

CNDO/2 STUDY OF INTERACTION OF 1-METHYL-1,4-DIHYDRONICOTINAMIDE AND ACETALDEHYDE*

Jiří KRECHL and Josef KUTHAN

Department of Organic Chemistry,

Prague Institute of Chemical Technology, 166 28 Prague 6

Received February 19th, 1980

The CNDO/2 method has been used for evaluation of energy relations between some configurations of 1-methyl-1,4-dihydronicotinamide (*I*) — acetaldehyde (*II*) supermolecule. Stabilization energies have been estimated for formation of the configuration type *A*, *B* and *C*, the energetically most favourable situation corresponding to the formulas *IIIa* and *IIIb*. Characters of some MO's and CNDO/2 and INDO electron distributions are discussed with respect to biochemical aspects of the interaction of NADH and acetaldehyde.

Mutual geometrical fixation of reaction partners can be one of important features of enzyme catalysis. In the case of the redox processes catalyzed by alcohol dehydrogenases, obviously the space orientation of the active part of coenzyme NADH and the acetaldehyde molecule is important from this viewpoint. In the previous communication¹ it was shown that detailed EHT study of the system 1-methyl-1,4-dihydronicotinamide (*I*)-acetaldehyde (*II*) resulted in a conclusion that evaluation of the local energy minima indicated the order $B > A > C$ of probable preference of mutual orientation of the discussed molecules. The EHT calculations carried out, however, did not lead to any stabilization energy of the *I-II* supermolecule, which could be due especially to neglect of electronic repulsion in the Hückel MO approximation. With the aim to verify this presumption we decided to reinvestigate the *I-II* system at the semiempirical SCF level, whereto the standard CNDO/2 method was applied. The results obtained are given in this communication.

CALCULATIONS

All the calculations were carried out with the use of standard CNDO/2 and INDO programs on an ICL-4-72 computer. For interpretation we used total 133 CNDO/2 calculations for various conformations of atomic centres of the *I-II* supermolecule. The used values of CNDO/2 parameters were the same as in ref.⁵. The initial arrangement of the supermolecule *I-II* is seen in Fig. 1. The geometries of 1-methyl-1,4-dihydronicotinamide (*I*) and acetaldehyde (*II*) were chosen the same as in the previous papers¹⁻³. The calculations of dependences of total energies

* Part XIV in the series On Calculations of Biologically Important Compounds; Part XIII: This Journal 45, 2425 (1980).

on the geometry parameters r and α were carried out with the steps 50 pm and 60° , respectively. In the situations where it was necessary to investigate in detail the extreme values E_{CNDO} the step was lowered down to 10 pm and 5° .

RESULTS AND DISCUSSION

The situations *A*, *B* and *C* given in Fig. 1 were chosen as in the previous communication¹. These conformations of the *I-II* supermolecule were chosen with respect to the biochemically proved⁴ transfer of hydrogen atom from 4 position of the di-

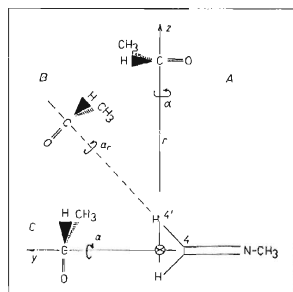
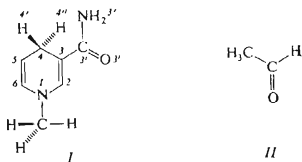


FIG. 1

The Studied Configurations of CNDO/2 Models of 1-Methyl-1,4-dihydro-2-pyridinone (*I*)-Acetaldehyde (*II*) System

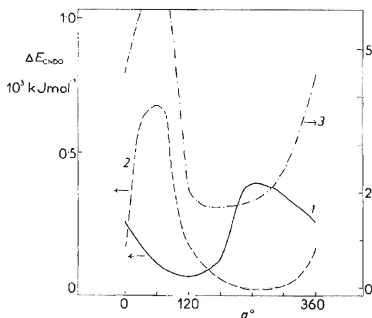


FIG. 2

Dependence of CNDO/2 Energy of *I-II* System on Rotation Angle α of Acetaldehyde (Fig. 1)

The minimum value at the curve 2 was chosen as zero energy.

hydropyridine ring to the carbonyl group of acetaldehyde. The conformations *A*, *B* and *C* were further modified by variation of two degrees of freedom – the distance *r* between the carbonyl carbon atom of acetaldehyde and 4-hydrogen atom in the heterocycle, and the angle α of rotation about the axis connecting the said centres or about the *y* axis in the case *C* (Fig. 1). Complete study was carried out for the arrangement given in Fig. 1 which is identical with that in ref.¹. In addition we also considered an alternative of isomeric arrangements of the *I–II* supermolecule in which the substituents H and CH₃ of the acetaldehyde molecule (*II*) are mutually interchanged as compared with the situation in Fig. 1. For these conformations *A'*, *B'* and *C'* the parameter α was varied within 0° to 360°, the parameter *r* being fixed at the energy optimum found for the analogous conformation *A*, *B* and *C*.

Energy of the supermolecule: If the parameter *r* exceeds 200 pm, then the E_{CNDO} value changes but slightly. Therefore, the changes of the rotation parameter α were only followed within $r = 100$ to 200 pm. To be clear, Fig. 2 only gives the functional dependence $E_{\text{CNDO}} = f(\alpha)$ for $r = 100$ pm. It is seen that the conformation *A* shows a local minimum of the curve $E_{\text{CNDO}} = f(\alpha)$ between 90 and 150° and a rotation barrier in the region $\alpha = 240^\circ$. Position of the local minimum was stated more exactly by shortening of the step of α to the value $\alpha = 120^\circ$ for the distance $r = 100$ pm. For the minimum found in this way we further studied the dependence of energy on the parameter *r*. This dependence $E_{\text{CNDO}} = f(r)$ shows a minimum at $r = 170$ pm. Further increase of the *r* value results in energy increase, the latter converging to a limit for *r* above 400 pm. Difference between this limit energy value and the energy minimum at $r = 170$ pm can be interpreted as theoretical stabilization energy of the *I–II* supermolecule. Its value is $E_{\text{stab}}(A) = 34.1 \text{ kJ mol}^{-1}$. According to Fig. 2 the local minimum of the function $E_{\text{CNDO}} = f(\alpha)$ of the configuration *B* can be found

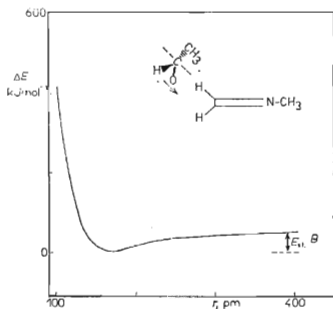
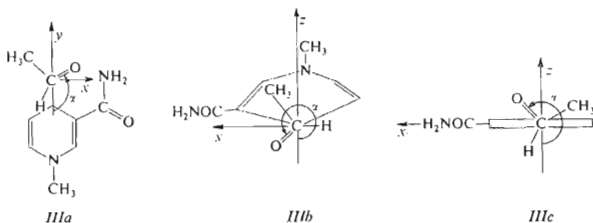


FIG. 3
Dependence of CNDO/2 energy of *I–II* System on the Distance Parameter *r* for the Optimum Rotation Angle of Conformation *B* (see *IIIb*)

within 180° to 360° . Shortening of the variation step of the parameter α resulted in finding the real energy minimum at $\alpha = 325^\circ$ for $r = 100$ pm. Furthermore the variation of the parameter r was investigated for this minimum. From Fig. 3 it follows that the dependence $E_{\text{CNDO}} = f(r)$ shows the minimum at $r = 170$ pm, the region above $r = 400$ pm being again (as in the previous case) denotable as one of convergence to a limit energy value. The theoretical stabilization energy of the *I-II* supermolecule is $E_{\text{stab}}(B) = 110.4 \text{ kJ mol}^{-1}$ in the case *B*. The dependence $E_{\text{CNDO}} = f(\alpha)$ of the configuration *C* at $r = 100$ pm is given in Fig. 2, too. A high rotation barrier in the region 310° to 110° includes a flat minimum at $\alpha = 120^\circ$ to 240° . By shortening of the variation step of rotation (α), this minimum could be stated more precisely ($\alpha = 210^\circ$). The dependence $E_{\text{CNDO}} = f(r)$ shows a minimum for $r = 220$ pm, again converging to a limit value above $r = 400$ pm. The theoretical stabilization energy of the *I-II* supermolecule is $E_{\text{stab}}(C) = 26.4 \text{ kJ mol}^{-1}$. Figure 3 gives, for clearness, the function $E = f(r)$ for the conformation *B* only. The course of the remaining two functional dependences is similar and is characterized in Table II. From comparison it follows that the conformation *C* is considerably unfavourable energetically, whereas the course of the functional dependence $E_{\text{CNDO}} = f(r)$ is very similar for the conformations *A* and *B*. The conformation *B* in its best arrangement is energetically better by 3.4 kJ mol^{-1} than the conformation *A*. Also the stabilization energy of the *I-II* supermolecule is three times greater in the case *B* than in the case *A*. The schemes *IIIa,b,c* show the most favourable arrangements of the *I-II* supermolecule for the individual conformations. As the same study was carried out by the EHT method in ref.¹, it is possible to compare the results of the EHT and the CNDO/2 calculations. The EHT method found the rotational minimum at $\alpha = 96^\circ$, the CNDO/2 method finds it at $\alpha = 120^\circ$ (see *IIIa*), the minima being very flat. Flexibility



of acetaldehyde should, therefore, be quite considerable in the conformation *A*. In the case of the conformation *B* the EHT and CNDO/2 results are more different. The EHT and CNDO/2 energy minima are at $\alpha = 210^\circ$ and 325° (see *IIIb*), respectively. However, it must be mentioned that the detailed positions of the minima are different in the two methods, but the course of the energy dependence is roughly

the same, the minimum in the region 180° to 350° being very flat. Rotation of acetaldehyde between the two said positions should thus be very easy. The position change as compared with EHT model could be due to the effort to avoid the electron repulsion at the carbonyl oxygen atom and the dihydropyridine ring. In the case of conformation *C* the α_{\min} values in the EHT and the CNDO/2 models are 148° and 210° ,

TABLE I

Comparison of Characteristics of EHT and CNDO/2 Models of *I-II* System

ΔE_{rel} the energy difference related to the most stable arrangement, ΔE_{stab} the CNDO/2 stabilization energy, both in kJ mol^{-1} .

Conformation	EHT ^a		CNDO/2			
	α_{\min}	ΔE_{rel}	α_{\min}	ΔE_{rel} ^a	ΔE_{stab}	r_{\min} (pm)
<i>A</i>	96°	10	120°	3.4 (4.5) ^b	34.1	170
<i>B</i>	$120-300^\circ$	0.0	325°	0.0 (0.0)	110.4	170
<i>C</i>	150°	16	210°	1.250 (1.218)	26.4	220

^a Based on data from ref.¹; ^b the INDO data in brackets.

TABLE II

The Most Important Terms ($|c_i| \geq 0.15$) in the LCAO Expansion in *I-II* Supermolecule for the Frontier Orbitals in Conformations *A-C*

Molecule	<i>A</i>		<i>B</i>		<i>C</i>	
	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO
<i>I</i>	-0.25 s (4')	-0.63 p (2)	0.25 s (4')	0.62 p (2)	0.72 s (2')	-0.67 s (2')
	0.24 s (4'')	0.39 p (3)	-0.24 s (4'')	-0.38 p (3)	0.21 s (2)	0.28 s (2)
	-0.57 p (1)	0.40 p (C3')	0.56 p (1)	-0.39 p (C3')	0.35 p (2)	0.38 p (2)
	0.22 p (2)	-0.34 p (O3')	-0.42 p (3)	0.33 p (O3')	—	—
	0.43 p (3)	—	-0.33 p (5)	—	—	—
	0.33 p (5)	—	0.29 p (O3')	—	—	—
	-0.30 p (O3')	—	—	—	—	—
<i>II</i>	-0.12 p (O) ^a	—	0.14 p (O) ^a	-0.16 p (C) ^b	—	—
	—	—	—	0.14 p (O) ^a	—	—

^a The carbonyl oxygen atom; ^b the carbonyl carbon atom.

respectively. As in the previous case here also the CNDO/2 model of *I-II* shows a higher repulsion between the acetaldehyde methyl group and the H(4ⁿ) atom. Table I summarizes quantitative comparison of results of the both semiempirical approaches.

The results obtained by investigation of the conformations *A'*, *B'* and *C'* were compared with the above-given ones. The course of the dependences $E_{\text{CNDO}} = f(\alpha)$ is practically the same for these configurations. For the conformation *A'* a local minimum was found within 120° to 180°, the corresponding minima of *B'* and *C'* being within 0° to 60° and 120° to 180°, respectively. These results indicate that the transition from the series *A-C* to the series *A'-C'* does not result in any marked differences concerning mutual orientation of the partners *I* and *II*.

Orbital analysis: The wave function of the conformations *IIIa,b,c* was analyzed, and the expansion coefficients of the frontier orbitals HOMO and LUMO were compared (Table II). In the case of the conformation *A* the π -HOMO is considerably delocalized over almost the whole heterocyclic molecule with participation of the oxygen *p*-AO of acetaldehyde (*II*). The π^* -LUMO is delocalized exclusively at the

TABLE III

The CNDO/2 and INDO Charge Density Change in the *I-II* Supermolecule Related to the Isolated Components *I* and *II*

The data in e . 10⁻⁴.

Centre	<i>IIIa</i>		<i>IIIb</i>		<i>IIIc</i>		
	CNDO/2	INDO	CNDO/2	INDO	CNDO/2	INDO	
<i>I</i>	H(4')	276	255	254	232	429	539
	H(4 ⁿ)	36	26	74	74	52	78
	C(3)	44	37	1	- 8	693	746
	C(4)	-143	-111	-153	-119	- 85	-105
	C(5)	- 39	- 41	- 22	- 26	- 23	31
	C(3')	- 1	23	- 11	- 1	31	102
	O(3')	- 1	- 1	- 21	- 24	192	272
	N(3')	34	66	- 43	- 46	-195	-247
<i>II</i>	H(-C)	- 89	223	- 59	276	- 52	275
	C(=O)	310	-563	293	-572	219	-654
	C(H ₃)	- 37	326	- 34	324	- 14	337
	O(=C)	-445	-129	-437	-141	-266	52
	total	-288	-298	-231	-245	- 26	- 13

atomic centres C(2)–C(3)–C(3')–O(3'), but it does not reach to the acetaldehyde part (*II*). A roughly the same conclusion can be drawn in the case of the π -HOMO of the conformation *B*, but in the π^* -LUMO there exists participation of the *p*-AO of acetaldehyde carbonyl group besides the centres C(2)–C(3)–C(3')–O(3'). In the conformation *C* the both π -HOMO and π^* -LUMO are only delocalized to the atoms of the heterocycle *I*. Hence it seems that the conformation *B* represents the most favourable initial state for reduction of the aldehyde *II* (as it was the case with the EHT model, too¹).

Electron distribution: From comparison of the relative CNDO/2 charge densities of the conformations *IIIa,b,c* related to the isolated molecules (Table III) it can be concluded that in all the three cases the *I–II* supermolecule shows (compared to the isolated molecules *I* and *II*) electron density decrease at the hydrogen atoms H(4') and H(4'') and at the carbon atom of amide group, too. On the contrary, an electron density increase is encountered in the *II* component at the carbonyl oxygen atom O(=C), the effect being more marked with *IIIa,b* than with *IIIc*. To exclude the possibility that these results are due to the known overestimation of the electron density at the hydrogen atomic centres in the CNDO/2 models, we also calculated the charge densities for the *IIIa,b,c* arrangement by the INDO method. Comparison of data in Table IV shows that, in contrast to CNDO/2, the INDO method predicts the electron density transfer to the carbonyl carbon atom of the acetaldehyde *II* in all the three cases *IIIa,b,c*, the effect being strongest in *IIIc*. The electron density at the acetaldehyde carbonyl oxygen atom is most increased in *IIIb*, being decreased in *IIIc*. At the same time the electron density is decreased at H(4'). Comparison of the total charge transferred to the acetaldehyde *II* molecule shows that the conformations *A* and *B* are preferred. This fact indicates that the electronic charge is transferred *via* the hydrogen centre H(4'), which agrees with the biochemical views⁴ about this reduction.

On the whole it can be stated that the CNDO/2 model of the *I–II* supermolecule prefers energetically the conformations *A*, *B* to the conformation *C*. Compared with the previous EHT model¹ of the same system, it is possible to find geometrical similarities of the optimum conformations; in addition, the CNDO/2 method gives information about the stabilization energy of this supermolecule. Comparison of the INDO electron densities at the *I–II* supermolecule with those at the isolated components *I* and *II* shows that in all the cases electronic charge is transferred to the acetaldehyde carbonyl group. Decision between the conformations *A* and *B* is difficult, because the energy difference between them is minimum (3.4 kJ mol⁻¹); the configuration *IIIb* is preferred on account of a somewhat lower energy of the optimum arrangement and the stabilization energy of the *I–II* supermolecule which is of higher order of magnitude. These results agree qualitatively with the previous EHT study.

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Translated by J. Panchartek.