CONTRIBUTION TO EHT CONFORMATION ANALYSIS OF 1-METHYL-3-CARBAMOYLPYRIDINIUM CATION*

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Variation of valence angle in the grouping C—C—CO has been shown to be inevitable in EHT conformation analysis of the ion *I* for calculation preferring the conformation *Ia* to the form *Ib* in accord with experimental findings. For the neutral amide *III* this procedure is not necessary, the conformation type *IIIb* being always preferred to the form *IIIa*. Furthermore the effects are discussed of parametrization of EHT models of *I* and *III* on quantitative conformational characteristics.

1-Methyl-3-carbamoylpyridinium cation (I) is a trivial model of the nicotinamide fragment NAD^+ (nicotinamide adenine dinucleotide), whereas its 1,4-dihydro derivative *II* is a similar model for the reduced form NADH. Semiempirical calculations on the basis of EHT (ref.[1,2]), PCILO (ref.[3]) and CNDO (ref.[4]) give the unambiguous conclusion that the energetically most favourable conformation of the latter compound corresponds to the formula *II*. On the contrary, relative EHT energies of the conformation types *Ia* and *Ib* were found[4,5] to depend on detailed choice of valence lengths and angles which remain constant during the calculation. As possible preference of the rotation isomer type *Ib* could lead to the theoretical presumption that the process $I + 2e + H^+ \rightarrow II$ modelling the biologically active redox system $NAD^+ + 2e + H^+ \rightleftarrows NADH$ should be accompanied by considerable conformation change of the amide group with respect to the heterocyclic ring $(Ib \rightarrow II)$, we decided to investigate in detail the factors affecting relative values of energy quantities in the EHT calculation of the ion *I*. On the one hand we extended number of geometrical degrees of freedom affecting the overall shape of the ion *I* and, on the other hand, we verified some of the used empirical parameters. The calculations of the ion *I* were confronted with the analogous ones of the structurally little different model of nicotinamide (III) for which the EHT method predicts[1,7,8] the conformer *IIIb* to be energetically more favourable. The obtained results are dealt with in this report.
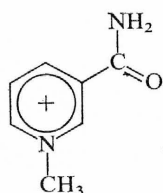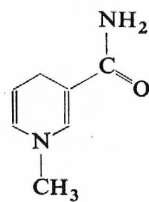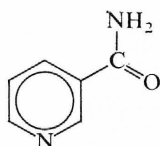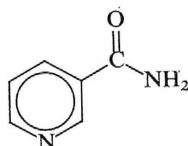
Ia
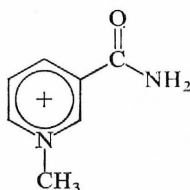
Ib

II

IIIa

IIIb

Calculations

The EHT calculations were carried out with computers IBM 370/145 and Tesla 270. The parameters used are given in Tables I and II. The so called "experimental" geometry of the EHT models was derived from the X-ray diffraction data[9−12] with bond length N^+—C 146 pm and C—H 106 pm and with idealized dimensions of CH_3 group[2] for the compound *I*, and it was identical with that used in the previous EHT calculations[8] of the compound *III*. For the so called "ideal geometry" of the both forms *I* and *III* all the angles at the sp^2 atom centres were 120°, the heterocycle being regular hexagon with 139 pm side, and the other bond lengths were 122 pm (C=O), 134 pm (C—NH_2), 110 pm (N—H and O—H) and 152 pm (N^+—CH_3 and C—CO). Orientation of the models with respect to coordinate system is given in Fig. 1.

TABLE I

The Parameters Used in the EHT Calculations
The ionisation potentials in eV.

Atom	Hinze–Jaffé[18]		Skinner–Pritchard[19]	
	I_s	I_p	I_s	I_p
H	−13·6	—	−13·6	—
C	−21·01	−11·27	−21·4	−11·4
N	−26·92	−14·42	−26·0	−13·4
O	−32·07	−18·53	−32·3	−14·8

TABLE II

Effect of Parametrization in EHT Model of Ion I on Relative Position of the Main Minimum at α_1 and Local Minimum at α_2 at the Curves $E_{tot} = f(\alpha)$

$H_{ij}{}^a$	K	$SE_H{}^b$	$I_p{}^c$	Rotation angle, °		Energy, kJ/mol^d		
				α_1	α_2	E_{trans}	E_{rot}	E_{rac}
1A	1·75	1·3	H.J.	174	35	11·4	11·4	0·1
2G	1·75	1·3	H.J.	180	27	12·3	12·3	0·0
3A	1·75	1·0	H.J.	145	44	8·0	13·3	1·5
4G	1·75	1·0	H.J.	157	42	9·8	11·9	0·5
5A	1·75	1·3	S.P.	170	34	10·5	10·5	0·1
6G	1·75	1·3	S.P.	177	34	10·9	10·9	0·0
7A	1·75	1·0	S.P.	147	48	5·6	14·6	1·8
8G	1·75	1·0	S.P.	154	44	8·8	13·3	0·9
9G	−1·50	1·0	S.P.	0	180	6 008·7	6 008·7	0·0
10G	−1·50	1·3	S.P.	0	180	1 119·9	1 119·0	0·0

^{a} Approximation of arithmetic mean A : $H_{ij} = KS_{ij}(H_{ii} + H_{jj})/2$, geometric mean G: $H_{ij} = KS_{ij}(H_{ii}H_{jj})^{1/2}$; ^{b} the Slater exponent for hydrogen; ^{c} ionisation potentials according to Hinze and Jaffé: H.J. (ref.[18]), according to Sinner and Pritchard: S.P. (ref.[19]); ^{d} transformation, rotation and racemization energies.
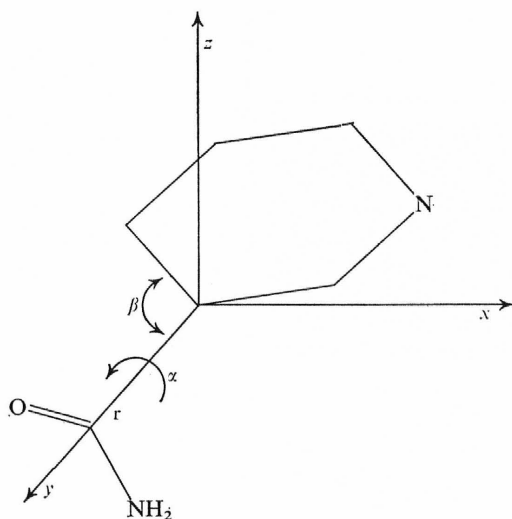

FIG. 1

Orientation of the Studied Molecules in Coordinate System and Geometric Degrees of Freedom

RESULTS AND DISCUSSION

As we were interested in conformation of the species *I* and *III* and not in their detailed geometry, the most important degree of freedom can be seen in the rotation angle α. It was proved earlier[6-8] that curves of EHT electron energy $E_{tot} = f(\alpha)$ show two energy minima E_1 and E_2 in these cases, *viz.* at $0° < \alpha_1 < 90°$ and $90° < \alpha_2 < 180°$, respectively. For the compound *III* it is generally true[7,8,13] that $E_1 < E_2$ regardless of detailed geometry of the EHT models from the viewpoint of the other fixed degrees of freedom. Therefore, within the EHT method the energy preference of the conformation type *IIIb* to *IIIa* can be considered unambiguous and consistent with experimental findings for solid phase[12] and solutions[14,15]. On the contrary, for the ion *I* it is[6,13] $E_1 \gtrless E_2$ depending on choice of detailed values of the constant geometry parameters, although in solid phase quarternary salts with nicotinamide fragment show exclusively[9-12] conformation type *Ia*. For better understanding of possible reasons of the EHT calculations ambiguity[6,13] of the ion *I* we investigated *a*) effect of parametrization of the EHT model *I* on the course of the curves $E_{tot} = f(\alpha)$, and *b*) effect of introducing of further independent variables r and β (Fig. 1) on relative values of the minima E_1, α_1 and E_2, α_2.

Parametrization of the EHT *Model*

From Table II it can be seen that, having respected the "experimental"* geometry of the cation *I*, qualitative prediction of relative energies of the conformations *Ia,b* can be changed in disfavour of the form *Ia* in a single case only, *viz.* with the choice of negative value of the constant $K = -1.50$, which was used for analogous calculation[7] of the neutral amide *III*. However, values of energy barrier E_{trans} are not realistic for this K value. Application of the "experimental" geometry is justified as it is seen from the results of calculations using "ideal" geometry which gave two minima at $\alpha_1 = 30°$ and $\alpha_2 = 150°$ with practically equal energies for the compounds *I* and *III*. The other considered parameter changes affect only quantitative part of the calculation to a different extent. Approximation of non-diagonal elements of the **H**-matrix by the method of arithmetic[16] or geometric mean[17] (*A* or *G*, respectively) does not result in any marked differences. The approach *G* only leads to systematically lower energy barriers E_{trans}, E_{tot} and E_{rac}** and to somewhat closer α_1 values with respect to analogous experimental[9,10] data 173·3 and 180°. Detailed choice of an alternative series of ionisation potentials of the atoms[18,19] proved to be quite insignificant. On the contrary, unity for the value of the Slater exponent of hydrogen atom (which

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*   Except for variable values α the geometry degrees of freedom are fixed according to experimental data (see Calculations).

**   For $0° < \alpha < 180°$ the ion *I* is chiral. The values E_{trans} and E_{rac} are the lowest energy barriers of transformation of the conformers and racemization of the enantiomers, respectively.

is yet used in some EHT calculations, as e.g.[2,8,20]) results, according to data of Table II, in exaggerated over-estimation of non-bonding interactions, and for the compounds type *I* and *III* it obviously has to be substituted by a higher value 1·3 in accord with practice of other authors (as e.g.[7,21]). This finding was also respected in further part of this report.

Simultaneous Variation of Two Geometric Degrees of Freedom

In order to be able to verify which of the fixed geometry parameters in EHT model of the ion *I* is critical for acceptability of results of the EHT conformational analysis using the function $E_{tot} = f(\alpha)$, we investigated the dependence $E_{tot} = f(\alpha, r)$, first of all. From the corresponding energy map in Fig. 2 it can be seen that it shows a valley with an approximately constant equilibrium bond length $C—CONH_2$ $r \simeq 165$ pm for all the rotamers differing in the angle α. In accord with the experience[22] that the EHT method does not reflect well the bond lengths, this value is greater than that from X-ray diffraction[9] by about 15 pm. From position of the main minimum at $\alpha_2 = 180°$ and that of the local one at $\alpha_1 = 21°$ the conformation *Ia* is preferred in accord with experiments[9-11] and more simple calculations (see ref.[6] and this report). A similar map of the amide *III* itself (Fig. 3) shows that at analogous equilibrium lengths r of the bonds $C—CONH_2$ there is the main minimum $\alpha_1 = 20°$ and a local one at $\alpha_2 = 150°$. In this case also the qualitative result of the EHT conformation analysis is similar to that of calculations[7,8] with one variable α,
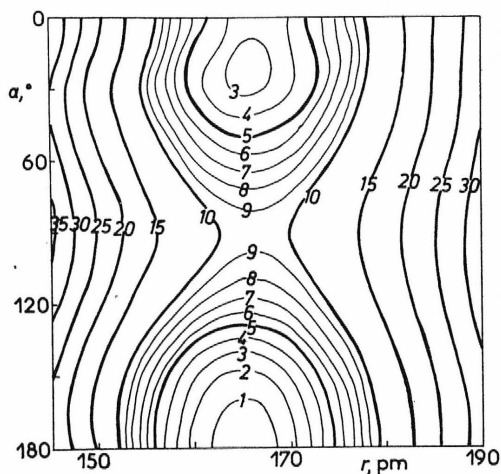

FIG. 2

EHT Energy Map of the Ion *I* for Independent Variables α and r
    The energy unit 0·01 eV.

only the qualitative relation to the date of X-ray analysis[12] ($\alpha = 24°$) being better. From results in Figs 2 and 3 it can thus be judged that the variable r does not affect markedly the qualitative conclusions of the EHT conformational analysis of the ion I. Therefore, we investigated another dependence $E_{tot} = f(\alpha, \beta)$ represented in Fig. 4. It can be seen that, in contrast to the maps in Figs 2 and 3, the energy valley does not pass in the region of approximately constant value of the other independent variable, *i.e.* the valence angle β (Fig. 1). Thereform we conclude that variation of its β value is necessary for finding physically justified position of the local

TABLE III

The EHT Characteristics Obtained at Two Variable Degrees of Freedom

Model	α_1	α_2	r_1	r_2	β_1	β_2	E_1^b	E_2^b	E_{rot}	E_{trans}	E_{rac}
I	180	21	1·65	1·66	—	—	0	0·7	8·7	8·7	0
I	165	15	—	—	123	119	0	0·2	9·5	9·5	0·2
III	20	150	1·67	1·68	—	—	0	1·6	6·7	6·7	0·2

[a] See Fig. 1; [b] the lower minimum was taken for zero level.
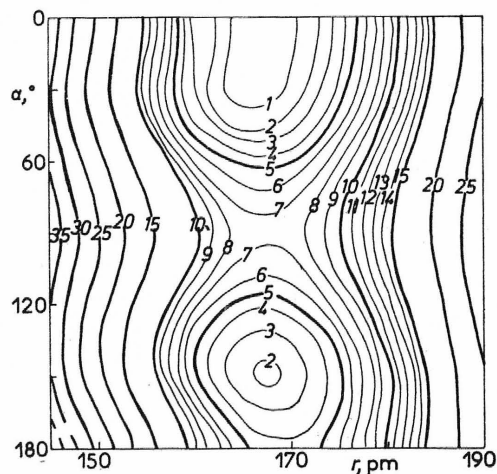

FIG. 3

EHT Energy Map of Amide III for Independent Variables α and r
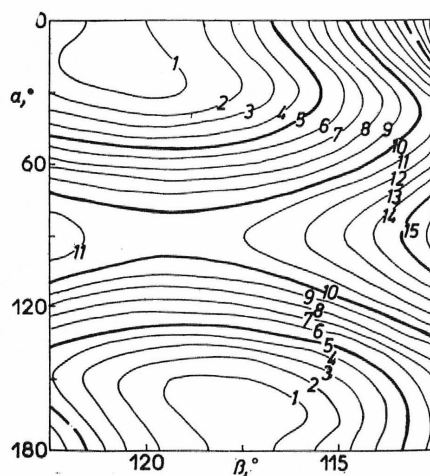
The energy unit 0·01 eV.

FIG. 4

EHT Energy Map of the Ion I for Independent Variables α and β

The energy unit 0·01 eV.

and main energy minima. From Fig. 4 it is obvious, furthermore, that the minima $\alpha_2 = 15°$, $\beta_2 = 119°$ and $\alpha_1 = 165°$, $\beta_1 = 123°$ found in this way show that processes of rotation around C—$CONH_2$ bond and transformation of conformers $Ia \rightleftarrows Ib$ are accompanied by more marked changes of the valence angle β in the case of the ion I. At the same time, the above-mentioned angles of the deeper minimum are closer to the values $\alpha = 174·3°$ and $\beta = 125·5°$ determined by X-ray diffraction[9]. The obtained energy characteristics are given in Table III.

The above-mentioned findings are now interpreted by the difference between the preferred conformations of the ion I and the neutral molecule III being mainly due to the effect of the positive charge of heterocyclic ring on deformation of the valence angle β. It is noteworthy then that it is not necessary for the process $NAD^+ + 2e + H^+ \rightleftarrows NADH$ to postulate theoretically any significant re-orientation of amidic group, which would inevitably necessitate interruption of bonding interaction with the corresponding fragments of apoenzymes.

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