A Semiempirical Conformational Analysis of the 3-Phenyl-1,2,3-oxathiazolidine 2-Oxide

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Received July 21, 1994

An extensive conformational search for the heterocyclic compound 3-phenyl-1,2,3-oxathiazolidine 2-oxide has been carried out using the semiempirical quantum-mechanical method PM3. All torsion angles were varied in the geometry optimization procedure which led to the prediction of four distinct conformers. Barriers to internal rotation leading to conformational interconversions were also calculated. The results of the present study indicate that this five-member ring substituted heterocyclic system may be expected to exist as a mixture of stable conformers rather than a unique molecular entity.

J. Heterocyclic Chem., **32**, 557 (1995).

Introduction.

A series of 1,2,3-oxathiazolidine 2-oxide compounds, with substituent groups attached to the five-member ring in distinct positions, have been synthesized recently and characterized *via* elemental analysis, infrared (ir) and nuclear magnetic resonance (^{1}H nmr, ^{13}C nmr) spectroscopy [1]. Assignments of the nmr spectra have been made which gave some insight into the molecular structure of these compounds. The determination of the coupling constants allowed the relative positions of the hydrogen atoms of the five-member ring to be estimated so information on the atomic spatial arrangement may be obtained. However, these nmr spectral data may not be sufficient to allow a precise determination of the molecular geometry to be made. This is a situation where a theoretical treatment is certainly of great value.

In the present study we selected the simplest heterocyclic system examined experimentally [1], *i.e.* 3-phenyl-1,2,3-oxathiazolidine 2-oxide (see Figure 1), to be investigated using a theoretical method. A low-temperature nmr study of the conformations of this compound has been carried out previously by Yamada *et al.* [2]. On the basis of the resulting vicinal coupling constants, the correlations between the ratios of the vicinal coupling constants and the corresponding torsion angles were obtained and made it possible to assign twist-envelope conformations. The experimental data also allowed an estimate of the parameters of the Karplus equation [3] to be made. It is well known that a low-temperature nmr study is required in order to detect the presence of more than one conformer that can coexist in equilibrium. Their experimental data enabled them to estimate only two dihedral angles involving the hydrogen atoms attached to the five-ring system, *i.e.* [H_c, C_4, C_5, H_a] and [H_d, C_4, C_5, H_b], and so a definitive assignment of which conformations are present could not be made. A room-temperature nmr spectral analysis was also carried out by Do Val [1] and the coupling constants ratios and torsion angles evaluated. Do Val [1] reached the conclusion that the elucidation of the conformation(s) of the five-member substituted ring cannot be accomplished solely on the basis of the knowledge of the coupling constants values. The combination of the experimental nmr data with a theoretical study appears to be a more adequate approach.

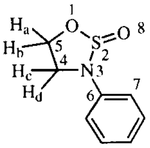


Figure 1. The 3-phenyl-1,2,3-oxathiazolidine 2-oxide heterocyclic system.

We propose then to carry on a conformational study of this five-membered heterocyclic ring system employing the semiempirical quantum-mechanical method PM3 (Parametric Method 3) developed by Stewart [4]. There have been many successful applications of semiempirical methods to a variety of different problems of general interest in chemistry. In particular these methods have been shown to yield very useful information regarding the conformational equilibrium in molecules biologically active such as herbicide species [5,6] which contain heterocyclic rings. In this article we intend to carry on a detailed conformational analysis of this heterocyclic system using the PM3 method which is well known to be more adequate for molecules containing sulfur atoms. In the present work the potential energy surface (PES) for the 3-phenyl-1,2,3-oxathiazolidine 2-oxide heterocyclic system will be extensively examined aiming to locate all possible minimum energy structures. Also the possibility of conformational interconversion will be investigated and so the characterization of the experimentally observed conformer(s) will be made.

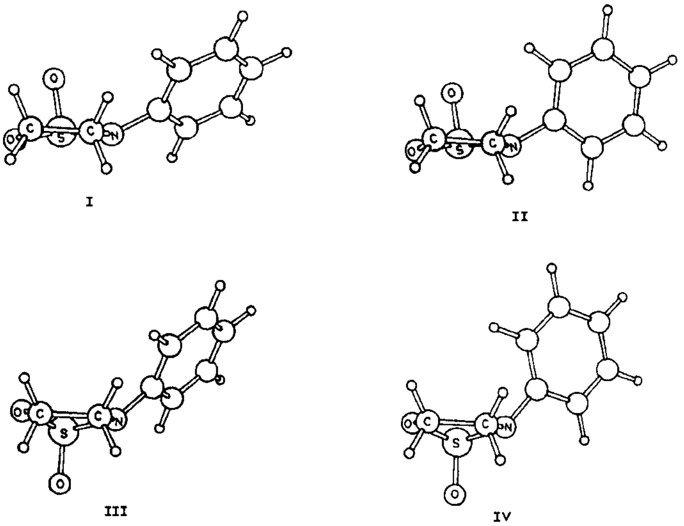
Methodology.

A systematic search for stationary points on the multidimensional potential energy surface (PES) for the 3-phenyl-1,2,3-oxathiazolidine 2-oxide heterocyclic system has been carried out with the aid of the quantum-mechanical semiempirical method PM3 [4]. The PM3 method has been shown to be the most adequate semiempirical approach for treating sulfur compounds [7]. All 3N-6 internal degrees of freedom, shown by Figure 1, were varied during geometry optimization. Several trial initial configurations were used as the starting point for the geometry optimization procedure which makes use of gradient techniques (evaluated analytically). The dihedral angles related to distinct conformations of the five-member ring and also the torsion angles of the hydrogen and phenyl substituents were varied consistently aiming to locate all possible stationary points on the PES for this heterocyclic compound. The stationary points located by this procedure were characterized according to the eigenvalues of the Hessian (second-energy derivative) matrix [8]. If all harmonic frequencies are positive the stationary point is a true minimum energy structure and the occurrence of *n* negative eigenvalues of the Hessian matrix characterizes a n-th order transition state (TS) structure. A one-dimensional torsional minimum energy path for rotation of the phenyl group was also calculated which led to the prediction of the rotational barrier for each stable conformer.

Table 1

PM3 Calculated Dihedral Angles (in degrees) for Distinct Conformations of the 3-Phenyl-1,2,3-oxathiazolidine 2-Oxide Compound

Dihedral Angles	Minimum Energy Structures I	II	III	IV
C_5O_1SN	19.9	19.0	-23.3	-21.6
$C_4C_5O_1S$	-21.8	-22.4	20.0	15.1
$NC_4C_5O_1$	12.0	14.0	-4.6	1.5
SNC_4C_5	2.0	-0.6	11.7	10.5
O_1SNC_4	-11.9	-9.9	19.6	21.6
C_6NSO_1	-154.4	-149.9	-122.9	-115.0
C_7C_6NS	-64.8	81.4	-55.2	88.5
O_8SO_1N	103.9	103.8	104.4	104.3
$H_cC_4C_5H_a$	14.2	16.4	-1.3	5.0
$H_dC_4C_5H_a$	133.4	135.7	-120.4	-120.4
$H_cC_4C_5H_b$	-108.4	-106.2	121.3	127.6
$H_dC_4C_5H_b$	10.9	13.2	2.3	8.3



I II III IV

Figure 2. The PM3 fully optimized conformers of the 3-phenyl-1,2,3-oxathiazolidine 2-oxide heterocyclic molecular system, structures **I**, **II**, **III** and **IV** given in Table 1.

Table 2

PM3 Calculated Energies and Thermodynamic Properties for the Conformers given in Table 1

Thermodynamic Properties	Minimum Energy Structures I	II	III	IV
ΔH_f/kcal mol^{-1}	-47.2	-47.0	-45.8	-45.3
ΔS/kcal mol^{-1} K^{-1}	104.0	104.9	104.5	104.7
ΔG/kcal mol^{-1}	-78.2	-78.2	-76.9	-76.5
ΔE_t/kcal mol^{-1}	—	0.272	1.60	1.98

All calculations were performed with the MOPAC package [9] as implemented on the Apollo HP-9000/300 workstation at the Laboratorio de Quimica Teorica, Departamento de Quimica, Universidade Federal de Minas Gerais (UFMG). All structures have been drawn with the program MOLMOP [10].

Results and Discussions.

The four true minimum energy structures located on the PES for the 3-phenyl-1,2,3-oxathiazolidine 2-oxide heterocyclic system, using the procedure described in the previous section, are shown in Figure 2 and the structural parameters, energies and thermodynamic properties are given in Tables 1 and 2. It can be seen from Table 1 that structure **I** is the global minimum energy structure on the multidimensional PES and so are expected, in principle, to be the experimentally observed conformer. It can also be seen from Table 2 that structures **I** and **II** are nearly degenerate and structures **III** and **IV** are *ca.* 2 kcal mol^{-1} energetically higher than the global minimum energy structure. This result is an indication that a conformational equilibrium is likely to take place and so, this can be a case where a unique equilibrium structure may not be observed. It can be seen from Table 1 and also from Figure 2 that the pair of structures **I** and **II** and **III** and **IV** are very similar regarding the conformation of the five-member ring. The only structural difference is the position of the phenyl substituent. However structures **I** and **III** and **II** and **IV** are quite distinct so far as the conformation of the five-member ring is concerned. The ΔH_f and ΔG values given in Table 2 show that structures **I** and **II** are the more thermodynamically stable conformers and then could be the experimentally observed species.

The conformational equilibrium involving the pair of structures **I** and **II** and **III** and **IV** has been investigated through a pointwise calculation of the one-dimensional

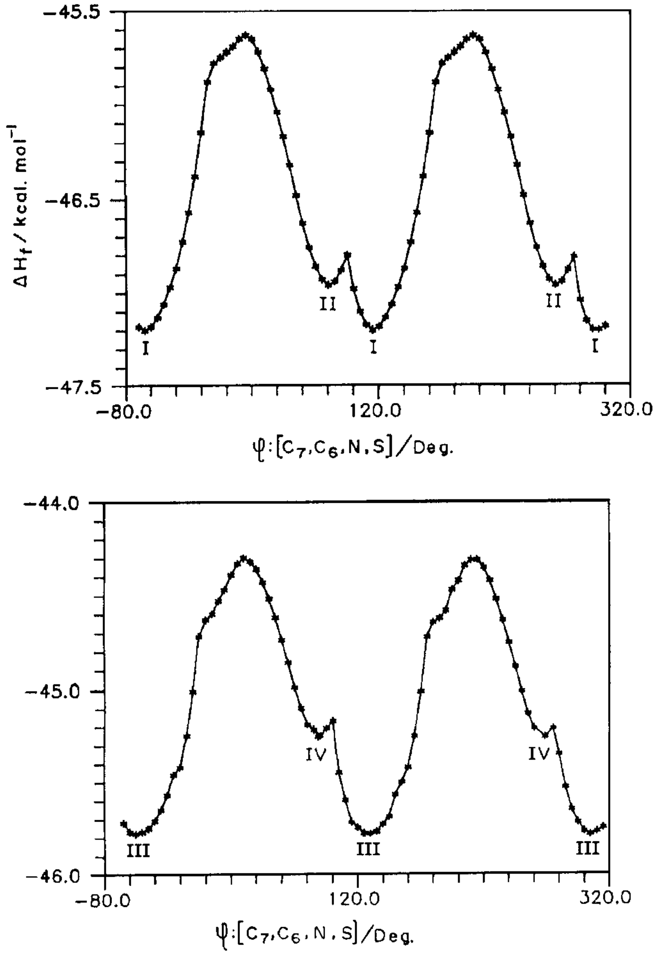


Figure 3. The PM3 pointwise calculated one-dimensional PES for rotation of the phenyl group around the N_3-C_6 bond (see Figure 1): a) **I** ↔ **II**; b) **III** ↔ **IV**.

torsional PES which is shown in Figure 3. In this pointwise calculated PES the dihedral angle for the rotation of the phenyl group with respect to the five-member ring, *i.e.* [C_7, C_6, N, S], was kept unchanged and all remain geometrical parameters being fully optimized. This procedure assures that the TS structure on the minimum energy path and the rotational barrier are precisely determined. It can be seen from Figure 3 that there are two mechanism of conformational interconversion involving energy barrier of distinct sizes. It can be seen that structures **I** and **III** are expected to be the preferred ones, since the internal motion leading respectively **II** to **I** and **IV** to **III** is favored (a very small energy barrier is present). The conformational interconversion *via* a higher energy barrier is very unlikely to take place since it would involve a rather steric hindered torsional motion. This result is very interesting because it left us with only two conformers as the probable candidates to be the experimentally observed conformer, *i.e.* structure **I** and **III**.

The possibility of interconversion between structures **I** and **III** deserve our attention. In order to calculate the energy barrier for interconversion the transition state structure connecting the two minima must be found. This is indeed a difficult task. The internal motion that leads **I** to **III** is very complex since it involves a torsional movement of the five-member ring and the phenyl group. The TS structures for the interconversion between the pair of conformers **I** and **II** and **III** and **IV** could be precisely determined since it involves rotation of the phenyl group around a single bond and so a reaction coordinate (here a torsion angle) can be unambiguously defined (see Figure 2). For the interconversion **I** ↔ **III** a single reaction coordinate, that could be one of the dihedral angles involving the five-member ring, cannot be easily found due to the multidimensional nature of the intramolecular motion. The reaction coordinate leading to a conformation interconversion is a combination of various torsion angles and so a pointwise calculation of a one-dimensional torsional PES, as it has been shown in Figure 3, is not possible.

In order to locate a TS structure distinct approaches, other than pointwise calculations of minimum energy paths, may be used as, for example, the Linear Sinchronous Transit (LTS) method [11]. The LTS procedure locates a maximum along a path connecting two structures and thus provides a guess as the transition structure connecting them. It does not actually locate a proper transition state. The structure resulting from an LST calculation may be suitable for input to subsequent geometry optimization and frequency jobs. This usually results in one or more negative eigenvalue of the Hessian matrix [8]. Although a maximum is always located this may not be the lowest energy maximum. The latter may be found by optimizing one or more selected parameters until the structure with the lowest energy and (after harmonic frequency analysis) one negative eigenvalue is found. The approaches developed for locating TS structures on a given PES presume a knowledge of at least approximate geometries of the saddle point. In the case of the five-ring heterocyclic, object of the present study, such information is not readily available due to the complex topography of the multidimensional PES.

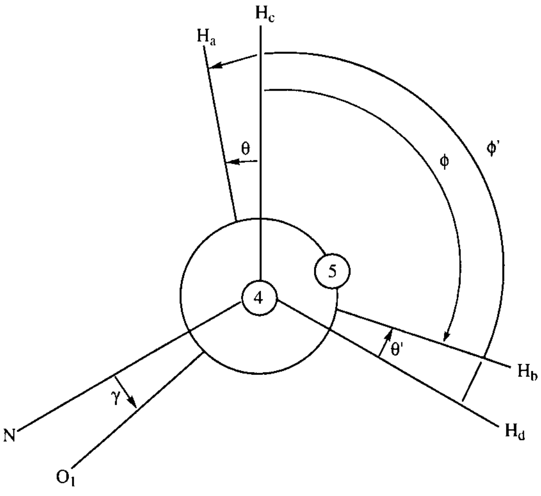
It is well known that nuclear magnetic resonance (nmr) spectra may be interpreted to give information both on energy differences between conformers and on energy barrier [3]. Conformational differences can be determined by measuring the relative populations of various conformers at a single temperature. Use of the Boltzmann equation then leads to the energy differences between the conformers. In order to measure the relative populations of various conformers by nmr, it is necessary that each conformer have a different nmr spectrum, that the energy differences between conformers be on the order of 1 kcal mol^{-1} or less (so that all conformers are present in observ-

Table 3

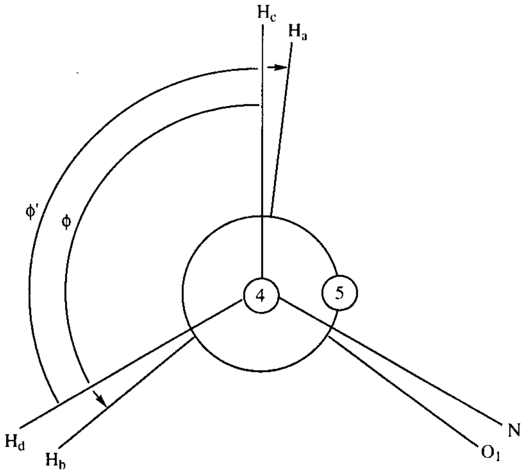
PM3 Calculated and Experimentally Estimated Dihedral Angles [a] (in degrees) for Structures **I** and **III** shown below in the Newman Projection Representation

Dihedral Angles	PM3 Structure **I**	PM3 Structure **III**	Expt [b]	Expt [c]
θ: $H_cC_4C_5H_a$	14.2	-1.3	12	14.1 (13.5) [d]
θ': $H_dC_4C_5H_b$	10.9	2.3		
ϕ: $H_cC_4C_5H_b$	-108.4	121.3	-123	-120.9 (-121.5) [d]
ϕ': $H_dC_4C_5H_a$	133.4	-120.4		
γ: $NC_4C_5O_1$	12.0	-4.6		
$\lvert\phi\rvert + \lvert\theta\rvert$ [e]	122.6		135	135
$\lvert\phi'\rvert + \lvert\theta\rvert$ [e]		122.7		

[a] The positive sign of the dihedral angle is defined as an anti-clockwise rotation around the C_4-C_5 bond. [b] Experimental value (solvent acetone) from ref [2]. [c] Experimental value (solvent benzene) from ref [1], using the Karplus equation from ref [2]. [d] Like [c] with acetonitrile being used as solvent. [e] This is the dihedral angle used in the Karplus equation: $J_{vic} = k_1 - \cos(\omega \pm \theta) + k_2\cos2(\omega \pm \theta)$, where $\omega = |\phi| + |\theta|$ e k_1,k_2 = empirical constants.



Conformer **I**



Conformer **III**

able quantities), and that the barrier between conformers be higher than about 5 kcal mol^{-1} (so that exchange between them is slow at temperatures accessible in present-day nmr spectroscopy) [12]. Determination of barrier heights also requires comparison of nmr spectra at several temperatures since as the temperature of a mixture of conformers is increased, the rate of interconversion increases. So if the barrier is not too high, interconversion may become so rapid that a single nucleus moves through several local environments within the time required for the (microscopic) nmr measurement. Another point to be considered regarding the determination of barriers to internal rotation is that the shape of the PES must be simple. Usually the experimentally determined barriers involve rotation around single bonds that can be described by periodic potential functions [13]. So in the light of the internal motion of the phenyl group shown by Figure 3, it can be seen that the torsional PES for the interconversion between structures **I** and **III** is very unlikely to be mimicked by a periodic type potential energy function. This result suggests that any experimental approach for the determination of the energy barrier for interconversion between structures **I** and **III** that relies on a fitting of a periodic potential energy function will have little chance to succeed. From Table 1 it can be seen that the energy difference between conformers **I** and **III** is 1.6 kcal mol^{-1}, and so both conformers may be present in observable quantities. However there is no guarantee that the energy barrier for conformational interconversion is higher than 5 kcal mol^{-1} in order to allow an nmr investigation of the barrier height. It should lastly be emphasized that in the nmr studies reported in refs [1,2] a definitive assignment of the spectra giving support to the existence of more than one conformer could not be made.

In an attempt to locate the first-order TS structure on the minimum energy path leading **I** to **III**, some trial molecular arrangements were examined using the PM3 method. Geometry optimization, keeping some dihedral angles frozen, were carried out followed by harmonic frequency analysis. Using this procedure a few first-order TS structures were located but it is hard to say if they are really on the lowest minimum energy path for conformational interconversion between **I** and **III**. It is important to say that there are many first-order TS structures on a multidimensional PES. They can be on a variety of distinct minimum energy paths depending on which internal variable (usually a dihedral angle) has been used as the reaction coordinate. So it is not safe to trust these TS structures, located by a sort of trial and error procedure, to be the "true" saddle point on the minimum energy path for conformation interconversion between conformers **I** and **III**.

Finally, a comparison between the theoretical geometrical parameters reported here and the experimental data available from the nmr studies [1,2] regarding the conformation of the 3-phenyl-1,2,3-oxathiazolidine 2-oxide compound is summarized in Table 3. It can be seen that the assignment of twist-envelope conformations based only on the knowledge of the dihedral angles θ and ϕ is far to be accurate. The theoretical study yield all of the torsion angles of the five-member ring and so reveal all its structural features. There is a good agreement for the angle θ reported for structure **I** and the experimental value, while the angle ϕ reported in this study is somewhat different from the experimental value. Nevertheless our theoretical value for $(|\phi| + |\theta|)$ of *ca.* 123 degree is more close to the value commonly used in the Karplus equation for heterocyclic rings [1] than the experimental value of 135 from ref [2]. It can be seen from the Newman's projection representation given in Table 3 that structure **III** is nearly eclipsed which correlates well with the fact that it is less stable than structure **I** at the PM3 semiempirical level of theory. Also the asymmetric nature of these heterocyclic compounds can be visualized. It is clearly seen from the Newman's projection representations that an interconversion path connecting the conformers **I** and **III** cannot be easily envisaged. The interconversion **III** ↔ **I** involves a simultaneous variation of at least five torsion angles of the five-member ring and so, it makes a precise determination of the true first-order TS structure on the lowest minimum energy path on the PES a difficult computational task.

Conclusions.

In the present work a theoretical investigation of the conformational equilibria for the 3-phenyl-1,2,3-oxathiazolidine 2-oxide heterocyclic system has been carried out using the semiempirical quantum-mechanical method PM3. The results showed that there are four structurally distinct conformers that may exist in equilibrium. Analysis of the one-dimensional torsional PES for rotation of the phenyl substituent groups (attached to the five-membered ring) around a single bond revealed that isomers **II** and **IV** are readily converted respectively to isomers **I** and **III**. This leaves only structures **I** and **III** as the likely candidates as the experimentally observed conformers. Due to the complexity of the interconversion energy path connecting conformers **I** and **III**, a pointwise calculation of the lowest minimum energy path on the PES leading **I** to **III** could not be carried out. So the most we can say is that there two energetically close conformers of the 3-phenyl-1,2,3-oxathiazolidine 2-oxide heterocyclic system, *i.e.* structures **I** and **III**. The present study also shows that a combination of experimental nmr studies and semiempirical quantum-mechanical calculations proved to be very promising in what the investigation of the conformations of heterocyclic compounds is concerned. It is important to say that the nmr studies are carried out in solution and so the conformational equilibrium may be influenced by the solvent used [1]. The next computational task will be then to carry on a PM3 conformational analysis taking into account the solvent effects.

Acknowledgments.

W. B. De Almeida would like to thank the CNPq (Conselho Nacional de Desenvolvimento Cientifico e Tecnologico) for support. A. M. G. Do Val and A. C. Guimarães thank the FAPEMIG (Fundação de Amparo a Pesquisa do Estado de Minas Gerais) for partial sponsorship of the experimental work. A. M. G. Do Val also thanks the Laboratorio de Quimica Teorica (Depto. Quimica-UFMG) for computational help.

REFERENCES AND NOTES

* Corresponding author.

[1] A. M. G. Do Val, Doctor in Sciences Thesis, Departamento de Quimica, U.F.M.G., Brazil, 1994.

[2] F. Yamada, T. Nishiyama, and H. Samukawa, *Bull. Chem. Soc. Japan*, **48**, 3313 (1975).

[3] J. A. Pople, W. G. Schneider, and H. J. Bernstein, High Resolution Nuclear Magnetic Resonance, McGraw-Hill, New York, 1959.

[4] J. J. P. Stewart, *J. Comput. Chem.*, **10**, 209 (1989).

[5] W. B. De Almeida and P. J. O'Malley, Theochem, **253**, 349 (1992).

[6] W. B. De Almeida, H. F. Dos Santos, and P. J. O'Malley, submitted for publication in *Struct. Chem.*

[7] J. J. P. Stewart, *J. Computer-Aided Molecular Design*, **4**, 1 (1990).

[8] P. G. Mezey, Studies in Physical and Theoretical Chemistry, Vol **53**, Potential Energy Hypersurfaces, Elsevier, Amsterdam, 1987.

[9] MOPAC Version 6.0: J. J. P. Stewart, Frank J. Seiler Research Laboratory, U.S. Air Force Academy, Colorado Springs, CO 80840-6528, USA, 1990.

[10] E. L. Teixeira and H. H. R. Schor, Program MOLMOP, Project Seraphin, IB410, 1989.

[11] T. A. Halgren and W. N. Lipscomb, *Chem. Phys. Letters*, **49**, 225 (1977).

[12] J. P. Lowe, Progress in Physical Organic Chemistry, Vol **6**,

A. Streitwieser Jr. and R. W. Taft, eds, Interscience Publishers, John Wiley & Sons, New York, 1968, p 1.

[13] W. J. Orville-Thomas, ed, Internal Rotation in Molecules, John Wiley & Sons, London, 1974.