Theoret. chim. Acta (Berl.) 27, 75—79 (1972)


# EHT Conformational Study of Nicotinamide and Related Amides

KATHRYN R. LONG* and J. H. GOLDSTEIN
Chemistry Department, Emory University, Atlanta, Georgia, 30322, USA

Received April 10, 1972

EHT rotational energy curves are presented for various nicotinamides and benzamide. The conformations calculated for nicotinamide and benzamide are comparable to those determined by X-ray methods. Protonation, N-methyl substitution and the introduction of a ring nitrogen meta to the amide group are discussed in terms of the corresponding calculated effect on the rotational energy curves. Some implications for the conformation of NAD⊕ are presented.

## 1. Introduction

Attention has recently been drawn by Sarma *et al.* to the relationship between side chain conformation and the folding mechanism in NAD⊕ [1, 2]. However, efforts by these workers to determine preferred conformations by *pmr* proved unsuccessful. Following this Coubeils and coworkers carried out a series of PCILO calculations in an effort to theoretically determine conformation preferences in nicotinamide, 1-methyl-4-hydronicotinamide and the reduced nicotinamide mononucleoside [3]. Calculations were carried out in 30° rotations around the ring-amide linkage.

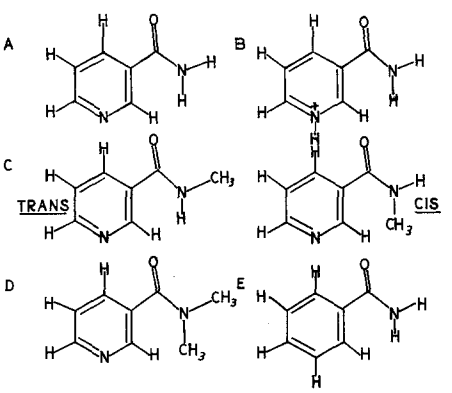


Fig. 1. Molecular formula of *a* nicotinamide, *b* nicotinamide cation, *c trans* and *cis* N-methyl nicotinamide, *d* N,N-dimethyl nicotinamide and *e* benzamide

* NSF Fellow 1971–1972.

This paper reports the results of a series of Extended Hückel molecular orbital (EHT) calculations carried out on nicotinamide, nicotinamide cation, N-methylnicotinamide, N,N-dimethylnicotinamide, and benzamide, the molecular formulas of which are given in Fig. 1. The purpose of this work was to determine, within the limits of the EHT method, the preferred conformations, if any, for this series of compounds. It will be noticed that only nicotinamide is common to this study and that of Ref. [3]. The results are presented in the form of plots of energy, taken relative to that of the least stable conformation, *vs.* angle of rotation. Although not one of the nicotinamides, benzamide is included to ascertain the effect of a ring nitrogen on the energy curves. Some implications of these results for the conformational situation in the biologically important system NAD⊕ are also presented.

## 2. Method of Calculation

The basic method employed in this study has been described previously in the literature [4] and will not be repeated here. The diagonal elements of the Hamiltonian matrix were approximated by the valence state ionization potentials of the appropriate orbitals [5, 6]. The off-diagonal elements, $H_{ij}$, were estimated by the Wolfsberg-Helmholtz-Mulliken geometrical-mean formula

$$H_{ij} = KS_{ij}(H_{ii}H_{jj})^{1/2}$$

with $K$ taken as $-1.50$.

Structural parameters used for nicotinamide [7] are identical to those of Coubeil *et al.* [3]. X-ray values were employed for benzamide [8] and average literature values [9] were used to specify the structure of N-alkyl substituents. The amide N–H bond distance was taken as that found in urea [10]. The $\overset{+}{\text{N}}$–H bond distance was the average of a number of tabulated values [10]. For the purposes of this study, the amide group is assumed to be planar. The orientation of the amide group relative to the ring was specified by the dihedral angle, $\theta$, between the two planes, measured from the planar *trans* arrangement of the ring $C_\alpha - C_\beta$ bond and the carbonyl group. The two stable N-methylnicotinamide rotamers will be referred to as *cis* and *trans*, with the understanding that in the *trans* form the N-methyl group is *cis* to the carbonyl oxygen.

Energy calculations were made for every 5° rotation of the amide group relative to the ring, except near the minima, in which case the interval was decreased to 1°. All calculations were performed on a Digital Equipment Corporation PDP-10 computer.

## 3. Results and Discussion

The energy dependence on amide conformation in nicotinamide systems and in benzamide is shown in Figs. 2 and 3. Fig. 2a is representative of the energy curves obtained for nicotinamide, nicotinamide cation and *trans* N-methylnicotinamide. The calculated minimum falls at 16°, 15° and 18°, respectively, for the above three molecules. Thus, within the approximations employed, the cal-

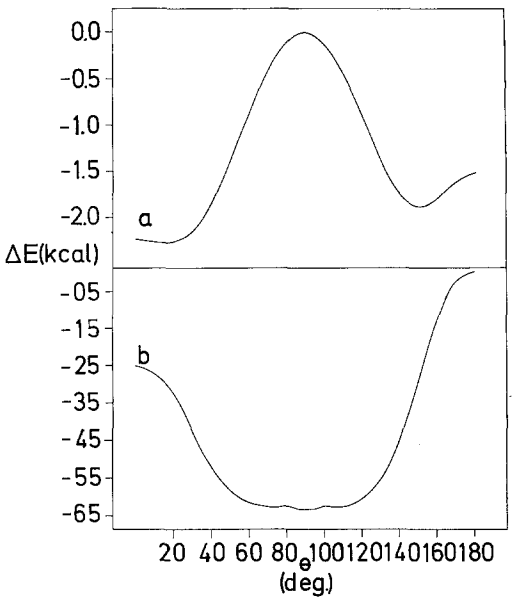


Fig. 2. Angular dependence of energy, measured relative to least stable conformer, in nicotinamide systems. *a* represents the $\Delta E$ curve for nicotinamide, nicotinamide cation and *trans*-N-methylnicotinamide. *b* represents the $\Delta E$ curve in *cis*-N-methylnicotinamide and N,N-dimethylnicotinamide

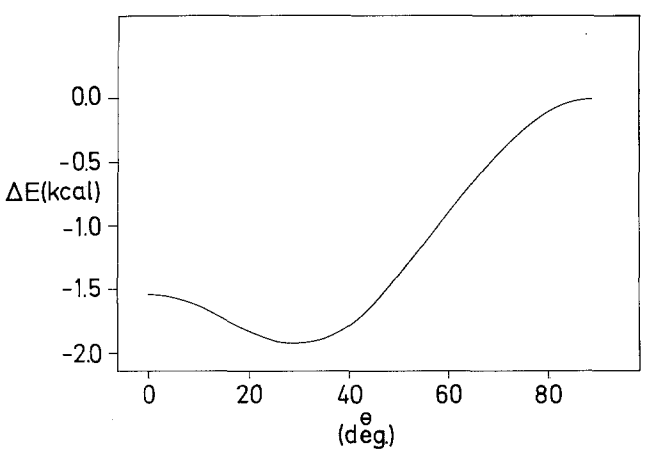


Fig. 3. Angular dependence of energy, measured relative to the least stable conformer, in benzamide

culated energy curves are largely unaffected by either protonation of the ring nitrogen or by N-alkyl substitution in the *trans* position of the amide group. The orientation calculated here for nicotinamide is not greatly different from the value of 24° obtained from an analysis of the X-ray data [7]. The corresponding calculated minimum reported by Coubeils *et al.*, using PCILO falls at 30° [3]. Hence, both calculated minima are within approximately 6° of the experimental value.

Moreover, the energy difference between orientations of 16° and 30°, as calculated in this study, is not very large due to the rather shallow nature of the minimum. It is interesting that the energy difference between the planar conformer and the most stable conformer is 0.042 kcal, which is much smaller than 0.62 kcal, the value of $kT$ at body temperature. Thus the amide group is able to oscillate rather easily over an angle of about 40° on either side of the molecular plane without significantly exceeding $kT$ in energy. A second stable conformation lies in a somewhat shallower minimum at an orientation of 150°, also reported by Ref. [3]. The barrier between the two stable conformers, $\sim 2.7$ kcal, is considerably larger than $kT$.

In the case of benzamide, Fig. 3, a calculated energy minimum occurs at 30°, compared with a value of 26° in the experimental case [8]. The calculated energy curve for benzamide, however, differs from that of nicotinamide in several respects. The height of the barrier between conformers is considerably smaller in benzamide, $\sim 1.53$ kcal. The minimum is also shallower, permitting facile rotation through an angle of about 65° on either side of the molecular plane. It appears, then, that the presence of a ring nitrogen atom *meta* to the amide increases the relative stability of the preferred conformation in nicotinamide as compared to that of benzamide. It also substantially restricts the extent of oscillation of the amide group.

Fig. 2b is representative of the rotational energy curves in N,N-dimethylnicotinamide and the *cis* isomer of N-methylnicotinamide. In these molecules the calculated energy minima occur at 89°, with a torsional energy barrier of 63.40 kcal. While this value may to some extent reflect the tendency of EHT to overestimate torsional barriers [4], it nevertheless suggests that the true barrier is quite sizeable compared to $kT$. Structural models also indicate qualitatively the existence of very sizeable barriers. The dihedral angle predicted from such models, 90°, is in surprisingly good agreement with those determined here. In addition, the amide group seems to be able to oscillate without significant interference in the range $80° \leqq \theta \leqq 100°$.

Some approximation of the steric interaction between the N-methyl group and the pyridine ring can be obtained from a comparison of the total energy of the two N-methylnicotinamide rotamers in the planar conformation $-21406.77$ kcal and $-21448.13$ kcal for the *cis* and *trans* rotamers, respectively. The energy of steric interaction, $\sim 41.36$ kcal, is decreased to $\sim 1.0$ kcal by rotation into the perpendicular conformation, i.e., $\theta = 90°$, where the total energy of the two rotamers is $-21444.86$ kcal and $-21445.50$ kcal for the *cis* and *trans* rotamers, respectively. Thus, the *trans* rotamer is, for all conformations, the more sterically favored rotamer. Simple calculations give more than 99% of N-methylnicotinamide molecules present as the *trans* isomer at body temperature, as calculated from the most stable conformations.

Sarma *et al.* have reported that, whereas the folding mechanism in NAD⊕ is unaffected by N-alkyl substitution, N,N-dialkyl substitution results in the dissociation of the nicotinamide and adenine base pairs. Sarma and coworkers then postulated that an alkyl substituent *trans* to the carbonyl oxygen is responsible for the changes in folding [1]. The results obtained here substantiate this hypothesis, insomuch as the only change in the calculated energy curve occurs upon formation of *cis* N-methylnicotinamide or upon N,N-dimethyl substitution. The shape of

the curve is thus essentially dependent upon the presence or absence of a *cis* N-alkyl substituent, as is the spatial relationship of the amide group with the pyridine ring. With the introduction of a *cis* N-alkyl substituent, steric interference with the adenine base should become prominent, the result being a change in the folding mechanism observed in NAD⊕.

*Acknowledgment.* The authors wish to thank S. Y. Randall for her assistance in program size reduction. This work was supported in part by a grant from the National Institutes of Health.

## References

1. Sarma, R. H., Ross, V., Kaplan, N. O.: Biochemistry **7**, 3052 (1968).
2. — Moore, M., Kaplan, N. O.: Biochemistry **9**, 549 (1970).
3. Coubeils, J. L., Pullman, B., Courriere, Ph.: Biochem. biophysic. Res. Commun. **44**, 1131 (1971).
4. Hoffman, R.: J. chem. Physics **39**, 1397 (1963).
5. Skinner, H. A., Pritchard, H. O.: Trans. Faraday Soc. **49**, 1254 (1953).
6. Pritchard, H. O., Skinner, H. A.: Chem. Rev. **55**, 745 (1955).
7. Wright, E. B., King, G. S. D.: Acta crystallogr. **7**, 283 (1954).
8. Penfold, B. R., White, J. C. B.: Acta crystallogr. **12**, 130 (1959).
9. Momany, F. A., McQuire, R. F., Yan, J. F., Scheraga, H. A.: J. physic. Chem. **75**, 2286 (1971).
10. Tables of interatomic distances and configuration in molecules and ions. L. E. Sutton, ed. Margent, Kent: Thanet Press 1965.

Prof. Dr. J. H. Goldstein
Chemistry Department
Emory University
Atlanta, Georgia 30322
USA