

## A MO TREATMENT OF SOLVENT INFLUENCE ON THE AMIDE GROUP ROTATION IN 1-METHYLNICOTINAMIDES

Hans-Jörg HOFMANN<sup>a</sup>, Christine BARTZSCH<sup>b</sup>, Cornelius WEISS<sup>b</sup> and Josef KUTHAN<sup>c</sup>

<sup>a</sup> *Sektion Biowissenschaften and*

<sup>b</sup> *Sektion Chemie, Karl-Marx-University, DDR-701 Leipzig and*

<sup>c</sup> *Department of Organic Chemistry,*

*Prague Institute of Chemical Technology, 166 28 Prague 6, Czechoslovakia*

Received November 19th, 1984

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Using the Huron-Claverie solvation model the conformations of 1-methyl-1,4-dihydronicotinamide (*II*) and corresponding quaternary ion *III* have been investigated by the semiempirical NDDO method. The calculated data show that *anti*-conformers *IIb* and *IIIb* should be more stabilized by polar solvents than *syn*-conformers *IIa* and *IIIa*, respectively, mainly due to electrostatic contributions within solvation energy.

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Detailed information concerning the conformational structure of nicotinamide derivatives is still of interest for two important reasons: The compounds are generally accepted as trivial bioorganic models of NAD-NADH coenzymes besides being also used as pharmaceuticals of the vitamin-B-type. The pharmaceutical application requires above all a satisfactory understanding of the interaction of aqueous solutions of substances with appropriate receptor systems. The knowledge of the conformational behavior of various nicotinamides in solution then seems to be an interesting starting point for further considerations concerning their biological activities

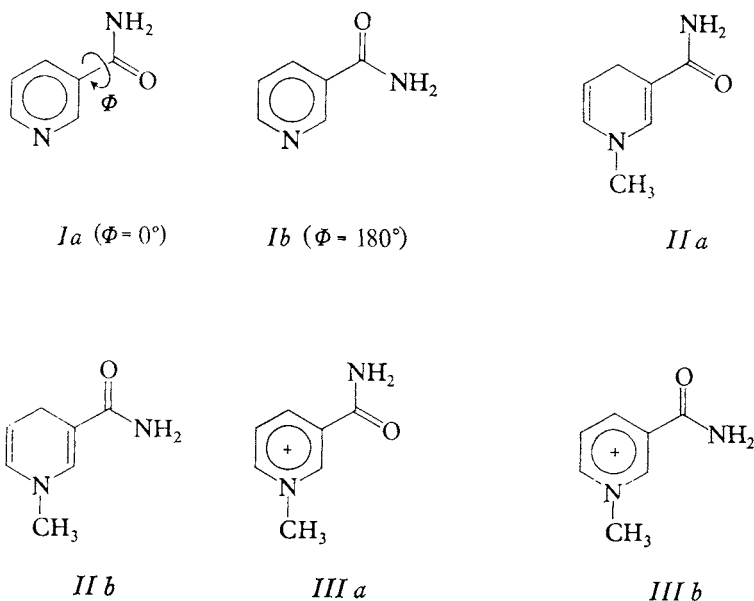
The major conformational problem in all simple nicotinamides is the amide group orientation with respect to the pyridine/dihydropyridine ring system. The majority of information unfortunately results from the X-ray analysis of crystals<sup>1-13</sup> or from simple calculations<sup>14-21</sup> that, in fact, model a gas phase situation. In the previous paper<sup>22</sup> we examined the amide group orientation of nicotinamide itself (*I*) and 1-methyl-1,4-dihydronicotinamide (*II*) in the gas phase as well as in solution by means of NDDO method and a trivial solvation model. The results have suggested the opposite preferred conformations for both amides *I* and *II*. Couple *II-III*, in which the individual compounds can be mutually transformed<sup>19,23</sup> by oxidation or reduction, respectively, is dealt with in this paper. On the basis of the NDDO calculations and a more sophisticated Huron-Claverie solvation model we wish to demonstrate that the transformations in polar solvents may probably proceed without change in conformation of the amide group.

## CALCULATIONS

For the determination of the conformational structure of the isolated species *II* and *III* the NDDO method was used. The parameterization was the same as in ref.<sup>24</sup>. The solvent influence was estimated by means of the solvation model suggested by Huron and Claverie and extensively described in refs<sup>25-27</sup>. This model is in many aspects superior to the classical continuum approximation used in our former paper<sup>22</sup>. It chiefly concerns the real shape of the solute which is represented by its atomic net charges and dipoles. Electrostatic, dispersion and repulsion energy terms contribute to the interaction energy between solute and solvent. The cavitation energy is also considered here. The molecular geometry of species *II* and *III* corresponds to that given in our paper<sup>22</sup>.

## RESULTS AND DISCUSSION

In order to approach the more realistic conditions, it seems necessary to estimate the solvent influence on the conformational structure and flexibility of compounds *II* and *III*. For cationic structure *III* the treatment was up to present impossible. Water was supposed to be the solvent in our considerations. Together with the results for the isolated species *II* and *III* simulating the situation in the gas phase or in a hydrophobic pocket of the enzyme, the prediction of the behaviour of the solutes at other receptor sites surrounded by an aqueous medium was possible while using the Huron-Claverie model.



Figs 1 and 2 show the calculated potential energy curves for the rotation of the amide group in compounds *II* and *III*, respectively. It can be seen that *syn*-con-

TABLE I

Changes in calculated energy terms (total  $E_{\text{tot}}^{\text{NDDO}}$ , cavitation  $E_{\text{cav}}$ , dispersion  $E_{\text{d}}$ , repulsion  $E_{\text{r}}$  and electrostatic  $E_{\text{el}}$ ) for the species *II* and *III* related to their conformations possessing  $\phi = 0^\circ$  ( $E_{\text{tot}}^{\text{NDDO}} = -256\,291.56$  and  $-253\,330.25$  kJ mol $^{-1}$ ). The values are given in kJ mol $^{-1}$

$\phi$	Species	$\Delta E_{\text{tot}}^{\text{NDDO}}$	$\Delta E_{\text{cav}}$	$\Delta E_{\text{d}}$	$\Delta E_{\text{r}}$	$\Delta E_{\text{el}}$
30°	<i>II</i>	6.6	0.3	-0.6	0.2	-1.3
	<i>III</i>	-1.5	0.5	-1.2	0.3	-5.1
60°	<i>II</i>	19.9	0.7	-0.8	0.3	-3.4
	<i>III</i>	3.2	1.0	-1.5	0.4	-5.8
90°	<i>II</i>	28.1	1.2	-1.3	0.6	-5.0
	<i>III</i>	7.5	1.4	-1.7	0.7	-9.2
120°	<i>II</i>	25.5	0.9	-1.3	0.5	-7.2
	<i>III</i>	7.1	0.9	-1.3	0.5	-12.2
150°	<i>II</i>	22.3	0.3	-1.1	0.3	-10.1
	<i>III</i>	6.1	0.5	-1.2	0.3	-12.7
180°	<i>II</i>	31.2	0.0	-0.3	0.1	-11.5
	<i>III</i>	9.6	0.2	-0.4	0.1	-12.7

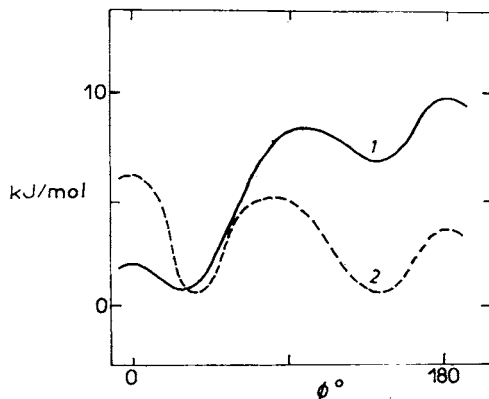


FIG. 1

NDDO Potential energy curves for 1-methyl-3-carbamoylpyridinium cation *III* without 1 and with 2 inclusion of the solvent (water)

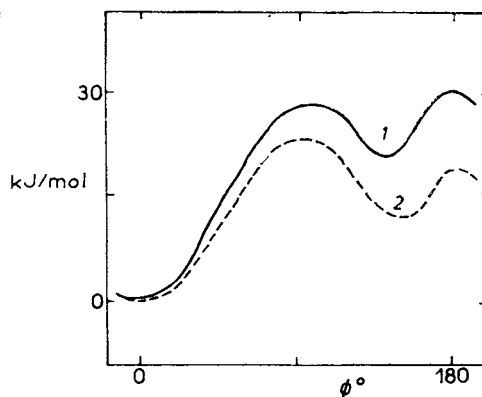


FIG. 2

NDDO Potential energy curves for 1-methyl-3-carbamoyl-1,4-dihydropyridine (*II*) without 1 and with 2 inclusion of the solvent (water)

formations *IIa* and *IIIa* represent the most stable forms in the gas phase and exhibit torsion angles about  $0^\circ$  in conformer *IIa* and about  $30^\circ$  in conformer *IIIa*, respectively. Very similar molecular shapes were found in the solid state, e.g. a planar or nearly planar structure for various 1,4-dihydrnicotinamides<sup>1,2</sup>, whereas for quaternized nicotinamides deviations from planarity as large as approx.  $40^\circ$  were ascertained<sup>3-10,12</sup>. The molecular energy differences within the coupled of *syn-anti* conformers corresponding to the absolute and the local minima ( $\Phi = 140^\circ$ ) in Figs 1 and 2 were calculated to be 20.9 and 7.4 kJ mol<sup>-1</sup> for *IIa,b* and *IIIa,b*, respectively. In addition, the NDDO torsion angles as well as the energy differences are in good agreement with nonempirical STO-3G data<sup>21</sup>. It may be, therefore, concluded that no important conformational changes should be expected during transformation from the gas phase to the crystals or to nonpolar solutions.

Calculating the influence of water, *syn-* and *anti-*conformers *IIIa,b* seem to be of comparable stabilities (energy difference about 0.1 kJ mol<sup>-1</sup>, see Fig. 1) in accord with NMR results<sup>28,29</sup> which indicate roughly equal proportions of both forms in an aqueous solution. Hence, the *anti-*conformer *IIIb* has been calculated to be more stabilized by the solvent in comparison to its rotational *syn-*isomer *IIIa*. An analogous effect of water on *anti-*conformer *IIB* appears to be, according to calculation, sufficiently smaller (see Fig. 2) thus it does not significantly influence the conformational behaviour of 1,4-dihydroderivative *II*. Considering the red-ox possibilities  $II \rightleftharpoons III + 2e + 2H^+$  it might be therefore suggested that both transformations to the right or to the left are able to proceed without large conformational changes *via* corresponding *syn-*conformers *IIa* and *IIIa* which will be present in sufficient proportions in aqueous or other strongly polar media.

An analysis of the solvation energy in Table I shows that the changes of the electrostatic energy terms are formally responsible for the solvent effect of water on the conformational structure of species *II* and *III*. The appropriate changes of cavitation, dispersion as well as repulsion energy may practically be neglected. If we should further generalize as far as our results are concerned it may be stated that the high conformational flexibility of the amide group in nicotinamide derivatives which already exists in the gas phase is additionally favored by solvents. As far as the importance of the electrostatic energy term is concerned the strongest influence can be expected in polar solvents. Simultaneously, the energy differences among all conformers decrease and cease being of significance.

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Translated by the author (J. K.).