EHT STUDY OF REACTIVITY OF METHYLENE GROUP IN 1-METHYL-1,4-DIHYDRONICOTINAMIDE*

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It has been demonstrated that the EHT method predicts an almost plane form of the heterocyclic ring in 1-methyl-1,4-dihydronicotinamide *I* (R = CH_3) and also reflects satisfactorily character of the covalent bonds in the 4-methylene group. An attempt has been made of calculation of the reaction profile of elimination of the centre 4', and electronic mechanism of its splitting off is discussed.

According to current knowledge, biochemical reductions with the coenzyme NAD(P)H proceed by a transfer of one hydrogen atom from 4-methylene group of the nicotinamide fragment *I* to the reduced substrate[1-3]. So far, however, it has not been unambiguously stated what is the electronic mechanism of these reductions, even though a number of authors presume a hydride-transfer[4]. The hitherto MO studies carried out in the pi-electron approximation[5-7] could not contribute to differentiation between alternative electronic mechanisms, though they showed[8,9] the ambiguity of the original arguments[5] in favour of the hydride-transfer. The present communication tries to apply the EHT method to study of the electronic mechanism of abstraction of the said hydrogen centre from 4 position for the case of the trivial NADH model given in formula I (R = CH_3).

CALCULATIONS

The calculations were carried out with the use of standard EHT programs on an IBM 370/145 and an ICL-4-72 computers. The starting geometry of the compound *I* and the parametrization used were identical with those used in the previous reports[10].

RESULTS AND DISCUSSION

Shape of the model molecule I. Information about adequate geometry of the coenzyme fragment *I* forms the starting point to the proposed reactivity considera-

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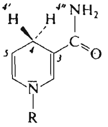
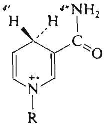
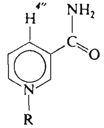
tions. The molecule *I* ($R = CH_3$) shows conformational flexibility due to two reasons: *1*) the rotation isomerism connected with rotation about the C—$CONH_2$ bond, *2*) a possible equilibrium distorsion of the dihydropyridine ring out of the strictly plane arrangement. As far as the conformation of the amide group is concerned, both the MO calculations[10] and experimental findings[11] prefer the arrangement given in formula *I*. On the contrary, the arguments in favour of the plane arrangement of the heterocyclic ring are ambiguous. The X-ray diffraction studies[11,12] of the derivatives *I* (R = n-C_3H_7 and $C_6H_5CH_2$) suggest a plane heterocyclic ring, however, with not too high precision degree which is also indicated by the markedly non-homogeneous interatomic distances given for the individual cases. The NMR studies[13] usually state chemical equivalence of the both protons in the 4 position of all simpler models *I* (R = alkyl), but they do not exclude the possibility of rapid interconversion of the non-plane conformers. Also the MO studies have provided ambiguous results so far. The CNDO/2 calculations[10] predict the plane 1,4-dihydropyridine ring, whereas the EHT method suggests a slightly deviated boat conformation[14]. In this context it is noteworthy that the recent X-ray studies of more complex 1,4-dihydropyridine derivatives[15–18] confirm the boat[15,16], plane[17] or envelope[18] conformation of the said heterocycle. With respect to the latter finding[18] we examined the advantage of the envelope conformation *Ia* ($R = CH_3$) within the framework of the EHT method. From Fig. 1 it is obvious that the envelope conformation really appears to be the most favourable energetically for the dihydropyridine derivative *I* and its radical-cation *II*, however, for the minimum values



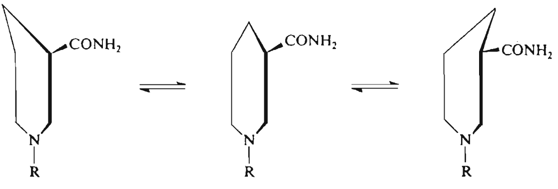
I



II



III



Ia *Ic* *Ib*

of the angle $\alpha = 0{\cdot}5$ or $0{\cdot}3°$. With respect to the low calculated energy barrier $0{\cdot}1$ kJ mol^{-1} between the conformations *Ia,b* for our case $R = CH_3$ it is, however, possible to consider the both hydrogen atomic centres in the 4-methylene group to be practically equivalent, and, for simplicity, in the rest of this report the model *I* will be approximated by the plane conformation *Ic* ($\alpha = 0°$) only.

Bonding relations in 4-methylene group. Due to approximative character of the EHT method it was desirable to verify how reliably it reflects the character of the covalent C—H bonds. The latter make themselves felt *e.g.* in the existence of coupled symmetrical and antisymmetrical stretching vibrations of the CH_2 group in the vibration spectra of the compound type *I*. The geometrical distorsion of the CH_2 group connected with the first of the mentioned modes was now simulated by following the EHT energy changes of the model *I* ($R = CH_3$) in dependence on synchronous change of interatomic distance in the C—H bonds (Fig. 2). The resulting dependence has obviously the shape of the classical Morse curve (the curve *1*) expressing the existence of the dissociation limit in the sense of the two-atomic model of anharmonic oscillator. On the contrary, the curve 2 obtained similarly for the antisymmetric mode is close to a simple parabola in the sense of the two-atomic model of harmonic oscillator without the dissociation limit. However, the dissociation limit can be reached, anyhow, in a speculative model of an isolated stretching vibration of one

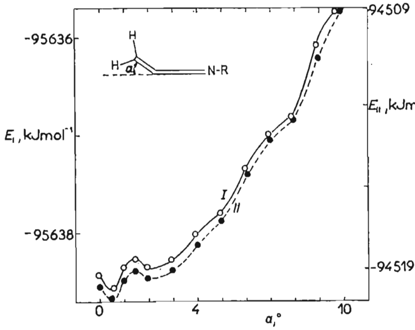


FIG. 1

Dependence of the EHT Energy Changes of the Models *I* and *II* ($R = CH_3$) on Devation of Methylene Group out of the Ring Plane single C—H bond, *i.e.* motion of a single atomic centre (the curve *3*). These results indicate that the EHT method represents satisfactorily the bonding relations especially in the regions not too far away from the equilibrium position of the atomic centres in the 4-methylene group. Only the calculated equilibrium bond length C—H is shorter by about 25 pm than the real one (Fig. 2), which is the expected result of the neglect of electron repulsion in the EHT procedure.

Energy profile of elimination of hydrogen centre 4′ *from the model* I ($R = CH_3$). For assessment of the energy relations during elimination of the centre 4′ especially two changes of geometrical degrees of freedom of the system can be considered

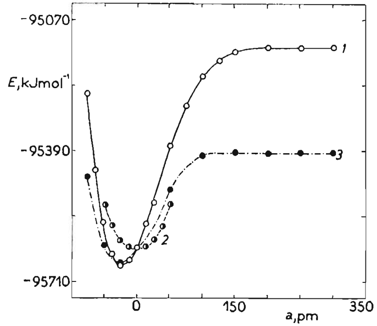


FIG. 2

Changes of EHT Energy of Model *I* ($R = CH_3$) Connected with Symmetrical and Antisymmetrical Stretching Vibrations of CH_2 Group (*a* means the H—C distance change in the CH_2 group)

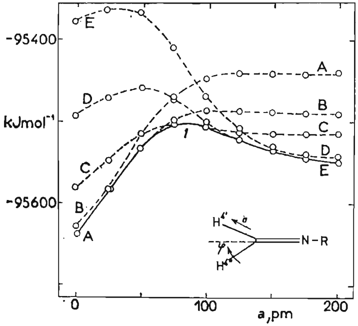


FIG. 3

Dependence of EHT Energy Changes of Model *I* on Parameters *a* and *φ* (*a* means the change of the bond length C(4)—H(4′), *φ* means the change of the angle between the bond C(4)—H(4″) and the ring plane)

The curves *A*, *B*, *C*, *D* and *E* correspond to $\varphi = 0°$, 13·7°, 27·4°, 41·1° and 54·7°, respectively. The heavy line *1* represents the EHT approximation of the reaction profile.

significant: the distance change a between the atomic centres at the split bond C(4)—H(4′) and the change of angle φ between the plane of the heterocyclic ring and the bond C(4)—H(4″) whose decrease reflects the motion of the non-reacting centre H(4″) during transformation of tetrahedral to trigonal arrangement of the bonds at the C(4) centre. Dependence of the EHT energy changes of the model *I* ($R = CH_3$) on the corresponding parameters a and φ is given in Fig. 3. (For the initial state it is $a = 0$, $\varphi = 0°$). It is obvious that the curves $E_{EHT} = f(a)$ only have the increasing character for low values of the angle $\varphi = 0$ and 13·7°, being convergent

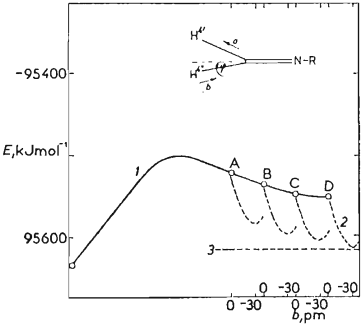


FIG. 4

Dependence of EHT Energy Changes of Model *I* in the Case of the Optimum Coordinate on Parameter b (b means the change of the bond length C(4)—H(4″))

The points correspond to the following a and φ values: *A*, 125 pm, 41·1°; *B*, 150 pm, 41·1°; *C* 175 pm, 54·7°; *D*, 200 pm, 54·7°. The dashed straight line *3* denotes the energy value for the system of the isolated particles *III* and H^-.

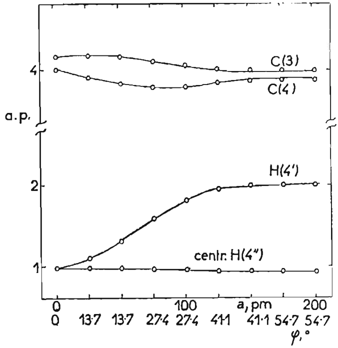


FIG. 5

The Atomic Abundances at Some Centres of Model *I* Calculated for Certain Points of the Optimum Coordinate (see curve *1* in Fig. 3)

a.p. atomic population.

for $a > 150$ pm. On the contrary, the analogous dependences for higher values $\varphi = 22{\cdot}4$, $44{\cdot}1$ and $54{\cdot}7°$ show energy maxima for $a = 25$ to 100 pm with the subsequent convergencies with the limit values at $a > 200$ pm. The curves with lower values are obviously close to the sought profile only in the initial phases when the distance of the reacting centre H(4′) is still so small that it does not stimulate **any** marked motion of the non-reacting centre H(4″). On the contrary the curves **with** the higher values φ, especially $\varphi = 54{\cdot}7°$, *i.e.* the state in which the bond C(4)—H(4″) already lies in the plane of the nucleus, rather simulate the situation after finished reduction of the substrate, *i.e.* the state when the non-reacting centre H(4″) already is in the plane of the heterocycle. Under these simplifying presumptions an acceptable approximation of the EHT reaction profile is given by the heavy line *1*, Fig. 3. The said profile can be further improved in that the bond length C(4)—H(4″) is optimized in the individual steps along the coordinate corresponding to the curve *1*. The change of this bond length is denoted as *b* (Fig. 4). It is obvious that lowering of the para-

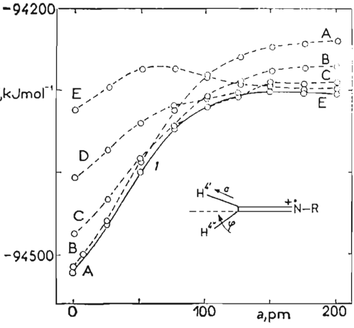


FIG. 6

Dependence of EHT Energy Changes of Model *II* ($R = CH_3$) on Parameter *a* and φ (for meaning of *a* and φ see Fig. 3)

The curves *A*, *B*, *C*, *D* and *E* correspond to $\varphi = 0°$, $13{\cdot}7°$, $27{\cdot}4°$, $41{\cdot}1°$ and $54{\cdot}7°$, respectively. The heavy line *1* represents the EHT approximation of the reaction profile.

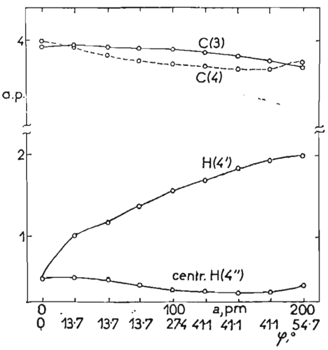


FIG. 7

Atomic Abundances at Some Centres of Model *II* Calculated for Certain Points of the Optimum Coordinate (see the curve *1* in Fig. 6)

a.p. atomic population.

meter *b* during the reduction process will result in further energy decrease, as the said bond changes from the type sp^3-s to sp^2-s. Combination of the curves *1* and 2 (Fig. 4) results in the "best" energy profile with the energy barrier 125 kJ mol^{-1} expressing that the reduction with *I* should be endoergic by about 22 kJ mol^{-1}. However, due to the character of the EHT procedure these results must be only considered semiquantitative.

Electronic mechanism. Fig. 5 gives the changes of atomic abundances at some centres of the model *I* ($R = CH_3$) in the course of the reaction path approximated by the curve *1* in Fig. 3. It is obvious that the reacting centre H(4') assumes practically the character of hydride ion already, as its distance from the centre C(4) is longer that 100 pm. Other changes in atomic abundances at the remaining positions are substantially lower and agree with the transformation of the electronic structure of dihydropyridine ring in the model *I* into that of pyridine ring in the model *III*. Hence, it can be concluded that the EHT profiles in Figs 3 and 4 represent the reduction *via* two-electron mechanism. Their relatively high energy barriers do not contradict the experimental experience[19-21] showing that simple compounds similar to the model *I* (R = alkyl) reduce only extraordinarily activated carbonyl and imine substrates.

Another alternative mechanism of reduction by the compounds *I* could consist in a preceding abstraction of electron $I - e \rightarrow II$. The calculated activation barrier of the subsequent elimination of the centre H(4') appears to be only slightly higher than that of the closed-shell system *I* (Fig. 6). However, its chemical reliability is decreased by the fact that, according to the calculated atomic abundance (Fig. 7), the leaving particle is a hydride anion again. This calculation is paradoxical, since it represents a tendency of the positively charged radical-cation *II* to split off a negative particle, *viz.* H^-, and it is most probably due to the failure of EHT in described the energy relations in the open-shell system *II*, which can be connected with non--respecting of both the repulsion and the correlation energies.

CONCLUSIONS

The EHT calculations carried out for the abstraction of the atomic centre H(4') from the molecule of the model compound *I* ($R = CH_3$) support the possible hydride mechanism of this process, however, they cannot exclude another alternatives with participation of the open-shell intermediates type *II*. The latter problem is now being studied by improved methods.

REFERENCES

1. Fischer H. F., Conn E. E., Vennesland B., Westheimer F. H.: J. Biol. Chem. *202*, 687 (1953).
2. Pullman M. E., San Pietro A., Colowick S. P.: J. Biol. Chem. *206*, 129 (1954).
3. Akhtar M., Jones C.: Tetrahedron *34*, 813 (1978).

4. Bruice T. C., Benkovic S.: *Bioorganic Mechanisms*, Vol. II. Benjamin, New York 1966.
5. Pullman B., Pullman A.: *Quantum Biochemistry*. Wiley, New York 1963.
6. Pullman B., Pullman A.: Proc. Nat. Acad. Sci. U.S.A. *45*, 136 (1959).
7. Pullman B., Pullman A.: Cancer Res. *19*, 337 (1959).
8. Skála V., Musil L., Kuthan J.: This Journal *42*, 843 (1977).
9. Skála V., Kuthan J.: This Journal *43*, 3064 (1978).
10. Kuthan J., Musil L.: This Journal *40*, 3169 (1975).
11. Karle I. L.: Acta Crystallogr. *14*, 497 (1961).
12. Koyama H.: Z. Kristallogr., Kristallgeometrie, Kristallphys., Kristallchem. *118*, 51 (1963).
13. Oppenheimer N. J., Arnold L. J., Kaplan N. O.: Biochemistry *17*, 2613 (1978).
14. Kuthan J., Musil L.: This Journal *42*, 857 (1977).
15. Krajevski J., Urbanczyk-Lipkowska Z., Gluzinski P.: Acta Crystallogr. B, *31*, 2967 (1977).
16. Mishnev A. F., Shvec A. E., Bleidelis Y., Duburs G., Sausins A., Lusis V. K.: Khim. Geterotsikl. Soedin. *1977*, 1229.
17. Lenstra A. T.: Bull. Soc. Chim. Belg. 88, 133 (1979).
18. Huml K., Ječný J., Kutschabsky L., Reck G.: Acta Crystallogr. *B33*, 444 (1979).
19. Shinkai S., Shiraishi S., Kunitake T.: Bull. Chem. Soc. Jap. 49, 3656 (1976).
20. Bucciarelli M., Forni A., Moretti I., Torre G.: J. Chem. Soc., Chem. Commun. *1978*, 456.
21. Shinkai S., Nakano T., Hamada H., Kusano Y., Manabe O.: Chem. Lett. *1979*, 229.

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