

SEMIEMPIRICAL MO STUDY OF NICOTINIC ACID AND OF ITS METHYL ESTER AT THE LEVEL OF ALL VALENCE ELECTRONS*

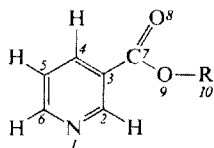
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The methods EHT and CNDO/2 were utilized in the study of conformation and electronic structure of nicotinic acid (*I*) and methyl nicotinate (*II*). The EHT procedure affords satisfactory results in conformational analysis, while the CNDO/2 treatment leads to the more realistic electron distribution.

Among organic compounds thoroughly investigated by the present quantum chemical methods a number of nitrogen containing heterocycles exhibiting notable biological activity can be found¹. The more detailed description of conformation and electronic structure of these molecules may be considered as an important starting material for the study of the relationship of molecular structure to biological activity. Hence it is not surprising, that the theoretical investigation of these characteristics constitutes the serious part of quantum biochemistry. Analysing the literature data in this sense we have unexpectedly found, that with exception of the recently published HMO calculation² no attention was given to nicotinic acid, which is a known vitamin and a precursor of nicotinamide in the nicotinamidic coenzymes. We decided to fill this gap by the communication, in which we describe the results of the application of standard EHT and CNDO/2 methods to the acid *I* and the methyl ester *II*.



I, R = H
II, R = CH₃

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CALCULATIONS

The EHT calculations were executed on Tesla 270 computer according to the standard procedure^{3,4} using the following definition of the non-diagonal matrix elements of $H_{ij} = 1.75 S_{ij} \cdot (H_{ii} + H_{jj})/2$. The calculations due to CNDO were performed on IBM 7040 in the CNDO/2 formalism following the original works⁵. The used empirical parameters are given in Table I. The real values of bond lengths and bond angles obtained for the case of the acid *I* with the aid of X-diffraction⁶ were utilized in computations. Additionally for the methyl ester *II* the lengths O—CH₃ 1.41 Å, C—(H₃) 1.09 Å and the angles C—O—CH₃ 110°, O—C—H 109.47° were used, while the CH₃ group was fixed with one C—H bond in the antiperiplanar arrangement relatively to the C=O groups. The models of molecules *I* and *II* were located in the cartesian space analogously to the previous study of nicotinamide⁷, the coordinate analysis of the input data being performed on Tesla 270 upon using the program KOORD (see⁸). The numbering of particular positions, which is used for the designation of the characteristics of electron distribution, follows from formulas *I* and *II*.

TABLE I
Empirical Parameters Used in the Calculations

Atom	ξ	EHT		CNDO/2		
		I_s , eV	I_p , eV	$(I_s + A_s)/2$, eV	$(I_p + A_p)/2$, eV	$-\beta_A^0$
C	1.0 ^a	-13.6	—	-7.176	—	9
H	1.625	-21.01	-11.27	-14.051	-5.572	21
N	1.95	-26.92	-14.42	-19.316	-7.275	25
O	2.273	-36.07	-18.53	-25.390	-9.111	31

^a The Slater exponent $\xi = 1.2$ was utilized in the CNDO/2 method.

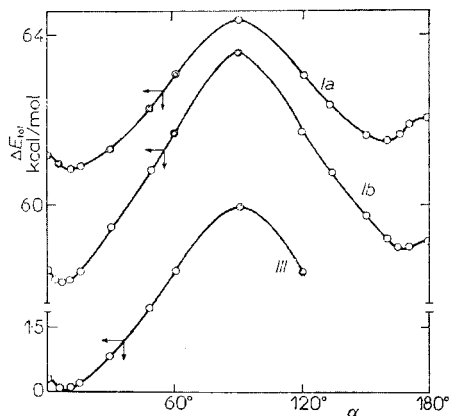


FIG. 1
Relation between the Electronic Energy of the EHT Model of Nicotinic Acid and the Torsional Angle α

TABLE II
Calculated Energetical Characteristics of the Compounds Under Study

Form	EHT			CNDO/2		
	α_{\min}	E_{ep}^a	E_{rot}	α_{\min}	E_{ep}^a	E_{rot}
<i>Ia</i>	8°	0.3	3.4	85°	0.6	1.1
	158°	0.5				
<i>Ib</i>	6°	0.2	4.9	86°	1.9	3.9
	168°	0.1				
<i>IIb</i>	10°	0.3	3.4	88°	0.6	0.9
	160°	0.5				
<i>III</i>	7.5°	0.2	4.3	—	—	—

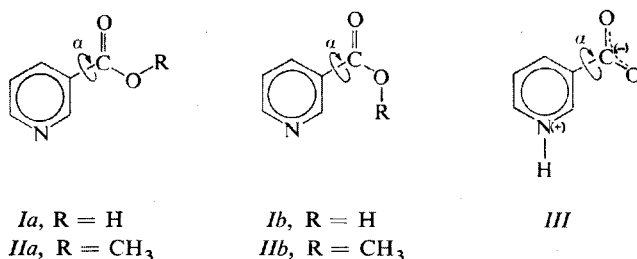
^a The lowest barrier to epimerisation between the two enantiomeric conformers.

RESULTS AND DISCUSSION

Electronic energy and conformation. The variations of the total electronic energy E_{tot} relatively to the value of the torsional angle α in the acid *I* were studied in the three structural series: the non-ionized form with *trans* and *cis* conformation of the hydroxylic group, *i.e.* *Ia* and *Ib* respectively and the ionized form *III*. The corresponding relations $E_{tot} = f(\alpha)$ calculated by the EHT method are given in Fig. 1.* It is clear that all the curves thus obtained exhibit the global energetical minimum at $\alpha_1 = 6-8^\circ$ and the second local minimum at $\alpha_2 = 158-168^\circ$. This finding is in a very good agreement with the value of $\alpha = 4^\circ$ determined by X-diffraction⁶ of the single crystal of the acid *I*. From the arrangement of molecules of the acid *I* found in the unit cell⁶ the compound *I* may be assumed to crystallize in the characteristic dimeric form of carboxylic acids, close to the *trans*-conformation *Ia*. If we compare the computed values of E_{tot} related to the most energetically advantageous conformers with the torsional angle $\alpha = \alpha_1$, we find, that the EHT method leads to the relative energetical preference of these forms in the order of $III > Ib > Ia$ (Table II), while the electronic contribution to the "neutralization" heat of the reaction $Ib \rightarrow III$ or $Ia \rightarrow III$ results as $\Delta H_e = E_{tot}(I) - E_{tot}(III) = 57.5$ and 58.2 kcal/mol respectively. On the contrary, the CNDO/2 calculation prefers uniquely the *trans*-conformation *Ia*

* The course of the separate relations $E_\pi = f'(\alpha)$ and $E_\sigma = f''(\alpha)$ derived from the equation $E_{tot} = E_\pi + E_\sigma$ is analogous to the case of nicotinamide⁷. The final curve passes through a maximum at $\alpha \approx 90^\circ$, while the second one exhibits a minimum in this range. However, the influence of π -electrons is remarkably larger for the acid *I*.

to the *cis*-conformation *Ib*. This characteristic difference in predicting the conformations of the carboxylic group is connected with the approximative character of the EHT and CNDO/2 calculations and was already mentioned in the literature⁹.



It is clear from the Fig. 2, that the CNDO/2 method, similarly to other functional derivatives of benzene and pyridine¹⁰⁻¹³, yields the relations $E_{\text{tot}} = f(\alpha)$ exhibiting physically improbable minimum at c. 90°. Recently, a considerable attention was given to this failure of the mentioned computational procedure in conformational analysis¹⁰⁻¹³, however no generally useful way of its elimination was found. In the case of the methyl ester *II* the situation is quite analogous (Fig. 3). As was expected, the EHT method predicts the more realistic value of the torsional angle ($\alpha_1 = 10^\circ$) for the *trans*-conformation of *Ia* than the CNDO/2 procedure, ($\alpha_1 = 88^\circ$) even though the explicit experimental evidence of the actual geometry of the compound *II*

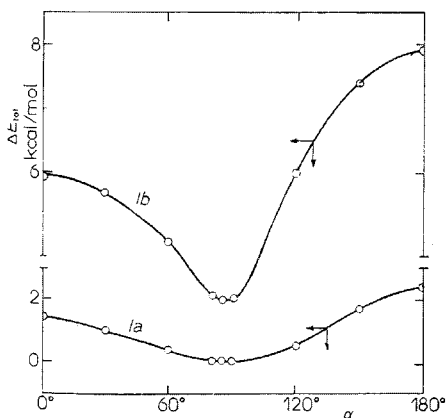


FIG. 2

Relation between the Electronic Energy of the CNDO/2 Model of Nicotinic Acid and the Torsional Angle α

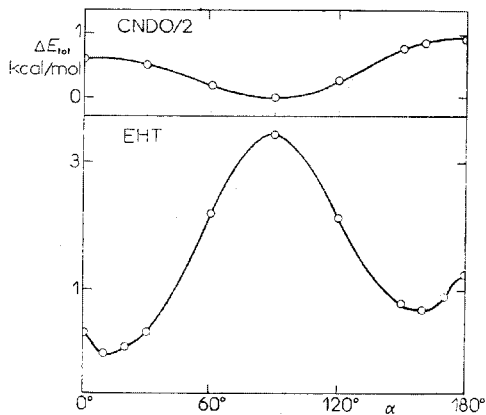


FIG. 3

Relation Connecting the Electronic Energy in the EHT and CNDO/2 Models of *trans*-Conformation of Methyl Nicotinate (*IIa*) with the Torsional Angle α

still lacks. Owing to this fact, the alternative *cis*-conformation *Iib* was not further considered in the computation especially due to the convincing experimental arguments^{14,15} favouring the *trans*-conformation to be the preferred one in the case of alkyl esters of carboxylic acids.

The calculated values E_{rot} of the barriers to internal rotation of the functional groups around the bond functional group — heteroaromatic nucleus in compounds *I* and *II* are given in Table II. The EHT data spread in the range 3.4–4.9 kcal/mol exhibit semiquantitative agreement with the CNDO/2 value given for the *cis*-form *Iib* (3.9 kcal/mol). The analogical values concerning *trans*-conformations *Ia* and *Iib* are probably too low (1.1 and 0.9 kcal/mol respectively), owing to the underestimation of the conjugative effects in the CNDO/2 method^{10,13}.

Electron distribution. Some characteristics describing the electron distribution in the acid *I* are given in Table III. In accord to the present knowledge¹⁶, the EHT data, especially the atomic populations seriously overestimate the localization of the electronic charge on the contrary to the CNDO/2 result. The electronic population of the methyl ester *II* is in the cases of EHT and CNDO/2 treatment very similar to that of the acid *I* (with exception of OH and OCH₃ group respectively) and therefore is not demonstrated in a table. It was already shown elsewhere^{1,17}, that the measured electric dipole moments of compounds *I* and *II* may be much more easily

TABLE III
The Calculated Characteristics of Electron Distribution in Nicotinic Acid ($\alpha = 0^\circ$)

Atom A	$Q_A(\text{EHT})^a$ <i>Ib-cis</i>	$Q_A(\text{CNDO}/2)^b$ <i>Ib-cis</i> <i>Ia-trans</i>		Bond A—B	$W_{AB}(\text{CNDO}/2)^c$ <i>Ia-trans</i>
N ₁	-1.0986	-0.1445	-0.1476	N ₁ —C ₂	1.4232
C ₂	0.4960	0.1211	0.1234	C ₂ —C ₃	1.4321
C ₃	-0.0524	-0.0825	-0.0698	C ₃ —C ₄	1.3663
C ₄	0.1002	0.0645	0.0621	C ₄ —C ₅	1.4701
C ₅	-0.1322	-0.0341	-0.0357	C ₅ —C ₆	1.4383
C ₆	0.4639	0.1140	0.1140	C ₆ —N ₁	1.4351
C ₇	1.6826	0.4049	0.4044	C ₃ —C ₇	1.0211
O ₈	-1.3261	-0.2980	-0.3138	C ₇ —O ₈	1.8369
O ₉	-1.1056	-0.2793	-0.2816	C ₇ —O ₉	1.0237
H ₁₀	0.5933	0.1587	0.1600	O ₉ —H ₁₀	0.9549
H(C ₂)	0.0996	-0.0101	-0.0125	C ₂ —H	0.9543
H(C ₄)	0.0947	0.0051	0.0037	C ₄ —H	0.9579
H(C ₅)	0.0973	0.0065	0.0052	C ₅ —H	0.9587
H(C ₆)	0.0841	-0.0259	-0.0118	C ₆ —H	0.9557

^a $\alpha = 6^\circ$; ^b $\alpha = 0^\circ$; ^c Wiberg bond indices¹⁸.

interpreted upon using the atomic charges Q_A calculated by the CNDO/2 method, than utilizing the EHT data.

The analysis of the relations between the characteristics of the electron populations of compounds *I* and *II* and the torsional angle α has shown courses very similar to those thoroughly analysed⁷ in case of nicotinamide. Especially the CNDO/2 data are little sensitive to the changes of the angle α , what is the favourable circumstance for their exploitation, disregarding the above mentioned failure of this method in optimizing the geometry of the compounds studied. The changes of the proton chemical shifts δ found in the NMR spectra of compounds *I* and *II* (Table IV) exhibit the same trend as do the CNDO/2 charges Q_C on the carbon atomic centers of the corresponding C—H bonds (Table III).

TABLE IV

Characteristics of ¹H-NMR Spectra of Compounds *I* and *II*^a (100 MHz, Varian XL-100 spectrometer)

<i>i</i>	δ_i , p.p.m.		<i>i</i> — <i>j</i>	J_{HH}^{ij} , Hz	
	<i>I</i> (D ₂ O)	<i>II</i> (CDCl ₃)		<i>I</i> (D ₂ O)	<i>II</i> (CDCl ₃)
2	9.15	9.10	2—4	2.0	2.0
4	8.86	8.19	2—5	0.7	0.8
5	8.09	7.32	4—5	8.0	7.9
6	8.95	8.70	4—6	2.0	1.9
10	—	3.89	5—6	5.0	4.9

^a The indices *i* and *j* designate the positions (see formulas *I* and *II*).

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Note added in proof: The problems concerning the reliability of the CNDO like methods for the conformational studies of larger conjugated molecules were recently investigated again (Hofmann H. J., Köhler H. J., Thieroff K., Uhlmann P.: *J. Prakt. Chem.* **316**, 659 (1974); Hofmann H. J., Birner P.: *Z. Chem.* **15**, 23 (1975)). The most favourite results are created by the least approximative NDDO procedure.