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Comment on "Structural and vibrational studies on 1-(5-Methyl- [1,3,4] thiadiazol-2-yl)-pyrolidin-2-ol" [Spectrochimica Acta Part A, 152 (2016) 252–261]. The importance of intramolecular OH ··· N hydrogen bonding in the conformational properties of thiadiazol-pyrrolidin-2-ol bearing species

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Comment on ‘‘Structural and vibrational studies on 1-(5-Methyl-[1,3,4] thiadiazol-2-yl)-pyrolidin-2-ol’’ [Spectrochimica Acta Part A, 152 (2016) 252–261]. The importance of intramolecular OH•••N hydrogen bonding in the conformational properties of thiadiazol-pyrrolidin-2-ol bearing species

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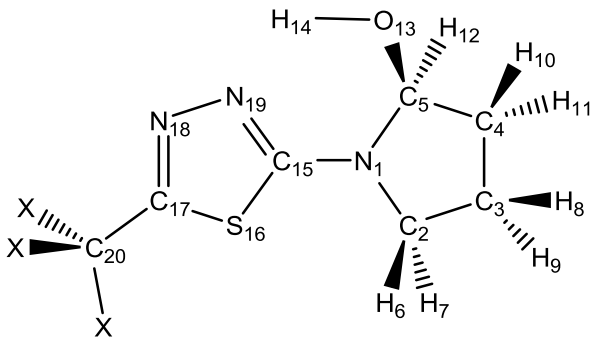
Abstract

The title paper [1] reports a study on the spectroscopic and physicochemical properties of 1-(5-methyl-[1,3,4]thiadiazol-2-yl)-pyrrolidin-2-ol (MTPN) based on experimental and theoretical data. The latter ones are based on the computed molecular structure for a rather unusual conformer. Here, after a careful analysis of the conformational space of MTPN, the most stable conformation was determined for the molecule isolated in a vacuum, which results to be 21.9 kJ/mol more stable than the conformer reported previously. Our study also includes the closely related species 1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-pyrrolidin-2-ol (FMTPN). An intramolecular OH•••N hydrogen bond determines the conformational behavior of the [1,3,4]thiadiazol-2-yl)-pyrrolidin-2-ol group as demonstrated by Natural Bond Orbital population analysis.

Keywords: Heterocyclic compounds; Thiadiazole; Pyrrolidine; Conformation; Hydrogen bond; NBO.

Comment

The title work [1] reports the preparation of 1-(5-methyl-[1,3,4]thiadiazol-2-yl)-pyrrolidin-2-ol (MTPN, Scheme 1, X= H), a substance with potential antimicrobial and pharmacological activity [2-4]. The synthesis procedure is similar to that recently reported by Suresh et al. for 2-hydroxypyrrolidine derivatives [5], in which the closely related compound 1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-pyrrolidin-2-ol (FMPTN, Scheme 1, X= F) was obtained.



Scheme 1. Representation of 1-(5-methyl/trifluoromethyl-[1,3,4]thiadiazol-2-yl)-pyrrolidin-2-ol compounds, MTPN (X= H) and FMPTN (X= F).

Ramesh Babu et al. also studied the vibrational properties of MPTN by using experimental data (FTIR and FT-Raman spectra) in conjunction with theoretical

calculations, including normal mode analysis. Moreover, intramolecular charge transfer and HOMO-LUMO gap were calculated, and non-linear optical properties were computationally studied. The UV-Vis spectrum was measured and interpreted in terms of TD-DFT methods [1].

For all these analyses, authors used the computed molecular structure at the B3LYP/6-311++G(d,p) level of approximation, as can be shown in the Figure 1 of the title article [1] (geometrical parameters are also given in Table 1). It is observed that the thiadiazole and the pyrrolidine rings adopt a non-coplanar conformation, and the authors state that "*the difference between the two dihedral angles of the adjacent rings is ~8º*". In this structure, the S atom and the O-H moiety are at opposite sides of the C15-N1 axis. Besides, the OH bond is placed out of the plane defined by the two rings, adopting a gauche conformation around the C5-N1 bond (dihedral angles are not listed in Table 1). It should be noted that according to the authors, "*In order to establish the stable possible conformers, the conformational space of MTPN compound was scanned with molecular mechanic simulations*" [1]. It is assumed that the only stable conformer they found was the structure already commented.

What drew our attention is that there are similar reported cases in which hydroxyl groups establishes O-H•••N internal hydrogen bonds with heterocyclic N atoms [6-8], and the case of the thiadiazol nitrogen present in MPTN should follow this behavior, specially due to the closeness of the O-H group and N19 (see Scheme 1 for atoms numbering). Thus, we decided to further scrutinize the potential energy surface of MPTN in order to better understand the conformational landscape of the thiadiazolyle-pyrrolidine system displaying 2-ol substitution. For completeness, the closely related species FMPTN is also included in this comment.

In principle, different conformations are expected depending on the mutual orientations of the thiadiazolyle and 2-hydroxyl groups with respect to the pyrrolidine ring. Thus, the computed potential energy curves around the N_1-C_{15} and C_5-O_{13} bonds are shown in Figures 1 and 2, respectively. The B3LYP computational method in conjunction with the 6-31G(d,p) and 6-311++G(d,p) basis sets has been selected, as used in [1].

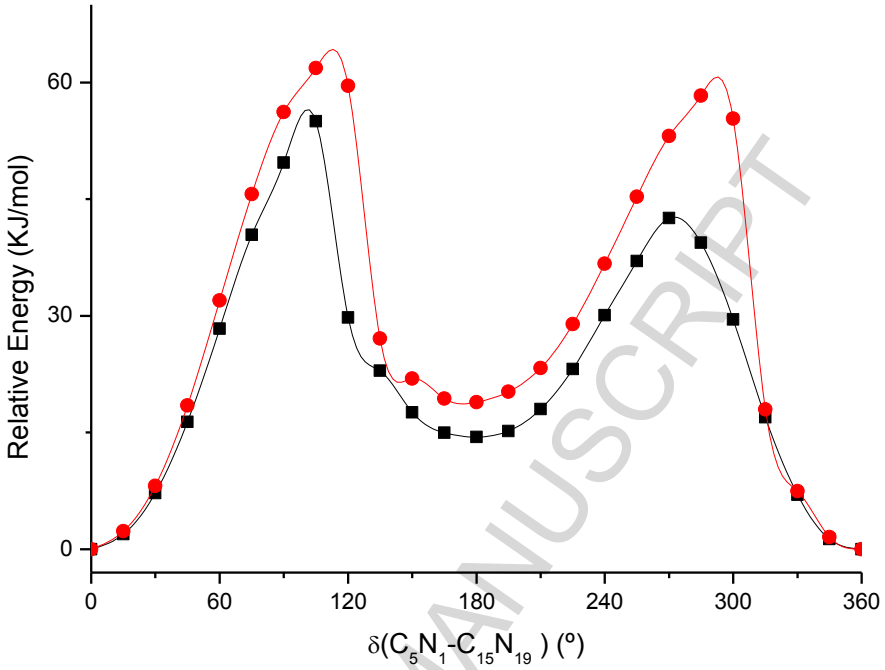


Figure 1. Calculated [B3LYP/6-31+G(d,p)] potential function for internal rotation around the C_5N_1-$C_{15}N_{19}$ dihedral angle for MPTN (–■–) and FMPTN (–●–) compounds. For atom numbering see Scheme 1.

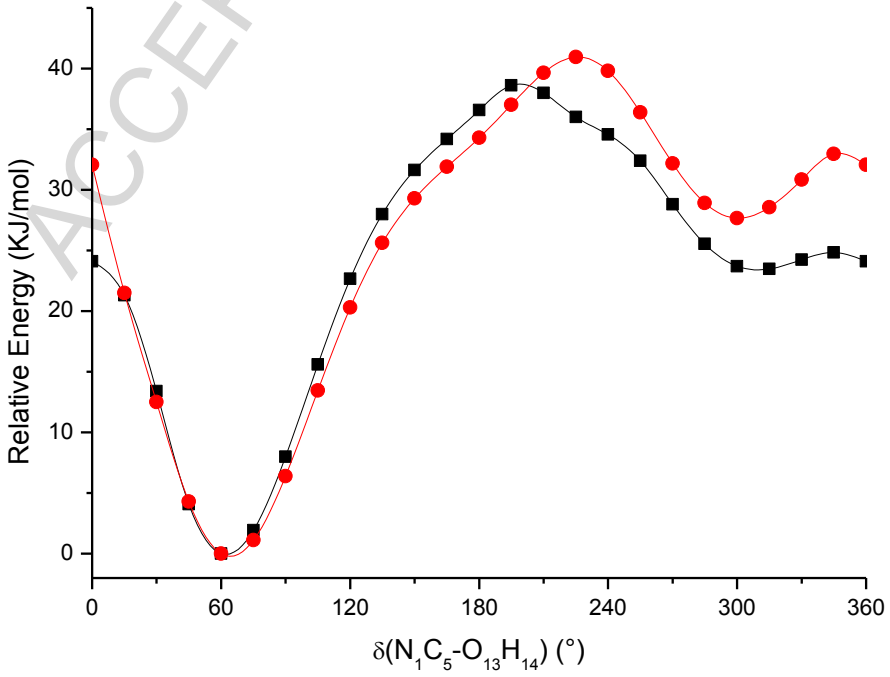
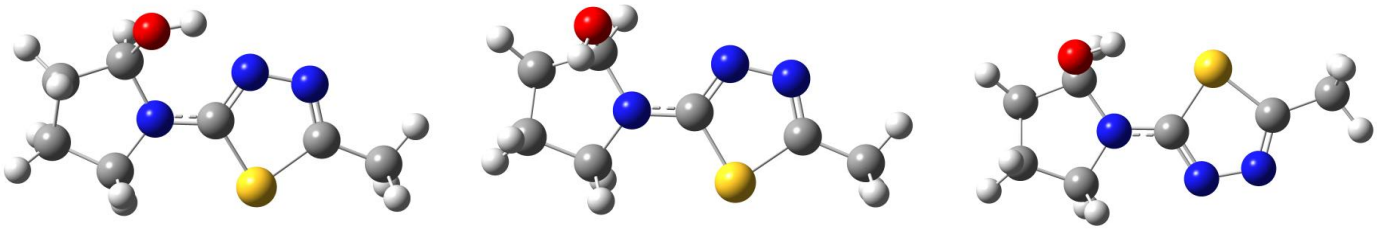


Figure 2. Calculated [B3LYP/6-31+G(d,p)] potential function for internal rotation around the N_1C_5-$O_{13}H_{14}$ dihedral angle for MPTN (–■–) and FMPTN (–●–) compounds. For atom numbering see Scheme 1.

When the potential energy curve for mutual rotation of the two ring is analyzed (Figure 1), it is clear that two forms are expected, corresponding to planar forms with different orientation of the N (or S) atoms of the [1,3,4] thiadiazole ring with respect to the –OH group of the pyrrolidin-2-ol moiety. The *E* and *Z* forms correspond to the structures with the $\delta(C_5N_1$-$C_{15}N_{19})$ adopting values of 0º and 180º, respectively, the *E* form being more stable by ca. 15 kJ/mol. The high rotational barriers connecting these forms (higher than 40 kJ/mol) support the partial double bond character for N_1-C_{15}.

More interesting, the potential energy curve for the rotation of the O–H group with respect to the pyrrolidin-2-ol ring for the *E* form, shows the presence of a deep minimum at ca. 60º (hereafter called *E*1) and a second local minimum, located higher in energy (ca. 25 kJ/mol, *E*2) in a rather flat portion of the curve at $\delta(N_1C_5$-$O_{13}H_{14})$ around 300º. When the same curve is obtained for the *Z* form (not showed), only one conformation is obtained.

As can be shown in Figures 1 and 2, similar conformational features are expected for the 5-methyl (MPTN) and 5-trifluoromethyl (FMPTN) derivatives. From these curves, three structures correspond to minima, for which full geometry optimization and vibrational frequency calculations at the B3LYP/6-311++G(d,p) confirm as truly conformers (i.e. no imaginary frequencies were computed). The molecular structures of these conformers of MPTN are shown in Figure 3.



*E*1 (0.0) *E*2 (21.9) *Z* (14.4)

Figure 3. Molecular structures optimized [B3LYP/6-311++G(d,p)] for the three main conformers of the title compound. Relative energies values (ΔEº, in kJ/mol) are given (Eº= –911.18686971 Hartrees for the most stable *E*1 form).

The most stable conformation of MPTN isolated in a vacuum corresponds to the *E*1 form, being the *E*2 and *Z* conformers located higher in energy by 21.9 kJ/mol and 14.4 kJ/mol respectively (ΔE^0 value, corrected by zero point energy). *E*2 corresponds to the structure analyzed and discussed in the title paper [1]. In the case of fluorinated analogue, FMPTN, the energy order shows the same trend: *E*1 is the most stable form (E^0 = –1208.99633905 Ha), being the *E*2 and *Z* conformers located higher in energy by 27.3 kJ/mol and 18.9 kJ/mol respectively.

Differences between the computed vibrational spectra for the *E*1 and *E*2 forms are clearly observed. The computed ν(OH) stretching mode for the *E*2 is 3801 cm^{-1} (unscaled) [1], whereas for the *E*1 form it is computed as an intense band at 3681 cm^{-1}. A very strong broad band centered at ca. 3400 cm^{-1} is observed in the experimental IR spectrum showed in the Figure 2 of the reference [1]. The red-shift and intensification of the ν(OH) mode is in agreement with the formation of O–H•••N hydrogen bond for the *E*1 form. The δ(OH) deformation mode for the *E*1 form is computed at 1296 cm^{-1}, similar to that of *E*2 [1].

Changes in the force constants of normal modes of the acceptor thiadiazol-2-yl group are also expected upon the formation of the O–H•••N intramolecular hydrogen bond. An intense absorbance at 1575 cm^{-1} in the infrared spectrum and a strong signal at 1512 cm^{-1} in the Raman spectrum were assigned to these modes in reference [1]. The computed values for the ν(C=N) stretching modes for the E2 conformer are 1582 and 1565 cm^{-1} [1], respectively. For the *E*1 form, these vibrations are coupled and better described as the symmetric and antisymmetric stretching modes, computed at 1526 and 1505 cm^{-1} values, respectively, in good agreement with the experimental IR and Raman spectra. The ν(N-N) stretching mode for both *E*1 and *E*2 conformers are nearly the same, i.e. 1128 [1] and 1129 cm^{-1}, respectively, and can assigned to the bands appearing at 1084 and 1082 cm^{-1} in the IR and Raman spectra [1], respectively.

The occurrence of the internal H bond in the FMPTN derivative is supported by the observation of scalar coupling between the OH and H_{12} (^3J = 5 Hz) in the ^{1}HNMR spectrum reported by Suresh et.al. [5]. Moreover, the chemical shift value corresponding to the –OH proton, δ= 9.21 ppm, is relatively high for an alcohol –OH group, indicating that the proton (H_{14} in scheme 1) is deshielded by formation of a hydrogen bond.

In order to understand the factors influencing the preference for the *E*1 conformation in MPTN and FMPTN, we evaluated the donor→ acceptor interactions using the Natural Bond Orbital (NBO) population analysis [10] at the B3LYP/6-

311++G(d,p) level of approximation. In general, the values determined for the donor→ acceptor interactions of the *E*1 conformer are similar to that determined by Ramesh Babu et al. for the *E*2 form of MPTN [1]. However, it was interesting to observe that a remote interaction of the type lpN_{19}→ σ*(O–H) occurs in the *E*1 form, which is absent in the *E*2 conformation. This interaction is a clear indication that an O–H•••N intramolecular hydrogen bond is established in the case of *E*1 conformer. In effect, for conventional O–H•••N hydrogen bonds, partial charge transfer from a lone pair electrons formally located at the nitrogen atom toward the O–H antibonding orbital is expected to occur [11]. It has been shown that such hyperconjugative interactions can operate between remote orbitals determining the conformational behavior of simple molecules [12] including 1-acyl thioureas [13, 14] and hydrazones [15], as well as the backbone conformation of peptides [16, 17]. For the compounds here studied, a representation of the lpN→ σ*(O–H) remote interaction between the nitrogen atom of the thiadiazol ring (N_{19} in Scheme 1) and the hydroxyl group substituting the pyrrolidine ring are given in Figure 4. The stabilization energies, $E_{i,j}^{(2)}$, associated with this hyperconjugative interaction is obtained as 3.15 and 2.32 kcal/mol for MPTN and FMPTN, respectively, at the B3LYP/6-311++G(d,p) level of approximation. To check whether the computed interaction values are sensitive to the basis set, further NBO calculations were done by using the more extended aug-cc-pVTZ basis set. For the title species, the lpN→ σ*(O–H) interaction amounts to 2.82 kcal/mol.

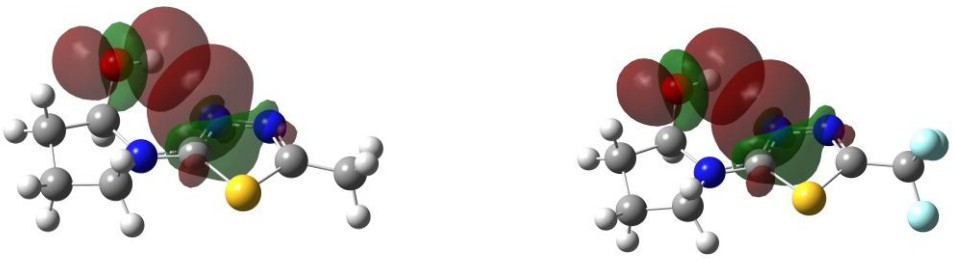


Figure 4. 3D representation of the remote lpN→ σ*(O–H) NBOs overlap responsible for the O–H···N intramolecular hydrogen bond in MPTN (left) and FMPTN (right).

In summary, the present results give strong evidence for the occurrence of the *E*1 form as the most stable conformation for 1-(5-methyl-[1,3,4]thiadiazol-2-yl)-pyrrolidin-2-ol isolated in a vacuum. An intramolecular OH•••N hydrogen bond favors this conformation, as demonstrated by NBO population analysis. The rather unusual *E*2 conformer is higher in energy by an amount of 21.9 kJ/mol. A similar conformational

preference is obtained for the close related 5-trifluoromethyl analogue. In the absence of experimental data on the molecular structure for these compounds, it is strongly recommended the use of the *E*1 form for analyzing spectroscopic, electronic and physicochemical properties of these compounds. In particular, the atypical *E*2 form studied in [1] corresponds to a high-energy conformer that hardly has any influence on the analyzed properties of MPTN.

Acknowledgments

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References

[1] N. Ramesh Babu, H. Saleem, S. Subashchandrabose, M. Syed Ali Padusha, S. Bharanidharan, *Spectr. Acta Part A.* 152 (2016) 252–261

[2] N.S. El-Gohary, *Eur. J. Med. Chem.* 63 (2013) 185-195.

[3] A.A. Kadi, N.R. El-Brollosy , O.A. Al-Deeb, E.E. Habib, T.M. Ibrahim, A.A. El-Emam, *Eur. J. Med. Chem.* 42 (2007) 235-242.

[4] S.S. Karki, K. Panjamurthy, S. Kumar, M. Nambiar, S.A. Ramareddy, K.K. Chiruvella, S.C. Raghavan, *Eur. Med. Chem.* 46 (2011) 2109-2116.

[5] M. Suresh, A.F.M. Mashood, K.K. Abdul, M.S.A. Padusha*, Eur. J. Chem* 5 (2014) 612-617.

[6] A. Simpeler, W. Mikenda, *Monatsh. Chem.* 128 (1997) 969-980.

[7] X.S.Huang, X. Liu, K.L. Constantine, J.E. Leet, V. Roongta, *Magn. Reson. Chem.* 45 (2007) 447-450

[8] P.I. Nagy, *Int. J. Mol. Sci.* 15 (2014) 19562-19633.

[9] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G.

Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople. Gaussian, Inc., Wallingford CT, 2004.

[10] A.E. Reed, L.A. Curtiss, F. Weinhold, *Chem. Rev.* 88 (1988) 899-926.

[11] I.V. Alabugin, M. Manoharan, S. Peabody, F. Weinhold, *J. Am. Chem. Soc.*, 125 (2003) 5973-5987.

[12] A.J. Lopes Jesus, M.T.S. Rosado, I. Reva, R. Fausto, M.E.S. Eusébio, J.S. Redinha, *J. Phys. Chem. A*, 112 (2008) 4669-4678.

[13] A. Saeed, A. Khurshid, J.P. Jasinski, C.G. Pozzi, A.C. Fantoni, M.F. Erben, *Chem. Phys.*, 431-432 (2014) 39-46.

[14] A. Saeed, A. Khurshid, M. Bolte, A.C. Fantoni, M.F. Erben, *Spectrochim. Acta, 143A* (2015) 59-66.

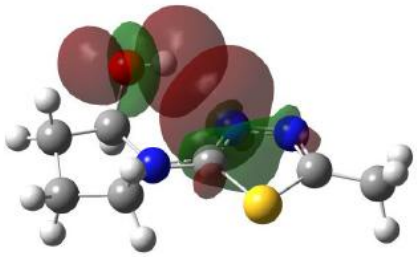
[15] A. Saeed, M. Ifzan Arshad, M. Bolte, A.C. Fantoni, Z. Y. Delgado Espinoza, M.F. Erben, *Spectrochim. Acta, 157A* (2016) 138-145.

[16] J.J. Koivisto, E.T.T. Kumpulainen, A.M.P. Koskinen, *Org. Biomol. Chem.*, 8 (2010) 2103-2116.

[17] L. Aguilar-Castro, M. Tlahuextl, L.H. Mendoza-Huizar, A.R. Tapia-Benavides, H. Tlahuext, *ARKIVOC*, (2008) 210-226.

Graphical abstract

Hydrogen bonding and remote lpN→ σ*(O–H) interaction



1-(5-methyl-[1,3,4]thiadiazol-2-yl)-pyrrolidin-2-ol

Highlights

► The conformational space of 1-(5-Methyl-[1,3,4] thiadiazol-2-yl)-pyrolidin-2-ol is reported.
► Three main conformers were determined.
► Thiadiazol and pyrolidin-2-ol groups are involved in N···H–O intramolecular hydrogen bond.
► Strong hyperconjugative lpN→ σ*(O–H) remote interaction takes place.
► Previous reported calculations are needed to be revised.