



Comment on “Molecular Structure analysis and Spectroscopic Characterization of Carbimazole with experimental (FT-IR, FT-Raman and UV-Vis) techniques and quantum chemical calculations” [J. Mol. Struct. 1052 (2013) 38–49]

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HIGHLIGHTS

- The conformational space of carbimazole is reported.
- Two main conformers were determined.
- Structural and vibrational properties are in agreement with the previously reported experimental data.
- A third high-level energy conformer is located at ca. 35 kJ/mol.
- Previous reported calculations are needed to be revised.

ARTICLE INFO

Article history:

Received 6 September 2013
Received in revised form 10 October 2013
Accepted 14 October 2013
Available online 23 October 2013

Keywords:

Carbimazole
Quantum chemical calculations
Infrared spectrum
Raman spectrum

ABSTRACT

The title paper [1] reports the analysis of the vibrational spectra (infrared and Raman) of solid carbimazole based on the computed molecular structure for a rather unusual conformer. The optimized structure does agree neither with the reported crystallographic data nor with previous vibrational studies omitted in [1]. Here, after a careful analysis of the conformational space, the proper molecular structure of carbimazole has been calculated and the vibrational spectra have been analyzed. These results are in agreement with the available experimental data.

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1. Comments

The title paper [1] reports the DFT-B3LYP/6-31G(d,p) and B3LYP/6-311++G(d,p) calculated structure of carbimazole (CBZ, ethyl 3-methyl-2-sulfanylidene-imidazole-1-carboxylate), a pro-drug used to treat hyperthyroidism (see Scheme 1). After structure optimization, the same level of calculations was further used to analyze the vibrational properties of solid carbimazole, including its infrared, Raman and UV-Vis spectra. Finally, a series of computed thermodynamic properties (entropy, heat capacity and enthalpy), electric dipole moment, first hyperpolarizability and population analysis data are provided.

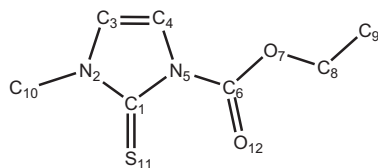
The computed molecular structure of CBZ is shown in Fig. 1 of the title article [1]. It is observed that the C=S and C=O bonds adopt a mutual *anticlinal* or *gauche* orientation, with the ethoxycarbonyl moiety displaying an unusual *antiperiplanar* conformation (the C=O double bond and the O—C(Et) single bond in mutual *anti* orientation) [3,4]. Surprisingly, this is the only conformer studied in [1], given that the conformational space was not pondered.

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Computed geometrical parameters for the supposed CBZ conformer are given in Table 1 of [1] and compared with reported data for similar molecules, since according to the authors “...the crystal structure of the exact title compound is not available as yet...”. The crystal and molecular structure of carbimazole, however, was already solved and reported by Delage and coworkers in [2]. The X-ray molecular structure of solid CBZ is quasi-planar, with the C=S and C=O double bonds in a pseudo-*synperiplanar* orientation, while the C=O and O—Et bonds adopt the usual *syn* conformation. Thus, the conformational disparity between the experimentally determined structure and that used in [1] is apparent.

The authors of the title article also say that “To the best of our knowledge, no experimental data on vibrational and structural parameters for these derivatives are yet reported” [1]. It should



Scheme 1. General chemical structure of CBZ with atom numbering according to [2] (hydrogen atoms are omitted for clarity).

be noted, however, that in 1998 Laurence et al. [5] reported infra-red and Raman studies of CBZ in solid- and solution-states. From the experimental determination of the dipole moment value (4.30 D) and the solvent variation of the two carbonyl bands in the IR spectrum, the conformational equilibrium between Z and E forms was clearly established, the E form being preferred in heptane and CCl_4 , whereas the more polar Z conformer is stabilized by polar solvents [6]. No evidence for the presence of the *gauche-anti* conformation determined in [1] was found in the quite detailed study aforementioned [5].

Prompted by these findings, we decided to scrutinize the potential energy surface of CBZ by computing the potential energy curves around the $\text{N}_5\text{—C}_6$ and $\text{C}_6\text{—O}_7$ bonds (given in Figs. S1 and S2, respectively, in the Supporting Information). From these curves, three structures correspond to minima, for which further full parameter optimization and vibrational frequency calculations confirm as truly conformers (i.e. no imaginary frequencies were computed). These were Gaussian 03 [7] DFT calculations, at the B3LYP computational method in conjunction with the 6-31G(d,p) and 6-311++G(d,p) basis, as used in [1]. The molecular structures for these forms are shown in Fig. 1. The Z-*syn* and E-*syn* forms are planar, both belonging to the C_s symmetry point group. On the other hand, the optimized structure with *anti* conformation for the ethoxycarbonyl group deviates from planarity, – possibly due to sterical requirements – with the C=O bond oriented nearly perpendicular to the sulfanylidene-imidazole-1-carboxylate ring (*gauche-anti* form in Fig. 1).

The most stable conformation of CBZ isolated in a vacuum corresponds to the E-*syn* form ($E^0 = -930.927331$ Ha), the Z-*syn* conformer located higher in energy by 6.28 kJ/mol (ΔE^0 value, corrected by zero point energy). This result is in qualitative good agreement with the conformational equilibrium observed in non-polar solvent, where the E-*syn* form prevails. The computed ΔE^0 value agrees with the experimentally determined from variable-temperature infrared spectra of CBZ in CCl_4 ($\Delta H^0 = 9.6 \pm 0.8$ kJ/mol) and with the energy difference previously calculated by the HF/6-31G** level of approximation [5]. On the other hand, the *gauche-anti* conformation – the form probably used through the Gnanasambandan's work [1] – is found in a local minimum located as high as 35.06 kJ/mol above the most stable form. Such a high-energy value is not surprising [8–10], given that resonance electronic stabilizations are decreased when the C=O bond and the heteroatom ring are not planar.

Table 1

Selected bond lengths [Å] and angles [°] in CBZ.

Bond length	Expl. ^a	Calc. ^b	Bond angle	Expl. ^a	Calc. ^b
$\text{C}_1\text{—S}_{11}$	1.67(1)	1.659	$\text{C}_1\text{—N}_2\text{—C}_{10}$	122.8(8)	123.1
$\text{C}_1\text{—N}_5$	1.41(1)	1.412	$\text{C}_3\text{—N}_2\text{—C}_{10}$	125.5(8)	125.7
$\text{N}_5\text{—C}_4$	1.40(1)	1.407	$\text{N}_2\text{C}_3\text{C}_4$	108.9(9)	108.3
$\text{C}_3\text{—C}_4$	1.32(1)	1.344	$\text{C}_3\text{C}_4\text{N}_5$	106.4(8)	107.1
$\text{C}_3\text{—N}_2$	1.40(1)	1.388	$\text{C}_1\text{N}_5\text{C}_4$	109.3(7)	109.8
$\text{N}_2\text{—C}_1$	1.35(1)	1.376	$\text{C}_1\text{N}_5\text{C}_6$	125.6(7)	125.9
$\text{N}_2\text{—C}_{18}$	1.47(1)	1.454	$\text{C}_4\text{N}_5\text{C}_6$	125.1(8)	124.2
$\text{N}_5\text{—C}_6$	1.41(1)	1.410	$\text{N}_5\text{C}_6\text{O}_7$	108.1(8)	108.9
$\text{C}_6\text{—O}_{12}$	1.20(1)	1.197	$\text{N}_5\text{C}_6\text{O}_{12}$	124.4(9)	125.7
$\text{C}_6\text{—O}_7$	1.32(1)	1.350	$\text{O}_7\text{C}_6\text{—O}_{12}$	127.4(9)	125.4
$\text{O}_7\text{—C}_8$	1.49(1)	1.453	$\text{C}_6\text{O}_7\text{C}_8$	114.7(8)	115.3
$\text{C}_8\text{—C}_9$	1.50(1)	1.514	$\text{O}_7\text{C}_8\text{C}_9$	105.4(8)	107.5

^a Experimental data from Delage et al. [2].

^b Optimized structure for the Z-*syn* form at the B3LYP/6-311++G(d,p) level of calculation.

In solid, as well as in polar solvents, the Z-*syn* conformer is favored. Having calculated the correct molecular structure we can now proceed to compare with the reported geometrical parameters in the solid state, as well as to complete the spectral assignments. As is shown in Table 1, the experimental bond lengths and angles [2] are well described, within the experimental error, by the B3LYP/6-311++G(d,p) level of approximation, as far as the optimized geometry of the Z-*syn* form is considered.

The comparison between the experimental and theoretical vibrational spectra is also of interest. We note, however, important differences between the 1800 and 1700 cm^{-1} region of the infrared and Raman spectra as reported in [1] and in [5]. In effect, Laurence et al. found one IR carbonyl band at 1758 cm^{-1} with a shoulder at 1754 cm^{-1} for CBZ in the solid state (KBr pellet) as well as for the Nujol mull. In the Raman spectrum of the powder, one carbonyl band at 1771 cm^{-1} with a symmetrical profile was observed [5]. An explanation for this frequency and shape differences was not provided [5]. The IR spectrum showed by Gnanasambandan et al. in Fig. 2 of [1] displays a carbonyl band centered at 1780 cm^{-1} , overlapped with an broad and intense absorption at 1470 cm^{-1} (values taken from Table 4 of [1]). In the Raman spectrum showed by Gnanasambandan et al. in Fig. 3 of [1], a low intensity signal is observed at 1783 cm^{-1} (the intensity is wrongly labeled as “strong” as listed in Table 4 of [1]). Unfortunately, details on the sample treatment employed in the measurement of the IR spectrum (KBr pellets, Nujol mull, etc.) are not given in the title article [1]. One point which is clear is that using the computed structure for the *gauche-anti* form leads to erroneous interpretations of the experimental solid phase spectra [10]. From the harmonic vibrational frequencies computed for the Z-*syn* form, absorptions at 1827 ($\nu\text{C=O}$), 1322 ($\nu\text{N}_2\text{C}_{10}/\text{N}_5\text{C}_6$), 1279 (495, $\nu_{\text{as}}\text{N}_2\text{C}_1\text{N}_5$) and 1161 ($\delta_{\text{s}}\text{C—H}$) cm^{-1} are expected to dominate the infrared spectrum of solid CBZ (assignments should be taken as tentative). For comparison with the experimental solid-phase infrared spectrum, the simulated one for the Z-*syn* form is given as Supporting



Fig. 1. Molecular models computed for the three main conformations of CBZ.

Information (Fig. S3). Important difference with that shown in Fig. 2 of the title article [1] are observed (it should be noted, also, that the “Wavenumber” axis is wrongly scaled in the simulated spectra).

As noted in [5], the carbonyl stretching vibration is specially suitable for studying the conformational behavior of CBZ since this mode is rather sensitive to conformation. When comparing the computed vibrational wavenumber of the $\nu\text{C=O}$ stretching mode for the *Z-syn* and *E-syn* forms, differences are observed for both frequency and infrared intensity. For the *Z-syn* form $\nu\text{C=O}$ is 1827 cm^{-1} , while the *E-syn* form shows a definitely red-shift to 1777 cm^{-1} with an increased band intensity. These B3LYP/6-311++G(d,p) values are in very good agreement with the experimentally determined frequency variation in non-polar solutions, where a $\Delta\nu\text{C=O}$ mean value of 39 cm^{-1} was reported for a series of six solvents [5]. The inclusion of a third form in the analysis, such as the *gauche-anti* proposed in [1], does not improve the description of the reported spectra.

In summary, the experimental data available for carbimazole show that the *Z-syn* form is present in the crystal, while a conformational equilibrium between the *Z-syn* and *E-syn* forms is suggested from the analysis of the solution-state infrared spectra. As showed here, quantum chemical calculations at the B3LYP/6-311++G(d,p) level give a good description of these properties, providing that the conformational landscape is firstly established. The atypical *gauche-anti* form studied in [1] corresponds to a high-energy conformer that has no influence on the analyzed properties of CBZ.

Acknowledgments

MFE is member of the Carrera del Investigador of CONICET (República Argentina). The author thanks to the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), the ANPCYT and to the Facultad de Ciencias Exactas, Universidad Nacional de La Plata for financial support.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.molstruc.2013.10.035>.

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