide *I* on the total valence electron energy E_{tot} , the following four degrees of freedom to molecular motion in certain chosen situations were considered:

TABLE I

Characteristics of ¹H-NMR spectra of the Amide *I* (CDCl₃, 37°C, 100 MHz, Varian HA-100 spectrometer)

δ , ppm	Assignment	Position	J_{HH} , Hz ^a	Positions
6.97	H ₁₃	2	1.70	2, 4
7.14	H ₁₄ , H ₁₅	4	1.60	2, 6
4.72	H ₁₆	5	3.50	4, 5
5.68	H ₁₇	6	1.60	4, 6
4.54	H ₁₁ , H ₁₂	9	7.95	5, 6
2.93	H ₁₈ , H ₁₉ , H ₂₀	10		

^a Chemical shifts were approximated by the centers of the particular multiplets. J_{HH} values were read in after the multiplicities had been simplified by the decoupling technique.

variations of the torsion angle α of the amide group, of the analogous angle β concerning the methyl group, of the dihedral angle γ of bonds C—C and C—N of the dihydropyridine ring and of the angle ω between the plane of the heterocycle and the N—CH₃ bond (Fig. 1). Conformation of the amide group: Considering the angles β , γ and ω to be fixed at 0° and varying the torsion angle α in the range 0° to 180°, the relation $E_{101} = f(\alpha)$ given in Fig. 2 is obtained. The curve exhibits two energy minima, one deeper at $\alpha_1 = 180^\circ$ and one shallower at $\alpha_2 = 41^\circ$. Both these minima are separated by an energy barrier of 26 kJ/mol (6.2 kcal/mol). The overall value of the barrier to internal rotation of the amide group is only slightly higher, *i.e.* 26.8 kJ/mol (6.4 kcal/mol). Hence, the position α_1 of the deeper minimum is in a full agreement with the results of the numerically more demanding CNDO and PCILO

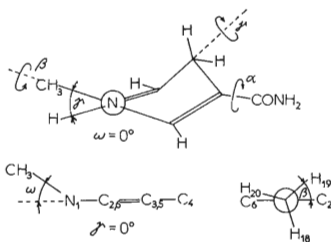


FIG. 1

Investigated Degrees of Freedom in the Various Conformations of the Amide I

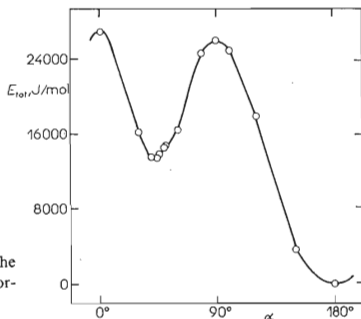


FIG. 2

Relation of the Electronic Energy of the EHT Model of the Compound I to the Torsion Angle α ($\beta = \gamma = \omega = 0^\circ$)

methods; only the EHT rotational barriers are slightly higher about 1.7 resp. 9.6 kJ/mol (0.4 resp. 2.3 kcal/mol). The value of α_1 exhibits also a reasonable correlation to the experimental value of 176° found³ in the single crystal of the 1-benzyl derivative *II*. However, it should be mentioned, that the X-ray analysis of the compound thought as being the analogous 1-propyl derivative *III* has led¹⁴ to a value of 22° , close to the more shallow EHT minimum at α_2 . Upon analysing the accuracy, with which the gradients of the electron densities were determined in this study¹⁴, it is hard to give an unambiguous proof of the identity of the 1,4-dihydro derivative *III*. The authors¹⁴ of this work reported¹⁵ the compound to be prepared by the borohydride reduction of the corresponding quarternary pyridinium salt. However, this procedure is known^{16,17} to result rather in 1,6-dihydro isomers or in a mixture of 1,4 and 1,6-dihydro derivatives. We intend to reinvestigate this problem in some of our future experimental studies. Nevertheless, it is clear, that the possibility to correlate the crystallographic data of the compound *III* with respect to the theoretical calculations of the compound *I* should not be overemphasized.

The relations of the π -electron component E_π and of the σ -electron component E_σ , separated from the summation $E_{\text{tot}} = E_\pi + E_\sigma$ under the same assumptions as those used in ref.⁴, are given in Fig. 3. It is obvious, that the conjugation influences the energetical advantage of the planar conformation *I* to a greater extent than in the case of nicotinamide^{4,5}. It is caused by the small increase of the E_σ component at $\alpha \rightarrow 180^\circ$ as compared with the situation at $\alpha \rightarrow 0^\circ$, which in the first case is unable to compensate the decrease of the E_π component. The cause of this change may be easily understood on the basis of the conformational formulas *Ia* and *Ib*. Considering the *Ia* arrangement, strong σ -electron nonbonded interactions, leading to a non-planar conformer *Ia* corresponding to a minimum α_2 , take place. In the course

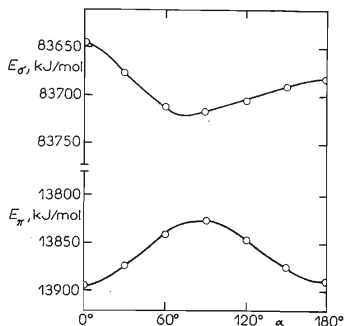
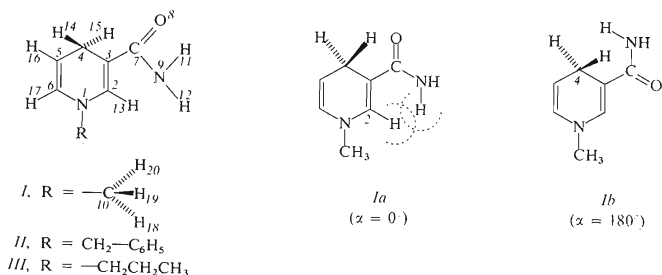


FIG. 3
Relation of the σ - and π -Electronic Energies of the EHT Model of the Compound *I* to the Torsion Angle α ($\beta = \gamma = \omega = 0^\circ$)

of the CNDO/2 treatment, the minimum α_2 exhibits no remarkable response on the curve E_{tot} , as a consequence of the emphasis given to these forces by an explicit account for electron repulsion. Therefore, the *Ia* conformation is not predicted by this method². On the contrary, in the case of the PCILO procedure, the apparent inclusion of some correlation effects causes the influences dominating in the CNDO method to compensate and, consequently, the existence of the conformer *Ia* may be accepted on the basis of the results obtained¹, although a certain shift of the minimum α_2 to higher values compared with the EHT calculation is exhibited. The advantage of the planar form *Ib* clearly follows from the fact, that at the value of the torsion angle $\alpha_1 = 180^\circ$ the N—H bond close to the carbon centre C_4 brings itself into a plane bisecting the bond angle H— C_4 —H. This orientation results in a remarkable decrease of the σ -component of the nonbonded electron repulsion among hydrogen atoms of the close coming parts of the molecule *I* and, hence, the increase of the energy E_σ is only slightly influenced by the electron repulsion between the C_2 —H bond and the lone electron pairs of the oxygen atom of the amide group. These influences are probably so dominating, that even the EHT prediction of the prevailing *Ib* conformation is fully consistent with the more sophisticated PCILO a CNDO/2 treatments.



Conformation of the methyl group: If the variables α , γ and ω are fixed at 0° , the energy minimum of the relation $E_{\text{tot}} = f'(\beta)$ is obtained for a conformation, in which one C—H bond of the methyl group lies in the dihydropyridine ring plane and the hydrogen atom is eclipsed with the part of the molecule *I* bonded to the amide group. Owing to the low computed barrier to internal rotation of the methyl group (1 kJ/mol, 0.24 kcal/mol), the variable β did not present itself as being too important for the purpose of the present conformational considerations.

Conformation of the dihydropyridine ring: Having fixed the variable parameters $\alpha = 180^\circ$ and $\beta = 0^\circ$ we tried to investigate the influence of a transformation of the heterocycle in the compound *I* into a non-planar boat conformation. The following

two situations were considered: a) the conservation of the formal sp^2 hybridization on the N_1 atomic centre; b) the change of the configuration of this centre towards the formal sp^3 nitrogen hybrid ($\omega = 5^\circ$ and 10°). The corresponding relation $E_{\text{tot}} = f''(\gamma)$ is given in Fig. 4. It is clear, that the both curves exhibit very flat minima in the range of $\gamma = 10^\circ$ to 17° , while the maximum decrease of E_{tot} with respect to a planar ring arrangement ($\gamma = 0^\circ$) is reached at $\omega = 5^\circ$ and amounts only to 3.2 kJ/mol (0.76 kcal/mol). Next, it follows from the Fig. 4, that a rotation of the amide group ($\alpha = 165^\circ$ to 180°) does not lead to a further decrease of the value E_{tot} in the case of two boat conformations with $\gamma = 15^\circ$ resp. 20° ($\omega = 5^\circ$). Hence, the additional optimization of the geometry of the molecule *I* needs not be considered much important. However, the above decrease of E_{tot} occurring in transforming the molecule into the boat conformation differentiates the EHT conclusion from the CNDO prediction² of the most advantageous planar conformation as well as from the X-ray study³ of the related compound *II*, in which no significant deviations from the dihydropyridine ring planarity were found in the crystalline state. NMR studies of solutions of both the compounds *I* and *II* are also in accord with the planar conformation, although the possibility of a fast interconversion of boat conformations¹⁸ is not eliminated. Of course, it remains questionable, whether the slight decrease in the EHT E_{tot} value in the case of the compound *I* is not an artefact arising from the fixed geometrical parameters, namely the bond lengths. For the time being, we satisfied ourselves in the additional calculations of the modified boat conformations with $\omega = 5^\circ$ or 10° , in which the bond lengths C_3-C_4 , C_4-C_5 , N_1-C_2 and N_1-C_6 were enlarged against the "experimental" (*cf.*³) data. Elongating these bonds by 0.004 Å to 0.01 Å led to a maximum decrease of E_{tot} 4.6 kJ/mol (1.1 kcal/mol). The energy increases again, when still larger interatomic distances are used. We think, that these results

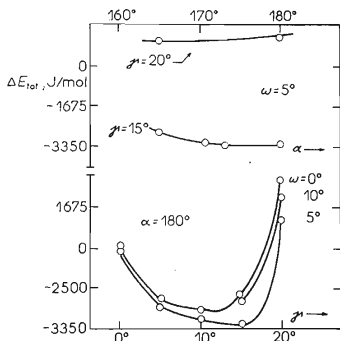


FIG. 4
Alterations of the EHT Electronic Energy of the *Ib* Amide Conformation Relatively to the Angles α , β , γ and ω

are a stimulation for the perspective inclusion of a larger set of variable geometrical parameters. However, such a research is still out of our computational possibilities.

Electron distribution: The computed electronic charges Q_X and the overlap populations N_{XY} concerning the atomic centres X and Y in the EHT model of the compound *I* are given in Table II. Fig. 5 brings the confrontation of the Q_X values with the analogous quantities obtained² by the CNDO/2 technique. The distribution of the EHT charge density in the molecule *I* follows not to be principally different; only the charge localization on heteroatoms and in their direct surrounding is overestimated. Consequently, the calculated dipole moment of the conformation *Ib* ($\alpha = 180^\circ$) is too large (10.20 D) and upon transformation to a form *Ia* this value grows up to 14.0 D. Only when the first value is adapted by the generally recommended correction¹⁹, the value of 3.1 D is obtained. The latter is somewhat closer to a moment 4.00 D calculated from the dielectric constant of the dioxane solutions of the compound *I*.

Investigating the action of rotating the amide group on the electron distribution we found four typical relations, connecting changes of the electronic charges Q_X and of the overlap populations N_{XY} with the value of the torsion angle α . The functions $Q_X = Q(\alpha)$ and $N_{XY} = N(\alpha)$ exhibit: 1. minima at $\alpha = 0^\circ$ and 180° and maxima at 90° (e.g. C₄, C₇, C₂-C₃, C₇-C₉, C₇-O₈); 2. maxima at $\alpha = 0^\circ$ and 180° and minima at $\alpha = 90^\circ$ (e.g. N₁, C₂, C₃, N₉, H₁₂, C₃-C₄, C₃-C₇); 3. irregular changes with extrema occurring at various values of α (e.g. H₁₃, H₁₄, C₂-H₁₃, C₄-C₁₄, C₄-H₁₅, N₉-H₁₂); 4. no sensitivity to changes of the angle α (e.g. O₈, H₁₁, H₁₅, N₁-C₂,

TABLE II

EHT Characteristics of the Valence Electron Distribution of the Amide *I* ($\alpha = 180^\circ$, $\beta = \gamma = \omega = 0^\circ$)

Atom	Atomic charges		Overlap populations				
	Q_X	atom	Q_X	bond	N_{XY}	bond	N_{XY}
N ₁	-0.6117	H ₁₁	+0.3577	N ₁ -C ₂	0.8514	N ₉ -H ₁₁	0.6406
C ₂	+0.3324	H ₁₂	+0.3699	C ₂ -C ₃	1.2243	N ₉ -H ₁₂	0.6496
C ₃	-0.1545	H ₁₃	+0.0942	C ₃ -C ₄	0.7700	C ₂ -H ₁₃	0.8205
C ₄	-0.1274	H ₁₄	+0.1060	C ₄ -C ₅	0.7405	C ₄ -H ₁₄	0.7841
C ₅	-0.1862	H ₁₅	+0.1060	C ₅ -C ₆	1.3253	C ₄ -H ₁₅	0.7841
C ₆	+0.1778	H ₁₆	+0.0999	C ₆ -N ₁	0.7368	C ₅ -H ₁₆	0.8343
C ₇	+1.2547	H ₁₇	+0.0931	C ₃ -H ₇	0.9734	C ₆ -H ₁₇	0.8254
O ₈	-1.4217	H ₁₈	+0.1099	C ₇ -O ₈	0.6806	C ₁₀ -H ₁₈	0.8119
N ₉	-0.7906	H ₁₉	+0.1040	C ₇ -N ₉	0.9449	C ₁₀ -H ₁₉	0.8046
C ₁₀	-0.0223	H ₂₀	+0.1061	N ₁ -C ₁₀	0.6636	C ₁₀ -H ₂₀	0.8053

N_9-H_{11}). It is noteworthy, that just the energetically most advantageous conformation *Ib* ($\alpha = 180^\circ$) corresponds to a situation, in which the atomic centre C_4 reaches the more negative value of charge Q_C than in the non-planar states characterized by lower α values. This situation is in accord with some biochemical ideas²⁰⁻²³, suggesting the pseudoaxial atom H_{14} attached to the centre C_4 of the boat conformation of NADH to move to the reduced substrate.

Orbital symmetry: In order to understand the origin of biochemical properties of NADH, it appears useful to investigate the HOMO character of the EHT model of the compound *I*. Following the perturbation theory²⁴, HOMO should undergo a strong interaction with LUMO of the reduced substrate. Considering the energetically most advantageous planar conformation *Ib*, the molecule of the amide *I* exhibits a sole symmetry element, *i.e.* the plane of all the carbon, nitrogen and oxygen centers. All the calculated EHMO's φ_1 to φ_{50} characterized by the eigenvalues in the range -34.2 to 60.3 eV exhibit symmetric or antisymmetric behaviour with respect to the mentioned plane and, hence are classified as being of σ - or π -type. 27 energetically lowest EHMO's are occupied by a total number of 54 valence electrons in the ground electronic state. HOMO φ_{27} is of the π -type according to the corresponding expansion

$$\varphi_{27} = \sum_i c_i x_i,$$

where c_i are the variational coefficients and x_i the respective i -th AO's (Table III). In this case the only nonzero coefficients c_i are those related to $2p_z$ and some 1s

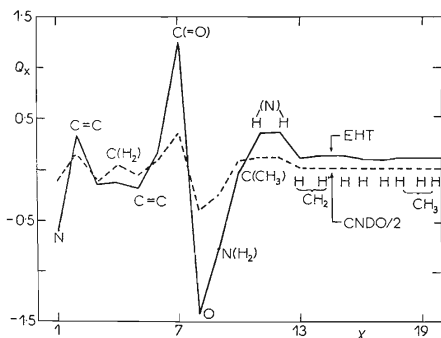


FIG. 5

Graphical Representation of the Magnitude of EHT and CNDO/2 Charges Localized on the Particular Atomic Centres in the *Ib* Conformation

TABLE III

Variational Coefficients of the LCAO Expansion of HOMO in the EHT Model of the Compound *I* ($\alpha = 180^\circ$, $\beta = \gamma = \omega = 0^\circ$); the Coefficients of the Residual AO's are $c_i = 0.0000$

Atom	χ_i	c_i	Atom	χ_i	c_i
N ₁	2p _z	+0.5307	O ₈	2p _z	-0.0979
C ₂	2p _z	-0.1902	N ₉	2p _z	+0.1742
C ₃	2p _z	-0.4521	C ₁₀	2p _z	-0.1070
C ₄	2p _z	+0.2441	H ₁₄	1s	+0.2235
C ₅	2p _z	-0.4315	H ₁₅	1s	-0.2235
C ₆	2p _z	-0.3109	H ₁₈	1s	+0.1163
C ₇	2p _z	-0.2106	H ₂₀	1s	-0.1163

orbitals. The wave function φ_{27} exhibits some remarkable properties: 1. The function is delocalized over all the heavier atoms of the molecule and exhibits nodes between the atomic centers C₂—N₁—C₆, N₁—C₁₀, C₃—C₄—C₅, N₉—C₇—O₈ and H₁₈—C₁₀—H₂₀. 2. The partial π -system of the dihydropyridine ring, C₅—C₆—N₁—C₂—C₃—C₄, is strongly conjugated with CH₂ and CH₃ groups or with the σ -bond antisymmetric combinations C₄—H₁₄, C₄—H₁₅ and with σ^* states of C₁₀—H₁₈ and C₁₀—H₂₀. (Taking into account the above mentioned σ -components, the orbital φ_{27} should be termed strictly pseudo π -orbital). Now, the interesting finding in connexion with the role of NADH follows: The spin densities in the HOMO in the area of hydrogen atoms are localized most on the CH₂ group, which participates in the enzymatic reduction²⁵. Hence, the EHT method affords the objective base reasoning the hyperconjugative effect of this group. Previously, this effect had to be intuitively and subjectively involved^{26,27} in the parameterizations of HMO and SCF calculations of the compound *I* in the π -approximation. It was already shown elsewhere², that CNDO wave function of the compound *I* leads to the same HOMO character, and therefore there is no doubt about its physical and chemical meaning.

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REFERENCES

1. Coubeils J. L., Pullman B., Courrière P.: *Biochem. Biophys. Res. Commun.* **44**, 1131 (1971).
2. Kuthan J., Musil L.: *This Journal* **40**, 3169 (1975).
3. Karle I. L.: *Acta Crystallogr.* **14**, 497 (1961).

4. Kuthan J., Musil L., Skála V.: *This Journal* 37, 2933 (1972).
5. Long K. R., Goldstein J. H.: *Theor. Chim. Acta* 27, 75 (1972).
6. Kuthan J., Musil L.: *This Journal* 41, 3282 (1976).
7. Kuthan J., Musil L., Skála V.: *Z. Chem.* 11, 390 (1971).
8. Wolfsberg M., Helmholtz L.: *J. Chem. Phys.* 20, 837 (1952).
9. Hoffmann R.: *J. Chem. Phys.* 39, 1397 (1963).
10. Mulliken R. S.: *J. Chem. Phys.* 23, 1833 (1955).
11. Karrer P., Schwarzenbach G., Benz F., Solmssen U.: *Helv. Chim. Acta* 19, 811 (1936).
12. Hutton R. F., Westheimer F. H.: *Tetrahedron* 3, 73 (1958).
13. Cilento G., De Carvalho-Filho E., Giora Albanese A. C.: *J. Amer. Chem. Soc.* 80, 4472 (1958).
14. Koyama H.: *Z. Kristallogr., Kristallgeometrie, Kristallphys., Kristallchem.* 118, 51 (1963).
15. Koyama H., Robinson J. M. M., Laves F.: *Naturwissenschaften* 50, 40 (1963).
16. Paiss Y., Stein G.: *J. Chem. Soc.* 1958, 2905.
17. Eisner U., Kuthan J.: *Chem. Rev.* 72, 1 (1972).
18. Meyer W., Mahler H., Baker R. jr: *Biochim. Biophys. Acta* 64, 353 (1962).
19. Andrews P.: *Theor. Chim. Acta* 14, 261 (1969).
20. Levy H. R., Vennesland B.: *J. Biol. Chem.* 228, 85 (1957).
21. Velick S. F.: *J. Biol. Chem.* 233, 1455 (1958).
22. Vennesland B.: *Fed. Proc., Fed. Amer. Sec. Exp. Biol.* 17, 1150 (1958).
23. Wallenfels K., Hofman D.: *Tetrahedron Lett.* 1959, 10.
24. Fukui K.: *Fortschrit. Chem. Forsch.* 15, 1 (1970).
25. Schellenberg K.: *Pyridine Nucleotide — Dependent Dehydrogenases*, p. 15. Springer, Berlin 1970.
26. Pullman B., Pullman A.: *Quantum Biochemistry*. Wiley, New York—London 1963.
27. Maggiora G., Johansen H., Ingraham L. L.: *Arch. Biochem. Biophys.* 131, 352 (1969).

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Note added in proof: While this paper was being edited, another communication appeared (Hofmann H. J., Thieroff K.: *Pharmazie* 30, 587 (1975)), where the authors have drawn, on the basis of HMO-NBI method, the same conclusion as to the conformation of the amide group of 1-methyl-1,4-dihydronicotinamide. Also the NDDO treatment (see Hofmann H. J., Birner P.: *Chem. Phys. Lett.* 37, 608 (1976)) leads to similar conclusions (Hofmann H. J.: Private communication) and has not, even in this case, the drawbacks of the CNDO/2 method in the studies of geometry of conjugated systems.