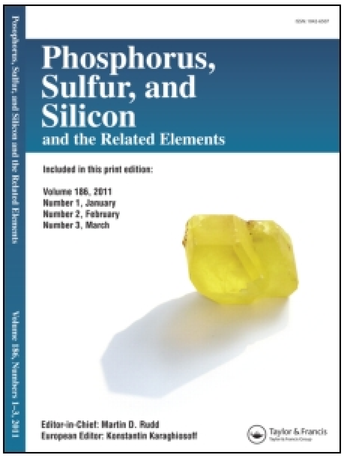

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A CNDO/2 STUDY OF ROTATIONAL BARRIERS IN THIOAMIDOPYRIDINES

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A CNDO/2 STUDY OF ROTATIONAL BARRIERS IN THIOAMIDOPYRIDINES

by

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ABSTRACT

Barriers to rotation about C–C and C–N bonds in 2-, 3- and 4-thioamidopyridine have been calculated by the CNDO/2 method. Comparisons between computed and experimental data are used to assess reliability of the calculations.

Introduction

Thioamidopyridines are of particular interest because of their antitubercular activity[1–4] and chelating ability.[5,6] The study of the molecular conformation of these compounds seemed to us to be a potentially useful addition to the understanding of their biological and chemical properties.

For this purpose, we have studied 2-thioamidopyridine, 3-thioamidopyridine (thionicotinamide), and 4-thioamidopyridine (thioisonicotinamide) within the framework of the approximate SCF method (CNDO/2) of Pople *et al.*[7] For these molecules the equilibrium conformations and barriers to internal rotation predicted by the method will be given and discussed.

The energy barrier to hindered rotation of the C–N bond in aromatic thioamides has been previously measured by the d-nmr method for thioamide of mesitylenecarboxylic acid[8] and for *N,N'*-dimethylthiobenzamide.[9,10] Furthermore, ir and nmr data have become available on the conformational properties of thioformanilides and thioacetanilides.[11,12]

No theoretical and experimental studies, however, have been reported on the energy barriers and the conformational preferences about the ring-thioamide linkage in aromatic thioamides. Only simple LCAO–MO calculations have been carried out to theoretically determine the electronic structure of thiobenzamide.[10,13,14]

Theoretical Treatment

Computational details

The calculations were all carried out on a CDC 6600 system, using a CNDO/2 program[7] with a full basis set of valence atomic orbitals including the 3*d*-orbitals of sulphur.

The geometry of the thioamido group was constructed from recent X-ray structure determination of 2-thioamidopyridine[15] and 2-ethyl-4-thioamidopyridine.[16] Bond angles and bond distances adopted in the calculations are summarized in Table I.

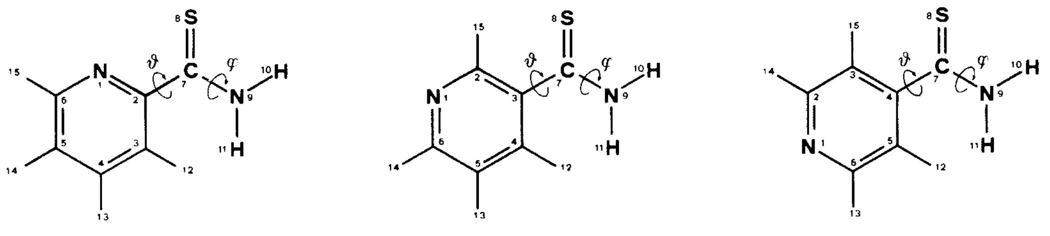
The pyridine ring was assumed as a regular hexagon with standard bond lengths (1.40 Å) and angles (120°).

TABLE I

Assumed Geometry of Thioamido Group

Bond distances (in Å)		Ref	Bond angles (in degrees)		Ref
C (ring)-C(7)	1.505 (±5)*	15	C (ring) C(7) N(9)	113.9 (±3)	15
C(7)-S(8)	1.657 (±4)	15	C (ring) C(7) S(8)	122.9 (±2)	15
C(7)-N(9)	1.325 (±4)	15	N(9) C(7) S(8)	123.0 (±3)	15
N(9)-H(10)	0.94 (±5)	16	H(10) N(9) H(11)	117 (±6)	16
N(9)-H(11)	0.91 (±5)	16	C(7) N(9) H(11)	120 (±6)	16

* Standard deviations are given in parentheses.



1 *2* *3*

FIGURE I

Molecular formula and labelling of atoms of 2-thioamidopyridine (1), 3-thioamidopyridine (2) and 4-thioamidopyridine (3) in the planar conformation with *cis*-arrangements of the N(pyridine)-S atoms ($\vartheta = 0, \varphi = 0$).

Total molecular energy was calculated as a function of the rotational parameters ϑ and φ describing the rotations about the C (ring)-thioamide and C–NH_2 bonds, respectively. These angles are measured in clockwise direction from the planar conformation ($\vartheta = 0, \varphi = 0$) shown in Figure I, with a scanning of 30°. Near the minimum this interval was decreased to 5°.

Molecular geometries were assumed unchanged during rotations.

Results and Discussion

The calculated variations in total energy for the molecules treated are reported in Tables II, III and IV. The minimum energy conformations were found at rotation angles $\vartheta = 180°, \varphi = 0$; $\vartheta = 90°, \varphi = 0$ and $\vartheta = 90°, \varphi = 0$ for 2-, 3- and 4-isomer, respectively.

The barriers for ϑ- and φ-rotation as estimated by the method are collected in Table V.

The results given in the Tables clearly indicate that the thioamide group, as predicted by the CNDO/2 approximation, is planar in all molecules. The calculated barriers for the C–N bond are in good agreement with experimental data reported for the hindered rotation of the dimethylamino group in *N,N'*-dimethylthioformamide.[17] On the other hand, the experimental barrier values for *N,N'*-dimethylthiobenzamide (15.4 and 19.1 kcal/mol) as determined by nmr method[9,10] are somewhat less than

TABLE II

2-Thioamidopyridine. The Variation in Total Energies as Function of Angles of Twist ϑ and φ

φ \ ϑ	0°	30°	60°	90°	120°	150°	180°
0°	−23.8	−25.6	−26.5	−26.8	−27.3	−28.0	−28.2
30°	−18.8	−19.4	−20.1	−20.4	−20.9	−21.7	−21.9
60°	−7.33	−6.96	−6.90	−6.77	−7.46	−8.59	−9.03
90°	−0.88	−0.94	−0.50	0.0	−0.44	−1.38	−1.63

Energies in kcal/mol.

TABLE III

3-Thioamidopyridine. The Variation in Total Energies as Function of Angles of Twist ϑ and φ

φ \ ϑ	0°	30°	60°	90°	120°	150°	180°
0°	−24.9	−26.6	−27.3	−27.4	−27.3	−26.6	−24.9
30°	−19.6	−20.5	−21.2	−21.5	−21.4	−21.1	−19.4
60°	−7.46	−7.52	−7.77	−7.77	−8.09	−8.34	−7.52
90°	−0.50	−0.69	−0.38	0.0	−0.31	−0.63	−0.56

Energies in kcal/mol.

TABLE IV

4-Thioamidopyridine. The Variation in Total Energies as Function of Angles of Twist ϑ and φ

φ \ ϑ	0°	30°	60°	90°
0°	−24.0	−25.9	−27.2	−27.6
30°	−18.6	−20.4	−21.4	−21.8
60°	−6.77	−7.84	−8.78	−8.15
90°	0.0	−0.25	−0.38	−0.38

Energies in kcal/mol.

TABLE V

Theoretical Rotational Barriers E in Thioamidopyridines

Molecule	Bond of rotation	Barrier (kcal/mol)
2-Thioamidopyridine	C(2)-C(7)	4.4
	C(7)-N(9)	26.6
3-Thioamidopyridine	C(3)-C(7)	2.4
	C(7)-N(9)	27.4
4-Thioamidopyridine	C(4)-C(7)	3.6
	C(7)-N(9)	27.3

Energies in kcal/mol.

those calculated for thioamidopyridines in the present work. It should be however noted that the model used in the calculations accounts enough well for this barrier, since the experimental values refer to barriers measured in solution while the calculated barriers correspond to gas-phase values. Furthermore it should be taken into account that in these calculations a variation of the geometries around the C–N bond in the transition state has been neglected.

As seen from Table V, the calculations predict a barrier about C–C bond in thioamidopyridines ranging from 2.4 to 4.4 kcal/mol. Experimental data for thioamide compounds do not seem available. The calculated values, however, compare fairly well with an observed barrier height of 4.7 kcal/mol of benzaldehyde in the gas-phase.[18] The presence of a ring nitrogen ortho to the thioamido group increases the relative stability of the preferred conformation in 2-thioamidopyridine, as compared to that of the 3- and 4-isomer compounds. This view is confirmed by the fact that the absolute minimum energy conformation predicted by the method for 2-thioamidopyridine is in good agreement with results of an X-ray structure determination.[15] In the solid phase this molecule was found to exist in a trans configuration (see Figure I) with a twist angle of 10° between the plane of the pyridine ring and that of the thioamido group. The agreement is more acceptable in view of the very slight energy difference, as calculated in this study, between angles $\vartheta = 170^\circ$ and $\vartheta = 180^\circ$, which clearly shows that the twist angle of the thioamido group in the crystal might be due to intermolecular forces.

The height of the calculated C–C barrier is smaller in 3- and 4-isomer compounds. The minimum is also shallower, thus indicating that the thioamide group can oscillate rather easily on either side of the molecular plane.

A discrepancy is observable between the twist angles predicted in the energetically preferred conformation of 3-thioamidopyridine and 4-thioamidopyridine, *i.e.*, 90°, and, for instance, the one of 38° determined in the molecule of 4-thioamidopyridine at the solid state.[19] We therefore assume that this is due to an inherent failure of the CNDO approximation, *i.e.*, its inability to predict the equilibrium conformations when small differences in total energy of the conformers occur.

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