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CHIH-DFT determination of the molecular structure, infrared and ultraviolet spectra of the antiparasitic drug megazol

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Abstract

Two diseases, both of great importance in the American and the African continents are the American Trypanosomiasis or disease of Chagas and the African disease, better known as sleeping disease. megazol is a drug which it turns to be widely effective to fight these diseases in the initial stage as in the chronical one. In this work, we make use of a new model chemistry within Density Functional Theory, which is called CHIH-DFT, to calculate the molecular structure of megazol, as well to predict its infrared and ultraviolet spectra. The calculated values are compared with the experimental data available for this molecule as a mean of validation of our proposed chemistry model. The predicted results are in excellent agreement with the experimental ones.

Keywords: Megazol; Chagas disease; Sleeping disease; DFT; Molecular structure; Infrared spectrum; Ultraviolet spectrum

1. Introduction

In agreement with information of the World Health Organization (WHO), one of the main causes of mortality at world-wide level are the infectious diseases [1]. As much in Mexico as in the rest of the world, significant advances in the control of the transmissible diseases have been carried out. Nevertheless the infections continues being the main cause of disease and death in zones mainly marginalized of the great cities and in the majority of rural areas.

Two of these diseases, both of great importance in the American and the African continents are: the American Trypanosomiasis or disease of Chagas and the African disease, better known as sleeping disease. Both are caused by protozoan parasites of the mastigosphora class (flagellated) and pertaining to the family of the Trypanosomatidae [2]. The relevance of these diseases is in the amount of infected people and the lack of medicines able to stop the disease in the chronical stages.

The risk of infection of these diseases is directly related to poverty, since its vector, or transmitting insect, finds a favorable habitat for its development in cracks in the walls and the roofs of the poor houses in rural areas and in the roofs covered with straw [3]. By this, one of the primary objectives of the research centers on infectious diseases around the world and of the WHO is to apply all the available technologies in the study, treatment and prevention of infectious diseases.

The disease of Chagas is caused by the parasite *Trypanosoma cruzi* and transmitted to the human beings by the insects popularly known in different countries as 'vinchuca', 'barbeiro' and 'chipo'. It affects between 16 and 18 million people of Latin America, from Mexico to Argentina [3].

The sleeping sickness is caused by the protozoan parasite *Trypanosoma brucei*, and is transmitted to the human beings through the bite of the 'tse–tse' fly. This disease is endemic in countries like Cameroon, Congo, the Ivory Coast, Guinea and Mozambique, and epidemic in Uganda, Sudan, Angola and the Democratic Republic of the Congo. The sleeping sickness is a daily threat for more of 60 million men, women and children in 36 countries of Africa, 22 of which are between the less developed in the world [4].

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The Program for Investigation and Treatment of Tropical Diseases (TDR), [5] (supported by the WHO, the World Bank and the United Nations), refers to the sleeping disease as category 1 and to the disease of Chagas as category 3. That is to say, the actions of control and prevention of these diseases is considered high-priority. At this moment, some drugs exist to fight them, such as benznidazol and nifurtimox, the pentamidine, and the eflornithianine. Nevertheless, they are not effective in the chronical stage and for this reason other drugs are being developed. This is the case of megazol, a drug which it turns to be widely effective to fight these diseases in the initial stage as in the chronical one. Nevertheless, at the same time of the study on the effectiveness of megazol, a series of investigations are being made on its toxicity. This makes necessary to perform studies about similar molecules to this medicine.

The COST, European Cooperation in the Field of Scientific and Technical Research, in their final report called 'Chemotherapy of Infectious Diseases' [6], confirms that the therapies available to fight the parasitic activity are extremely limited and that is the reason why it is necessary to continue with the development and investigation of the megazol molecule, since it has been proven with great effectiveness in monkeys in the combat to the sleeping disease and the disease of Chagas, even in the chronical stage.

Megazol is an alternative drug for the treatment of the Chagas disease and is included in the list of experimentally assayed drug after 1992/1993 against *T. cruzi* presented by investigators of the Instituto Oswaldo Cruz-Fiocruz of Brazil [7].

The objective of this work is to perform a detailed calculation of the molecular structure of megazol (2-amino-5-(1-methyl-5-nitroimidazole-2-yl)-1,3,4-thiadiazole), as well as to predict its infrared (IR) and ultraviolet (UV–vis) spectra, by using a new model chemistry within Density Functional Theory (DFT) [8] specially tailored to study heterocyclic systems and to validate the calculated results by comparison with the experimental available data for this molecule. Megazol will be the first of several analogous molecules to be studied in this way [9].

2. Theory and computational details

All computational studies were performed with the GAUSSIAN 03W [10] series of programs with density functional methods as implemented in the computational package. The equilibrium geometries of the molecules were determined by means of the gradient technique. The force constants and vibrational frequencies were determined by the FREQ calculations on the stationary points obtained after the optimization to check if there were true minima. The basis sets used in this work were 3-21G* and 6-31G(d,p) (for their explanation see Ref. [11]). Additionally, the CBSB2**, CBSB7, CBSB4 and CBSB1 basis sets were used. The CBSB7 has the form 6-311G(2d,d,p) and has been developed by Petersson and co-workers [12] as a part of the Complete Basis Set CBS-QB3 energy compound method. It was designed for obtaining the best results for optimization of geometries and they found that this basis set was necessary for obtaining acceptable results on the full G2 test set [13]. The CBSB2** basis set is esentially the same as 6-31G(d,p), but with the exponents for the *d* functions taken from the 6-311G basis set, and is also called 6-31G†† [11,14,15]. The CBSB4 basis set is identical to 6-31 + G(d,p) on H–Si and to 6-31 + G(df,p) on P, S and Cl. The CBSB1 basis set is identical to 6-31 + g(d,p) on H and He, to 6-311 + G(2df) on Li–Ne, and to 6-311 + g(3d2f) on Na–Ar. The CBSB2**, CBSB4 and CBSB1 basis sets are also part of the CBS-QB3 method [12].

Density functionals used in this study are a modification of those incorporated in the GAUSSIAN 03W computational package [10]. To this end, we have defined a new model chemistry that we have found empirically that works well with heterocyclic molecules. The implementation is a slight different version of the PBE0 hybrid density functional [16]. In the PBE0 (or PBE1PBE one-parameter) functional, there is only one coefficient which is theoretically adjusted to 0.25, reflecting the mix of Hartree–Fock or exact exchange and the DFT exchange which is represented by the PBE density functional [17]. The correlation part is also represented by the PBE correlation functional [17] with coefficient equal to one. Our proposed density functional model, which we have called PBE *g*, is the same as PBE0, but with the mixing coefficient *g* which adopts different values depending on the number of heteroatoms in the studied molecule, or, in turn, of its molecular structure. The value of *g* can be calculated through the following empirical formula: $g = 0.02 + 0.14 \times \mathrm{FHA} \times \mathrm{FV} + 0.03 \times \mathrm{AHA}$, where FHA is the first heteroatom chosen as the one less electronegative, FV is valence factor which represents the oxidation state of the FHA (i.e. one for the first oxidation state, two for the second, and so on), and AHA are the number of additional heteroatoms besides the FHA. For example, for the 1,2,5-thiadiazole molecule, the *g* coefficient will be $g = 0.02 + 0.14 \times 1 + 0.03 \times 2 = 0.22$, thus implying that 22% of HF exchange will be mixed with 78% of PBE exchange. Similarly, for 1,2,5-thiadiazole 1,1-dioxide, the *g* coefficient will be $g = 0.02 + 0.14 \times 3 + 0.03 \times 2 = 0.50$, reflecting 50% of HF exchange and 50% of PBE exchange. For those cases in which the molecule has several heterocyclic rings, we will calculate the coefficient *g* by averaging the coefficient for each heterocycle. Thus, in our case for the molecule of megazol, where we have two heterocyclic rings, one with $g = 0.22$ and the other with $g = 0.19$, the value of the mixing coefficient *g* for the entire molecule will be $g = 0.205$, implying the mix of 20.5% of HF exchange and 79.5% of PBE exchange.

In order to define our model chemistry, we have to couple the proposed density functional with one or more basis sets.

Table 1
Interatomic bond distances (Å) for megazol

Bond distances	PBE0/3-21G*	PBE0/CBSB2**	CHIH (s)[a]	CHIH (m)[a]	CHIH (l)[a]	Exp.[b]
C(1)–S(3)	1.750	1.753	1.754	1.759	1.753	1.727
C(1)–N(4)	1.308	1.299	1.311	1.302	1.299	1.293
C(1)–C(7)	1.430	1.450	1.431	1.449	1.447	1.465
C(2)–S(3)	1.748	1.743	1.751	1.747	1.740	1.722
C(2)–N(5)	1.331	1.312	1.334	1.317	1.314	1.320
C(2)–N(16)	1.346	1.360	1.348	1.349	1.349	1.345
N(4)–N(5)	1.402	1.345	1.404	1.346	1.345	1.374
C(6)–C(8)	1.383	1.380	1.385	1.382	1.378	1.348
C(6)–N(11)	1.364	1.345	1.366	1.346	1.344	1.348
C(7)–N(10)	1.365	1.360	1.368	1.362	1.360	1.346
C(7)–N(11)	1.350	1.333	1.354	1.336	1.333	1.329
C(8)–N(10)	1.386	1.378	1.388	1.380	1.380	1.390
C(8)–N(19)	1.398	1.420	1.400	1.422	1.423	1.418
N(10)–C(12)	1.475	1.460	1.477	1.461	1.462	1.469
N(19)–O(20)	1.282	1.221	1.287	1.226	1.225	1.227
N(19)–O(21)	1.278	1.217	1.282	1.282	1.220	1.225

[a] For an explanation of symbols, see text.
[b] X-ray crystallographic results [23].

In this way, the new model chemistry that we have called CHIH-DFT can be represented by the expression CHIH = PBEg/basis sets. There are three different CHIH-DFT model chemistries: CHIH (small) that uses the 3-21G* basis set for geometry optimizations and frequency calculations, and the CBSB2** basis set for the calculation of the electronic properties; CHIH (medium) that uses the CBSB2** basis set for geometry optimizations and frequency calculations and the CBSB4 basis set for the electronic properties; and *CHIH*(*large*) the which uses the CBSB7 basis set for geometry optimizations and frequency calculations and the CBSB1 basis set for the electronic properties. In this way, by considering a compromise between accuracy and CPU time, the CHIH (large) will be used for small heterocyclic molecules, the CHIH (medium) for medium-sized molecules and the CHIH (small) for large heterocyclic molecules.

The calculation of the ultraviolet spectrum (UV–vis) of megazol has been performed by solving the time dependent Kohn–Sham equations according to the method implemented in GAUSSIAN 03W [18–21]. The equations have been solved for 10 excited states.

The IR and ultraviolet (UV–vis) spectra were calculated and visualized using the Swizard program [22].

3. Results and discussion

The results for the equilibrium conformation of the neutral molecules of megazol calculated with the CHIH (large), CHIH (medium) and CHIH (small) together with the PBE0 results with two different basis sets are reported in Table 1, and the representation of the molecular structure of this molecule showing the atomic labelling and numbering are presented in Fig. 1. The results are compared with the experimental X-ray crystallography determination of the molecular structure of megazol [23]. The agreement is generally good: the standard error of the differences between the experimental and the calculated bond lengths and bond angles being very low. Although not shown in the tables, an analysis of the torsional angles reveals that both heterocycles are planar. The standard deviation for the comparison of the calculated versus the experimental results are 0.01556 for the CHIH (large) model, 0.01728 for the CHIH (medium) model, 0.03068 for the CHIH (small) model, 0.01637 for PBE0/CBSB2** and 0.02839 for PBE0/3-21G*, in all cases for the interatomic bond distances. For the interatomic bond angles, the standard deviations are 0.948 for the CHIH (large) model, 0.937 for CHIH (medium), 0.936 for CHIH (small), 0.899 for PBE0/CBSB2** and 0.926 for PBE0/3-21G*. It should be noticed that although we have considered the CHIH (large) model because the studied molecules are small, the CHIH (medium) model can give almost the same results. The only noticeable difference is with the S(3)–C(1) and S(3)–C(N)

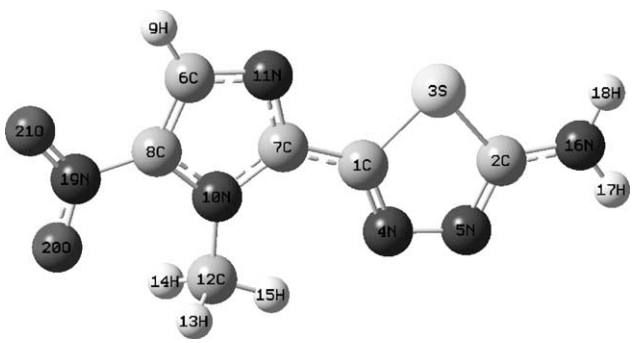

Fig. 1. Molecular structure of megazol calculated with the CHIH (large) model chemistry.

Table 2
Interatomic bond angles (°) for megazol

Bond angles	PBE0/3-21G*	PBE0/CBSB2**	CHIH (s)[a]	CHIH (m)[a]	CHIH (l)[a]	Exp.[b]
S(3)–C(1)–N(4)	115.0	113.6	115.1	113.6	113.4	115.5
S(3)–C(1)–C(7)	116.9	118.5	116.8	118.4	118.4	117.4
N(4)–C(1)–C(7)	128.1	127.9	128.1	128.0	128.2	127.1
S(3)–C(2)–N(5)	115.4	114.6	115.4	114.7	114.5	114.6
S(3)–C(2)–N(16)	122.9	122.8	122.9	123.0	123.1	122.5
N(5)–C(2)–N(16)	121.8	122.5	121.7	122.3	122.4	122.9
C(1)–S(3)–C(2)	85.9	85.5	85.9	85.4	85.6	86.0
C(1)–N(4)–N(5)	112.9	114.2	112.9	114.4	114.4	112.1
C(2)–N(5)–N(4)	110.8	112.1	110.8	112.0	112.0	111.9
C(8)–C(6)–N(11)	109.3	109.5	109.4	109.6	109.5	110.1
C(1)–C(7)–N(10)	127.2	126.9	127.1	126.9	127.1	127.1
C(1)–C(7)–N(11)	120.9	120.4	120.9	120.4	120.4	119.7
N(10)–C(7)–N(11)	112.0	112.8	112.0	112.7	112.6	113.2
C(6)–C(8)–N(10)	107.5	107.5	107.5	107.4	107.4	107.7
C(6)–C(8)–N(19)	127.9	127.4	127.9	127.5	127.5	127.3
N(10)–C(8)–N(19)	124.6	125.1	124.7	125.1	125.1	125.0
C(7)–N(10)–C(8)	105.4	104.6	105.4	104.6	104.7	104.0
C(7)–N(10)–C(12)	126.4	127.5	126.4	127.4	127.3	126.8
C(8)–N(10)–C(12)	128.2	127.9	128.2	127.9	128.0	129.2
C(6)–N(11)–C(7)	105.8	105.7	105.7	105.6	105.9	105.0
C(8)–N(19)–O(20)	118.0	118.4	118.0	118.5	118.4	120.1
C(8)–N(19)–O(21)	115.9	116.2	115.9	116.2	116.3	116.6

[a] For an explanation of symbols, see text.
[b] X-ray crystallographic results [23].

distances, which are a bit longer with the CHIH (medium) model chemistry. It is concluded that the CHIH (medium), which is faster, could also be used to study the molecular structures of the systems considered in this work Table 2.

The molecular dipole moment is perhaps the simplest experimental measure of charge density in a molecule. The accuracy of the overall distribution of electrons in a molecule is hard to quantify, since it involves all the multipoles. From the present calculations, the total energy and the total dipole moment of the ground state with the CHIH (large) model chemistry are -1108.607 a.u. and 6.5566 Debye for the megazol molecule.

The shapes of the total electron density for the mogazol molecule is presented in Fig. 2. The calculated molecular volume is 139.232 $cm^3\ mol^{-1}$.

The IR for the megazol molecule calculated with the CHIH (large) model chemistry is displayed in Fig. 3. To the best of our knowledge, the experimental spectrum has not been reported in the literature. The principal peaks are as follows:

- 858 cm^{-1}: $-NO_2$ scissoring
- 1213 cm^{-1}: N(4)–N(5) stretching
- 1257 cm^{-1}: N(10)–C(12) stretching and imidazole ring deformation
- 1337 cm^{-1}: C(6)–N(11) stretching
- 1428 cm^{-1}: C(8)–N(10) and C(1)–N(4) stretching
- 1537 cm^{-1}: C(2)–N(16) stretching
- 1643 cm^{-1}: $-NH_2$ scissoring
- 3639 cm^{-1}: $-NH_2$ symmetric stretching
- 3778 cm^{-1}: $-NH_2$ asymmetric stretching

The ultraviolet spectra (UV–vis) of the megazol molecule calculated with the CHIH (large) model chemistry is displayed in Fig. 4. The wavelength belonging to the HOMO–LUMO + 1 transition will take place at 291.6 nm, while the HOMO–LUMO transition and thus the maximum wavelength will take place at 389.1 nm. As the HOMO–LUMO transition takes place in the ultraviolet region, close to but out of the visible zone, it can be predicted that this molecule will be colorless or slightly colored.

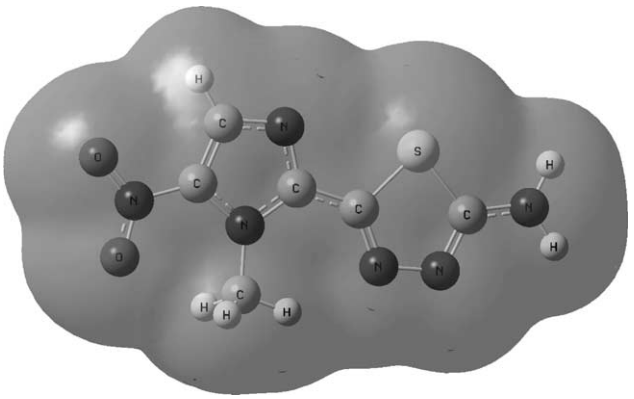

Fig. 2. Total electron density of the megazol molecule calculated with the CHIH (large) model chemistry.

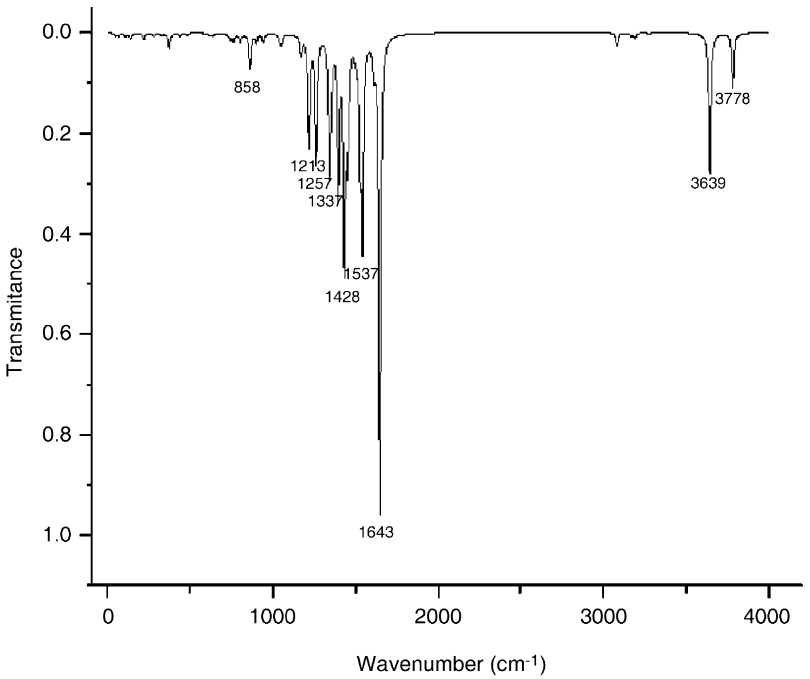

Fig. 3. Infrared spectrum (IR) of the megazol molecule calculated with the CHIH (large) model chemistry.

4. Conclusions

In this work, a new model chemistry within DFT (the CHIH chemistry model) has been presented and the methodology has been applied to the study of a molecule which is a potentially antiparasitic drug. The molecular structure for megazol 2-amino-5-(1-methyl-5-nitroimidazole-2-yl)-1,3,4-thiadiazole) has been determined by using the CHIH (large) model chemistry. A comparison has been made with the results from the experimental X-ray crystallography for this molecule. The agreement is generally very good. It is worth to note that the results obtained with the (faster) CHIH (medium) model chemistry are very similar, thus implying that equally accurate results could be obtained in a reasonable time in the study of heterocycles.

The shape of the total electronic density of this molecule was displayed as well as some electronic parameters like the total energy and the dipole moment. The calculated molecular volume for the molecule has been also reported.

The infrared (IR) and ultraviolet (UV–vis) spectra for megazol have been predicted according to the CHIH (large) model chemistry, and an assignment of the principal peaks have been achieved. The results were compared to take note of similarities and differences. The shape of the UV–vis spectra and the maximum absorption wavelength belonging to this molecule have been presented.

The CHIH model chemistry appears to be a useful tool for the study of the molecular structure and electronic properties of heterocycles, and further applications to several molecular systems are being pursued in our laboratory.

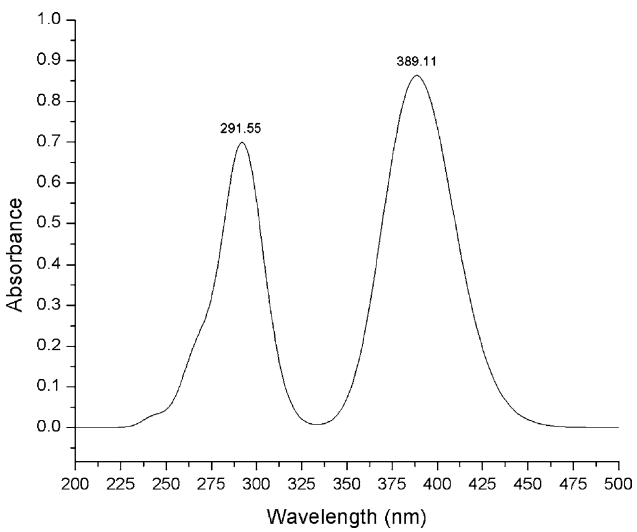

Fig. 4. Ultraviolet spectrum (UV–vis) of the megazol molecule calculated with the CHIH (large) model chemistry.

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