

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

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With the use of the method of local energy minima it has been postulated that energetically preferred tight configurations of the "supermolecule" 1-methyl-1,4-dihyronicotinamide-acetaldehyde (*I*) can be formulated as the mutual orientations of the both partners *Ia, b*. Possible biochemical aspects of these arrangements are discussed.

Reversibility of the red-ox processes catalyzed by alcoholdehydrogenases results from both the oxidation action of NAD^+ on hydroxy substrates and reduction action of NADH on the oxidation products. It can be presumed that mutual spatial arrangement of the substrate and the nicotinamide fragment will not be markedly changed during the red-ox process, and, therefore, knowledge of mutual configuration of the both partners can afford a deeper insight into sterical conditions of efficiency of the catalyzed process. Several modes of the mutual orientation between the carbonyl substrates were proposed intuitively¹⁻³ on the basis of interpretation of experimental data. On the contrary, no theoretical test of these proposals on the basis of MO theory has been submitted so far. Therefore, we tried to submit to a preliminary theoretical investigation a simplified system in which NADH and the reduced substrate are modelled by 1-methyl-1,4-dihyronicotinamide and a single acetaldehyde molecule, respectively. To start with we chose the calculations using the evaluation of local energy minima (LEM) as in ref.⁴ on the simple EHT basis. The obtained results from this approach are presented in this communication.

CALCULATIONS

All the numerical calculations were carried out with the use of the standard EHT program with controlled variation of geometrical parameters using an IBM 370/145 computer. The interpretation was based on total 226 energy values E_{EHT} of various configurations of the atomic centres of the supermolecule *I*. The diagonal elements of the **H**-matrix were altogether ionization potentials of the corresponding valence states, the non-diagonal elements were calculated

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by the Wolfsberg-Helmholz approximation with the empirical constant $K = 1.75$. Values of the other parameters are given in Table I. Arrangement of the components of the supermolecule *I* in coordinate systems can be seen in Fig. 1. Geometry of the individual components was the same as that in refs^{5,6}. Calculation of the dependences of the E_{EHT} values on the geometrical parameters was realized by the maximum steps 100 pm and 60° . In the regions of extreme E_{EHT} values the step was lowered to 10 pm and 6° .

RESULTS AND DISCUSSION

Geometry of supermolecule I. With respect to limited scope of the LEM approach⁴ we decided to examine the energetical advantages of three types of mutual configurations of the closely approached reactants denoted as A, B and C (Fig. 1). These configurations were chosen with respect to the possibility of their representing initial situations of transfer of one hydrogen atom from 4 position of dihydropyridine ring to carbonyl group of acetaldehyde. Besides, they should involve the situations suggested intuitively¹⁻³, too. From Fig. 1 it can be seen that two degrees of freedom are considered in each configuration of the system *I*: the distance r between the carbonyl carbon atom of acetaldehyde and the said hydrogen atom, and the angle α of rotation of the substrate about the axis determined by the H—C(O) bond. In principle the problem is thus reduced to a search for local minima of the function $E_{\text{EHT}} = f(\alpha, r)$, especially that minimum which corresponds to the minimum r value.

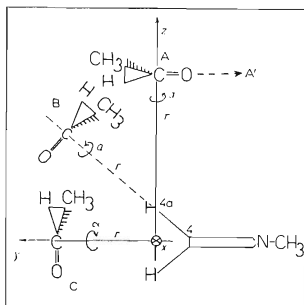


FIG. 1

Configuration Study of EHT Models of System 1-Methyl-1,4-dihydropyridinamide-Acetaldehyde

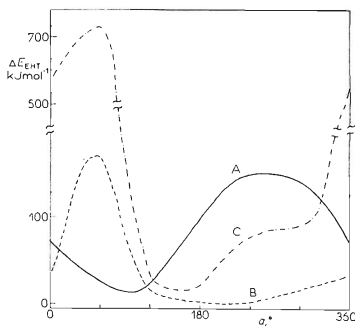
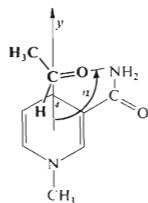
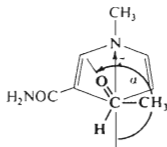
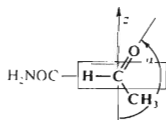


FIG. 2

Dependence of EHT Energy of System *I* on Rotation Angle of Acetaldehyde (Fig. 1)

Energy of system 1. It was found that the E_{EHT} quantity is sufficiently variable only for $r < 300$ pm in all the configurations A, B, C. At higher r values the obtained E_{EHT} values are not very different and converge asymptotically to the sum of energies of the individual partners, *i.e.* $1.284 \cdot 10^5 \text{ kJ mol}^{-1}$. Hence the EHT models of the supermolecules *I* do not lead to absolute energy minima for physically reasonable distances of the both reactants. As far as the local extremes are considered, the LEM method was shown (in accord with previous experience⁵) to be most advantageous for following the E_{EHT} changes within $r = 100$ to 300 pm. In Fig. 2 it can be seen that the configuration A shows local minima of the curves $E_{\text{EHT}} = f(\alpha)$ at $\alpha = 96^\circ$ and a rotation barrier of the acetaldehyde molecule at $\alpha \approx 250^\circ$. According to our calculations shifting of the acetaldehyde molecule further above the plane of the heterocycle always results in relative increase of the E_{EHT} quantity, the alternative modified configurations A' appearing thus not energetically favourable. For the configuration B the curves $E_{\text{EHT}} = f(\alpha)$ show rather broad local minima within $\alpha = 120$ to 300° (Fig. 2), *i.e.* with a relatively little reduced mobility of the acetaldehyde molecule around the C(4)—H bond direction. The relatively narrow but marked rotation barrier at $\alpha = 60^\circ$ is obviously due to steric interaction between the groups C—CH₃ and CO—NH₂ of the two partners. The configuration C again gives local energy minima at $\alpha \approx 150^\circ$ and a marked rotation barrier at $\alpha \approx 50^\circ$ (Fig. 2) connected obviously with the steric interaction C—CH₃...H₂NCO—, too. The most probable shapes of the supermolecules in the electronic ground state can be formulated as *Ia-c*.

*Ia* ($\alpha = 96^\circ$)*Ib* ($\alpha = 210^\circ$)*Ic* ($\alpha = 148^\circ$)

As the E_{EHT} values of the minima at the maps $E_{\text{EHT}} = f(\alpha, r)$ correspond figuratively, in the LEM method, to valleys cutting into the massifs with peaks of these energy "mountains" of the system *I*, the parameter r represents a critical quantity of an energy path through the valley to the closest configuration of the reactants. Figure 3 compares the curves $E_{\text{EHT}} = f(r)$ of all three configurations A, B, C for the minimum angles α . It is obvious that the configuration C provides the worst fulfilment of the requirement of the closest approach. On the contrary, the most favour-

able appears to be the configuration B, in which, however, the mentioned energy valley is very broad and, hence, does not lay claims to a too precise position of the acetaldehyde molecule with respect to the model of the coenzyme part I. The configuration A, which is not too distant energetically from the situation B, represents, on the contrary, a more deeply cut valley with higher claims to a defined orientation of the aldehyde substrate with respect to the model of the dihydronicotinamide group. It is noteworthy that the alternative A out of the preferred configurations of the

TABLE I

The Parameters Used in EHT Calculation

$IP(s)$ Ionization potential of s orbital, $IP(p)$ ionization potential of p orbital, S.E. the Slater exponent.

| Atom | $IP(s)$, eV | $IP(p)$, eV | S.E. |
|------|--------------|--------------|-------|
| H | -13.6 | — | 1.300 |
| C | -21.4 | -11.4 | 1.625 |
| N | -26.0 | -13.4 | 1.950 |
| O | -32.3 | -14.8 | 2.275 |

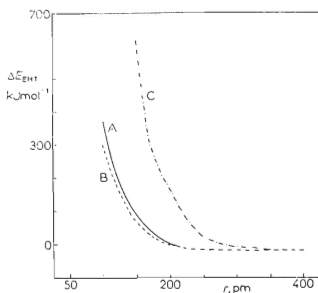


FIG. 3

Dependence of EHT Energy of System I on Distance r between Hydrogen Atom at 4 Position of 1-Methyl-1,4-dihydronicotinamide and Carbonyl Carbon Atom of Acetaldehyde (Fig. 1)

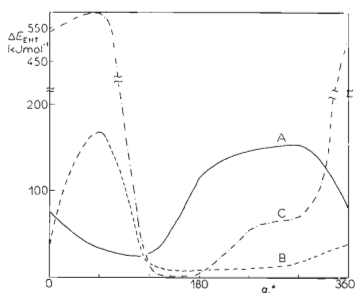


FIG. 4

Dependence of EHT Energy of System I after Excitation by $\pi \rightarrow \pi^*$ Transition on Rotation Angle of Acetaldehyde (Fig. 1)

supermolecule *I* is close to the configuration suggested intuitively on the basis of stereochemical considerations¹⁻³. In addition, the both configurations A and B are not in contradiction with the proposal⁷ derived on the basis of an NMR relaxation study of the complex of the reduced alcoholdehydrogenase with acetaldehyde. Furthermore, Fig. 4 gives the curves $E_{\text{EHT}} = f(\alpha)$ of the configurations A, B, C in excited electronic states (the $N \rightarrow V_1$ transition) for the fixed r values. Comparison with the analogous curves of the ground states (Fig. 2) indicates that the said electron excitation does not markedly change the situation with respect to the overall shape of the preferred forms *Ia-c*. There only exists a certain shift of the energy minima to the values about $1.2808 \cdot 10^5 \text{ kJ mol}^{-1}$.

Orbital analysis. In the energy-optimized EHT models of the supermolecule *I* we further examined (at $r = 150 \text{ pm}$) the frontier MO's from the viewpoint of participation of the individual partner parts of the reactants. In the configuration A (*Ia*) the HOMO of the supermolecule *I* is in fact a combination of π, σ -HOMO of 1-methyl-1,4-dihydronicotinamide and π^* -LUMO of acetaldehyde (ref.⁸). As a result there exist positive overlap ($S = +0.1467$) between the $\sigma\text{-C}^4\text{-H}^{4a}$ component and $\pi^*\text{-CH=O}$ component of the whole HOMO, so that the used starting EHT model of the configuration A can be considered productive from the viewpoint of reduction of the carbonyl substrate by action of NADH. Analogous conclusions also apply to the total HOMO of the configuration B, but here the overlap is higher ($S = +0.1539$). On the contrary, the HOMO character of the configuration C appears to be a combination of the HOMO of 1-methyl-1,4-dihydronicotinamide with the HOMO of acetaldehyde, the overlap between the above-mentioned critical parts

TABLE II
Density Changes of Electron Charge Related to Isolated Components of the Supermolecule *I* at Infinite Distance

| Molecule | | Configuration | | |
|-------------------------------|----------------------------------|---------------|-----------|-----------|
| | | <i>Ia</i> | <i>Ib</i> | <i>Ic</i> |
| Nicotinamide part of <i>I</i> | H(C ⁴) | 0.1013 | 0.0983 | 0.2053 |
| | C ³ | 0.0049 | 0.0111 | 0.0224 |
| | C ⁴ (H ₂) | 0.0327 | 0.0305 | -0.1481 |
| | C ⁵ | 0.0045 | 0.0072 | 0.0281 |
| Acetaldehyde part of <i>I</i> | C(=O) | 0.0404 | 0.0639 | 0.0131 |
| | C(H ₃) | 0.0033 | 0.0056 | 0.0043 |
| | O(=C) | 0.1098 | 0.1073 | 0.1936 |

of the supermolecule *I* being negative and little significant ($S = -0.0101$). Hence the configuration *C* can be considered non-productive from the viewpoint of biochemical interaction of the carbonyl substrate with NADH, at least so in the electronic ground state. The LUMO's of all the configurations *A*, *B*, *C* of the system *I* are but slightly different from the π^* -LUMO of 1-methyl-1,4-dihydronicotinamide itself, which suggests that a potential excitation $\pi \rightarrow \pi^*$ does not appear biochemically interesting.

Electron distribution. Table II gives the more marked changes of the charge densities for the said configurations *Ia-c* ($r = 150$ pm). First of all, it seems that, from the viewpoint of the overall transfer of negative charge from 1,4-dihydropyridine ring to the substrate, the configuration *Ib* (0.2034) should be somewhat preferred to the configurations *Ia* and *Ic* (0.1842 and 0.1884). Furthermore it is seen that the most marked increase in the electron charge takes place at the carbonyl group of the aldehyde (0.1073 to 0.1936) predominantly to the detriment of the charge decrease at the hydrogen atomic centre at 4 position (0.0983 to 0.2053). All the configurations *Ia-c* can thus be considered to be initial states of the acetaldehyde reduction. However, the configurations *Ia,b* show a more marked trend to the charge-transfer *via* a single hydrogen centre 4a in accordance with the course of the biochemical reduction in which also a single hydrogen atom is transferred from NADH to the substrate⁹.

CONCLUSIONS

On the whole it can be stated that, according to the energy criteria and orbital interaction analysis between the reactants of the system, the configuration *Ib* is somewhat preferred to *Ia* as an EHT model of biochemical reduction of carbonyl substrates. The configuration *Ib* seems, in addition, to show higher geometrical flexibility from the viewpoint of fixation of the substrate. The arguments contradicting the configuration *Ic* are the antibonding relation between the aldehyde and the heterocyclic parts in the HOMO of the system *I* and the characteristics of charge distribution at the interacting centres. According to the EHT calculations, all the configurations *Ia-c* show the transfer of electron density from 1,4-dihydropyridine ring to acetaldehyde.

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