Rotation barrier of the azide group in azidopyridines: Molecular orbital treatment

Rafie H. Abu-Eittah *, Mahmoud K. Khedr [1]

Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt

Abstract

The height of the rotational barriers around C(pyridine)─N(azide) single bond in azidopyridines has been determined via ab initio molecular orbital calculations. The optimized geometry obtained from RHF/6-31G** results was used as an input for a single-point MP2/6-31G** calculation, the results of which are reported in this work. The potential energy function of rotation was subjected to Fourier analysis and terminated nicely at V_3 as is shown from the results of least square treatment. The s-*cis* conformer of 2-azidopyridine is slightly more stable than the s-*trans* conformer and both are more stable than others obtained during rotation. A transition state is identified and confirmed, during rotation, via the location of a stationary point through a saddle-point calculations. A Hessian-type run is carried out to calculate the frequency of vibration, only one imaginary, negative, frequency was obtained. The height of the rotational barrier of the azide group in 2-azidopyridine is the largest, about 7 kcal/mol, whereas it amounts 3.32 and 4.04 kcal/mol for 3-azido and 4-azidopyridine, respectively.
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1. Introduction

The way in which the energy of a molecule changes with rotation about its single bonds is of considerable interest. If internal rotation is possible only about one bond, the stable rotational isomers (local minima), their relative energies and the energies required for their inter conversion (potential barriers) may be obtained from the potential function for this rotation. Experimental data on rotational barriers, conformational energy differences, and, in some cases, full potential curves are becoming increasingly available and provide tests for the theoretical approaches for this subject [1–3].

Aryl azides are widely used in photoaffinity labeling [4]. Azidoderivatives of N[6] substituted adenines, analogs of neutral cytokinins, have been synthesized as potential photoaffinity labeling reagents [5]. 2-Azido-2-deoxycytidine and 2-azido-2-deoxyuridine were evaluated for their inhibitory activity against ribonucleotide reductase and for subsequent cell growth inhibition [6]. Several new alpha-azidoacids have been synthesized and their use in solid phase peptide synthesis has been demonstrated [7]. The biological activity of the azide derivative is primarily dependent on the conformation of the molecule.

Pyridine azides, 2- and 3-azidopyridines, can exist in the *cis*- and the *trans*-conformers, the *cis*-conformer is of lower energy, 3.33 kcal/mol, than the *trans*-conformer. Rotation about the C(pyridine)─N(azide) single bond changes one conformer to the other. The conformation of the azide group as well as of the azidomolecule is determining factor in the reactivity of the molecule. It is important to investigate the structural stability which results from the rotation of the azide group in pyridine azides. The PES diagram obtained from the energy of the conformer against the torsion angle reveals many structural properties of the molecule.

* Corresponding author.
  E-mail address: aboeittah@yahoo.com (R.H. Abu-Eittah).
[1] Abstracted from M.Sc. Thesis, Department of Chemistry, Faculty of Science, Beni Suef, Egypt.

The internal rotation about the C—N bond has been widely observed experimentally and calculated theoretically. Rotation about the C—N bond in amides provides information in understanding conformational characteristics of the bulk bone of peptides and proteins. The barrier to rotation varies in the range of 15–23 kcal/mol in gas phase and in solutions [8], which is attributed to the partial double bond based on the resonance model [9,10].

The structural stability of carbamothioic acid: NH_2CO—SCl was investigated by DFT-B3LYP and ab initio MP2 calculations using 6-311+G^{**} basis set [11]. The molecule was predicted to exist in the trans-conformation. The twofold NH_2 barrier about the N—C bond was calculated to be about 12 kcal/mol, while the asymmetric OCSCl barrier about the C—S bond to be about 8 kcal/mol.

The molecular structure of trichloronitromethane has been studied in the gas phase using electron diffraction data [12]. The molecules are found to undergo low barrier rotation about the C—N bond with HF/MP2/B3LYP/G-311 (p, d) calculations. The conformation with the C—Cl bond eclipsing the N—O bond was found to be the most stable form in all calculations.

The solvent effect on the C—N rotational barriers of *N,N*-dimethylthioformamide and *N,N*-dimethylthioacetamide has been investigated using ab initio theory and NMR spectroscopy [13]. Selective inversion recovery NMR experiments were used to measure rotational barriers in a series of solvents. These results are compared to ab initio results at the G2(MP2) theoretical level. Solvation effects were calculated using reaction field theory which gives barriers in good agreement with experiment.

The rotations of methyl group in some methylazabenzenes: *ortho*- and *meta*-methylpyridines, 2-methylpyrazine and 4-methylpyrimidine, in the ground, excited and anionic states were investigated [14]. The calculated rotational barriers reproduce well the experimental data. A correlation is found between the rotational barriers and the lowest and next lowest unoccupied molecular orbitals.

In this work the potential function of rotation of the azide group about the C(pyridine)—N(azide) single bond has been calculated at different values of the torsion angles by the RH/MP2/6-31G^{**} calculations. A transition state has been located, identified and confirmed. Fourier analysis was applied to the potential function, V, of rotation which terminated nicely at V_3. The height of the rotational barrier varies in the range 6.65–3.32 kcal/mol and is comparable the height of the barriers of rotations about C—C single bond in many compounds. Such a study has not been reported before.

2. Computational methods

Theoretical calculations of the height of the barrier of rotation of the azide group in azidopyridines, gas phase, were calculated using both RHF and MP2 procedures and 6-31G^{**} basis set. Geometry optimized structure of the studied molecules was calculated at the RHF level

and the output was used as an input for a single-point calculation using the MP2/6-31G^{**} procedures through a Gamess code [15], data reported in this work are the results of MP2/6-31G^{**} calculations.

The parameters of the maximum of the PES are used as an input to carry out the saddle-point calculations till one gets to a stationary state. The stationary state is a full optimized transition state. At this state a Hessian run is carried to calculate the frequency of vibrations, one negative (imaginary) frequency characterizes the transition, stationary, state. To be sure that there is only one transition state, Hessian runs were carried out on different conformers at different dihedral angles, except the one which gives a maximum in the PES and no negative frequency was obtained.

The potential energy function $V(\varphi)$ describing the internal rotation of one part of a molecule (rotomer) against the reminder can be expanded in a Fourier series

$$V(\phi) = \sum_i 1/2 V_{Ni}(1 - \cos iN\phi) \qquad (1)$$

where φ is the angel of rotation and N represents the degree of symmetry of molecule. In general, φ is taken as zero for the minimum energy conformer. If both rotomer and framework are symmetric a full potential energy function with $N = 1$ is used [16]

$$V(\phi) = \frac{V_1}{2}(1 - \cos \phi) + \frac{V_2}{2}(1 - \cos 2\phi) + \frac{V_3}{2}(1 - \cos 3\phi) + \cdots \qquad (2)$$

This function commonly terminates after three terms, if not additional terms are added. The value of $V(\varphi)$ is equal to the difference $E(\varphi) - E(\text{opt})$ where $E(\text{opt})$ is the total energy of the geometry optimized conformer and $E(\varphi)$ is the energy at the torsion angle (φ) both calculated at the MP2/6-31G^{**} level. The individual components, $V_i(\varphi)$, of the total potential function, $V(\varphi)$, are identified with specific physical effects. The value of V_1 is related to the dipolar or steric interaction, V_2 corresponds to the conjugative or hyper conjugative interactions whereas V_3 is correlated with the repulsion between electrons of the bond pairs.

3. Results and discussion

3.1. 2-Azidopyridine

The potential function of rotation of the azide group around the single C(pyridine)—N(azide) bond in 2-azidopyridine has been calculated at different values of the torsion angle (φ). The relative energy, $E_r = E(\varphi) - E(\text{opt})$ gives the value of the total potential energy $V_t(\varphi)$ at the torsion angle φ. Fourier expansions are used to calculate the potential functions $V_i(\varphi)$ $i = 1$–3 through a mathlab386 program. The input data are: $V_t(\varphi)$, (φ) and the equation to be analyzed, the output data are: $V_i(\varphi)$ in addition to a plot of the potential energy curve of the rotation.

Table 1 gives the results. One observers that $\sum_i V_i$ is equal to V_t which means that the termination of the Fou-