A CNDO STUDY OF NICOTINAMIDE
AND 1-METHYL-1,4-DIHYDRONICOTINAMIDE*

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The electronic structures of nicotinamide (*I*) and 1-methyl-1,4-dihydronicotinamide (*II*) have been studied by the standard CNDO/2 procedure. The coherence of calculated electron distribution and energetical characteristics with some physical and chemical properties of *I* and *II* is discussed.

Nicotinamide (*I*) and 1-methyl-1,4-dihydronicotinamide (*II*) are of interest due to their structural similarity to the pyridinoid parts of the NAD^+-type coenzymes. The main aim of the reported EHT (refs[1-3]) and PCILO (ref.[4]) calculations of *I* and *II* was the prediction of optimum conformations. Both semiempirical procedures mentioned predict a slightly twisted form *Ia* of *I* and the planar conformation *IIb* of *II* to be energetically most preferable. This was assumed[1-4] to be in excellent agreement with X-ray solid state diffraction data for *I* (ref.[5]) and 1-benzyl analogue of *II* (ref.[6]). However, little is known about conformations of *I* and similar dihydropyridine derivatives in solution[7]. The total electron distribution of *I* was studied by the Hückel method[3,8]. Unfortunately, this method exaggerates charge density localization in molecules[9,10]. A limited number of CNDO charge densities on carbon atoms of *I* have been reported recently[11], in connection with NMR investigations of this compound. On the other hand, no data on electron distributions of *I* and *II* have been reported in the communication on the PCILO treatment[4].

In this paper we wish to present the CNDO/2 calculations of *I* and *II*. It is hoped that the electron distribution calculated by this procedure can be useful for discussing a number of biochemically interesting properties related to the pyridinoid fragments in NAD^+-type coenzymes[8,12].

Calculations

The calculations of *I* and *II* were carried out by using standard CNDO/2 and MINDO/2 programmes on the IBM 7040 computer. The procedures reported by Pople, Santry and Segal[13] and by Dewar and coworkers[14] were followed, including definition by the authors of charge density Q_A on the atomic centre A and Wiberg's formulation of bond indices W_{AB} for a given A-B bond[15].

Theoretical dipole moments were computed while taking into consideration their hybridization and charge components[16]. The CNDO/2 and MINDO/2 parameters of our calculations, using interatomic distances determined by X-ray diffraction[5,6], are shown in Table I.

RESULTS AND DISCUSSION

In order to achieve the „optimum" electron distribution of a given molecule, attempts are usually made to optimize its geometry with respect to some degrees of freedom. Some complications arise here in connection with the finding[17-19] that standard CNDO/2 procedure leads to total energy — torsion angle curves with artificial minima for such conjugated molecules as butadiene, glyoxal, biphenyl, 2,2′-difluoro-biphenyl and benzaldehyde. Fortunately, we have found that the electron distribution characteristics of *I* are in general little sensitive to the rotation around angle α and, in the case of *II*, the optimum α value is the same as that calculated by EHT and PCILO procedure[4,20].

Electron energy. In agreement with the results of the foregoing semiempirical calculations[1-4], we have decided to investigate at first the changes of the total electron energy E_{tot} in dependence on the torsion angle α. As follows from Fig. 1 the curve $E_{tot} = f(\alpha)$ exhibits the expected artificial minimum at 84° which differs both from those obtained by EHT and PCILO calculations[2-4] and from the experimental solid state value 24° (ref.[5]). On the other hand, the E_{tot} curve of *II* displays a similar minimum at 180° (Fig. 2), analogously to other calculations[4,20], and its value agrees well with the solid state angle 176° for 1-benzyl-1,4-dihydronicotin-amide[6].

In the mentioned papers[17-19] an acceptable reason of the CNDO/2 failure for certain conjugated molecules has not been suggested. It has been stated[17], however, that the method "underestimates the conjugation effect and thus leads to conformations which are twisted too much". The E_{tot} curve of *II* (Fig. 2) clearly demonstrates that such a generalization does not seem to be fully justified. An additional example in favour of this assumption is given in Fig. 2 which shows also the E_{tot} curve for 1,4--dihydronicotinic acid (*IIIa → IIIb*), a possible intermediate in the biosynthesis of nicotine[21]. It is evident that the CNDO/2 calculation of *III* yields a maximum near 90° and the lowest minimum at 180°, similarly as that of *II*. Therefore, the CNDO/2 treatment can hardly be considered to produce only incorrect results for dihydro-pyridine derivatives. In connection with this it appears to be of interest to follow changes of the nuclear repulsion term
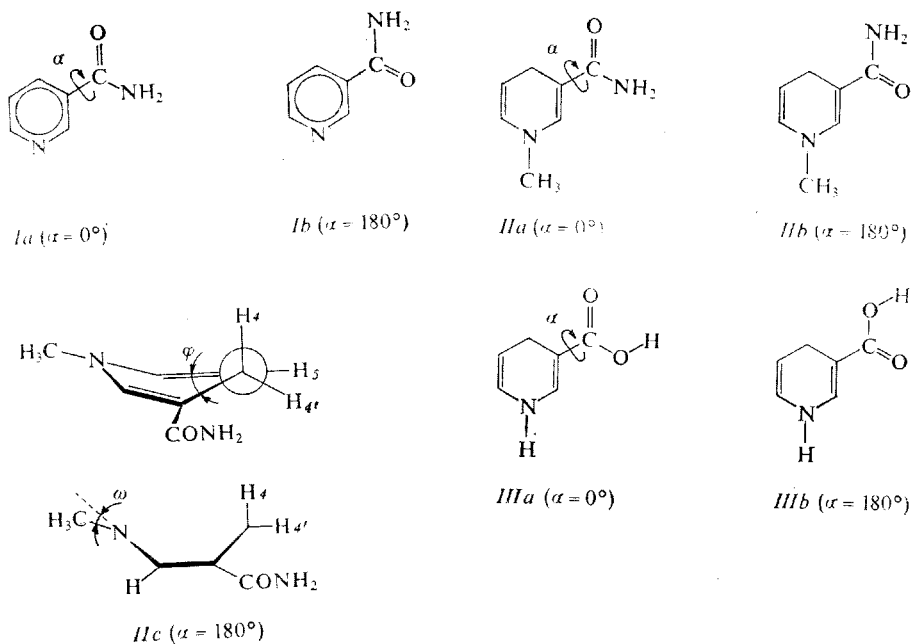
$$E_{rep} = E_{tot} - E_e = \sum_A \sum_B Z_A Z_B R_{AB}^{-1} , \qquad (1)$$

where R_{AB} is the distance between the atomic centres A and B resp., Z_A, Z_B are the corresponding effective nuclear charges, and E_e may be called the electronic term.

TABLE I

Data Used in the CNDO/2 Calculation

Atom	$-0.5(I_s + A_s)$	$-0.5(I_p + A_p)$	$-\beta_A^0$	ξ
H	7·176	—	9	1·2
C	14·051	5·572	21	1·625
N	19·316	7·275	25	1·95
O	25·390	9·111	31	2·275

Figs 1 and 2 show that, in contradistinction to E_{rep} curves, the E_e curves of I and II exhibit maxima near 90°. Consequently, one may conclude that relative underestimation of the E_e magnitude might cause the typical lack of analogical maxima on E_{tot} curves in cases where the torsion angle corresponds to rotation of aromatic and heteroaromatic rings[17-19] or of very polar bonds, as in glyoxal[17]. Less polar olefinic systems such as butadiene (ref.[17,19]) or dihydropyridine derivatives are displaying more or less distinct E_{tot} curve maxima for their twisted conformers (see ref.[17-19] and Fig. 2). This conclusion seems to be in good accordance with the assumption of Gropen and Seip[17], since the E_e term also includes electronic conjugation effects.

$Ia\ (\alpha = 0°)$ $Ib\ (\alpha = 180°)$ $IIa\ (\alpha = 0°)$ $IIb\ (\alpha = 180°)$

$IIIa\ (\alpha = 0°)$ $IIIb\ (\alpha = 180°)$

$IIc\ (\alpha = 180°)$

To check whether the charge-point approximation (1) of E_{rep} within the CNDO/2 treatment might cause a failure in the conformational considerations, we have also calculated the MINDO/2 version of the E_{tot} curve for *I*. Fig. 1 demonstrates that such a modification does not lead to qualitatively different results as compared to those achieved by the standard CNDO/2 procedure. The rotational barriers of *I* and *II* calculated by different semiempirical methods are compared in Table II.

Two additional degrees of freedom, *i.e.* valence and dihedral angles ω and φ, were included in our CNDO/2 calculations of *IIb* in order to investigate the probability of boat-like conformations *IIc*. We have found that any small deviation out of the dihydropyridine ring plane ($|\varphi| > 0°$) as well as the rehybridization of heterocyclic nitrogen ($|\omega| > 0°$) results in an increase of the E_{tot} energy. For example, the space configurations of the *IIc* type with $\varphi = 10°$, $\omega = 0°$ and $\varphi = 15°$, $\omega = 5°$ correspond to the E_{tot} energy increase of 0·67 kcal/mol or 1·15 kcal/mol respectively, being in good agreement with the fact[6] that the heterocyclic ring of 1-benzyl-1,4-dihydro-nicotinamide in the solid state seems to be planar within limits of the accuracy of the
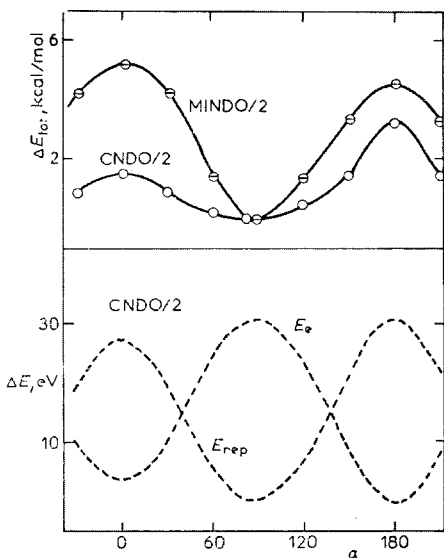

FIG. 1

Angular Dependence of Energy for Nicotin-amide (*I*)
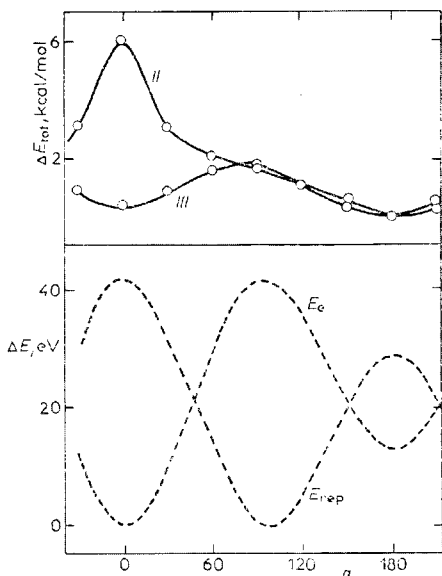
Measured relatively to the lowest minimum.

FIG. 2

Angular Dependence of Energy in 1-Methyl-1,4-dihydronicotinamide (*II*) and 1,4-Dihydronicotinic Acid (*III*)

Measured relatively to the lowest minimum.

X-ray measurement. It is noteworthy, however, that the above-mentioned E_{tot} consumption is very small and analogical EHT treatment[20] prefers the boat-like conformation *IIc* with energy gain which does not exceed 0·8 kcal/mol.

TABLE II

Comparison of Calculated Rotational Barriers (kcal/mol) for Compounds *I* and *II*

Method	I^a	II^a
EHT	4·0[b] (3)	6·4[b] (20)
	2·7[c] (2)	
CNDO/2	3·2[d]	6·0[d]
PCILO	2·6 (4)	4·1 (4)

[a] Taken from the literature given in parenthesis. [b] $H_{ij} = 0.875\, S_{ij}(H_{ii} + H_{jj})$. [c] $H_{ij} = -1.5 \cdot S_{ij}(H_{ii}H_{jj})^{1/2}$. [d] This paper.

TABLE III

Charge Densities and Bond Indices of *Ia* ($\alpha = 30°$), *IIb* ($\alpha = 180°$) and *IIc* ($\varphi = 10°$, $\omega = 0°$)

Atom	Q_A			Bond	W_{AB}		
	Ia	*IIb*	*IIc*		*Ia*	*IIb*	*IIc*
N_1	−0·1434	−0·1175	−0·1205	N_1—C_2	1·4315	1·1035	1·0992
C_2	+0·0970	+0·1517	+0·1537	C_2—C_3	1·4180	1·7629	1·7697
C_3	−0·0638	−0·1221	−0·1209	C_3—C_4	1·4031	1·0141	1·0117
C_4	+0·0556	+0·0490	+0·0484	C_4—C_5	1·4404	1·0260	1·0256
C_5	−0·0338	−0·0557	−0·0533	C_5—C_6	1·4571	1·9183	1·9199
C_6	+0·1057	+0·0932	+0·0922	C_6—N_1	1·4300	1·0259	1·0232
C_7	+0·3581	+0·3600	+0·3605	N_1—CH_3	—	1·0222	1·0219
O_8	−0·3540	−0·4014	−0·4002	C_3—C_7	0·9972	1·0396	1·0377
N_9	−0·2428	−0·2434	−0·2435	C_7—O_8	1·7394	1·6598	1·6614
$C(H_3)$	—	+0·0902	+0·0908	C_7—N_9	1·1579	1·1758	1·1762
H_2	−0·0149	+0·0099	+0·0076	C_2—H_2	0·9570	0·9566	0·9555
H_4	+0·0073	−0·0182	−0·0167	C_4—H_4	0·9589	0·9457	0·9428
$H_{4'}$	—	−0·0182	−0·0191	C_4—$H_{4'}$	—	0·9457	0·9498
H_5	+0·0068	+0·0020	+0·0032	C_5—H_5	0·9601	0·9544	0·9548
H_6	−0·0157	−0·0034	−0·0035	C_6—H_6	0·9542	0·9584	0·9584
H_9	+0·1158	+0·1159	+0·1163	N_9—H_9	0·9560	0·9600	0·9598
$H_{9'}$	+0·1224	+0·1234	+0·1237	N_9—$H_{9'}$	0·9505	0·9574	0·9574
$H(CH_2)$	—	−0·0041[a]	−0·0065[a]	H—$C(H_2)$	—	0·9798[a]	0·9774[a]

[a] Averaged values were slightly dependent on the conformation of the 1-methyl group.

TABLE IV
Comparison of Dipole Moments μ (in D) for I and II

Method	$\mu(I)^a$	$\mu(II)^b$
Experiment	$3{\cdot}37 \pm 0{\cdot}05$	$4{\cdot}00 \pm 0{\cdot}05$
CNDO/2	$1{\cdot}70 - 5{\cdot}33^c$	$5{\cdot}83 - 3{\cdot}72^c$
EHT	$4{\cdot}56 - 13{\cdot}53$	$14{\cdot}00 - 10{\cdot}20$

[a] Ref.[3]. [b] Ref.[20]. [c] This paper.

Electron distribution. Calculated electron distribution characteristics, Q_A and W_{AB}, of twisted form Ia as well as of planar and boat-like forms IIb, c are presented in Table III. The numbering of individual atomic centres is given in Fig. 3. The confrontation of the calculated and experimental dipole moments of I and II given in Table IV suggests that the physical reality is satisfactorily depicted by the CNDO/2 electron distribution. Likewise, the trend in changes of Q_C values and the carbon-13 chemical shifts in the NMR spectra of I (refs[11,20,22]) remains the same, except for an insignificant exchange of the Q_C values for position 3 and 5. Comparison of data in Table III shows that, contrary to I, the heterocyclic ring of II exhibits considerable C_2—C_3 and C_5—C_6 double bond localization. This becomes apparent from the high W_{CC} values for the bonds mentioned, when compared to others, *e.g.* N_1—C_2, C_3—C_4, C_4—C_5 and N_1—C_6. This is in accordance with the higher frequency of the C=C stretching vibration maxima $\left(1\,625\ \mathrm{cm}^{-1}\right)$ for II relative to I $\left(1\,594\ \mathrm{cm}^{-1}, \mathrm{ref.}[20]\right)$. On the other hand, the double bond character of the carbonyl group C_7—C_8 of II is lowered $\left(W_{CO} = 1{\cdot}6598\right)$ with respect to that of I $\left(W_{CO} = 1{\cdot}7394\right)$, in agreement with the difference in the corresponding stretching vibrational modes, which were found[20] to be $1\,694\ \mathrm{cm}^{-1}$ for I and $1\,683\ \mathrm{cm}^{-1}$ for II under the same measurement conditions. The total electron charge Q_N at N_1 of heteroaromatic I is more negative than that of hetero-olefinic II, which is in harmony with generally smaller basicity of the nitrogen in 1,4-dihydropyridine derivatives[7].
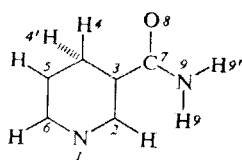

FIG. 3
Numbering of Individual Centres for Nicotinamide (*I*) and 1-Methyl-1,4-dihydronicotinamide (*II*)

The CNDO/2 charge densities Q_A as well as the Wiberg's indices W_{AB} show in general small sensitivity to rotation around angle α and their changes are in most cases similar to analogical EHT population data [3,20]. Electron distribution characteristics of II are of interest in relation to biochemical reactivity. The fundamental process of the NADH action is the abstraction of one hydrogen atom at position 4 (ref.[23]), e.g. the splitting of one of C_4—H bonds. In connection with our findings the ability of II to be effective in such a way might be interpreted such that, firstly, the centres H_4 and $H_{4'}$ possess the highest electron densities (1·0182) of all hydrogen atoms and can be thus considered as reducing agents; secondly, the bonds H_4—C_4—$H_{4'}$ possess the lowest value of Wiberg's indices ($W_{CH} = 0·9457$) and their cleavage ought to be then preferred. Thus, the results of CNDO/2 calculations consent to the knowledge about the mechanism of NADH reductions[23].

Orbital symmetry. When comparing the calculated orbital configurations of I and II, we have found that calculations of all planar forms Ia, b and IIa, b result in the same number, e.g. five bonding MO's of the π-symmetry with respect to the heterocyclic ring plane. This is somewhat surprising for IIa and IIb, since the tetrahedral atomic centre 4 is formally taken out of the conjugation. In fact, such a simplification would not apparently be correct description of the electronic structure of II, due to neglection of the significant overlap between the antisymmetrical combination of C_4—H_4 and C_4—$H_{4'}$ σ-MO's and of the p_z-AO's at C_3 and C_5 (Fig. 3) resulting in important hyperconjugation effect of the 4-methylene group. In fact, the corresponding MO is the HOMO of IIb and for its LCAO expansion it holds that

$$\phi_{27} = 0·24s(H_4) - 0·24s(H_{4'}) + 0·15p_z(C_4) - 0·43p_z(C_3) -$$
$$- 0·34p_z(C_5) - 0·22p_z(C_2) - 0·18p_z(C_6) + 0·58p_z(N_1)\,,$$

where only the terms with $c_i \geqq 0·15$ are shown, the index 27 denotes the order from the lowest MO ϕ_1 and the numerical coefficients refer to z-axis AO direction components. A similar hyperconjugative effect has been ascertained for 1,4-cyclohexadiene[24] and 1,3,5-cycloheptatriene[25]. One may therefore assume that the pseudo--π-orbital responsible for the reactivity of II in the sense of H_4 or $H_{4'}$ abstraction will be just the HOMO ϕ_{27}, in accordance with non-negligible magnitudes of expansion coefficients for AO's $s(H_4)$, $s(H_{4'})$ and $p_z(C_4)$ respectively, given above.

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