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CBS-QB3 calculation of quantum chemical molecular descriptors of isomeric thiadiazoles

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Abstract

The results of the calculation of several molecular descriptors of isomeric thiadiazoles through the CBS-QB3 model chemistry are presented in this work. The results could be useful in quantitative structure–activity relationship (QSAR) or quantitative structure–property relationship (QSPR) studies of derivatives of the nitrogen-containing analogs of thiophene.

Keywords: CBS-QB3; Thiadiazoles; Electronegativity; Hardness; Electrophilicity; Polarizability

1. Introduction

A number of useful molecular descriptors related to the physical properties and chemical reactivity of molecules can be derived on the basis of the information available within the molecular orbital formalism [1]. These quantum chemical derived molecular descriptors are useful because they help to characterize the electronic environment of a molecule. Popular qualitative chemical concepts such as electronegativity [2] and hardness [3] have been widely used in understanding various aspects of chemical reactivity [4]. A rigorous theoretical basis for these concepts has been provided by density functional theory (DFT) [2,4]. Many other calculated physicochemical properties can be used as molecular descriptors, and they include the heat of formation, ionization potential, electron affinity, HOMO, LUMO and their difference, dipole moment and average polarizability [5].

Organic heterocycles are systems of growing interest in materials science in view of the potential technological applications in fields such as electronics, photonics, sensors or corrosion protection [6,7]. Several potentially conducting polymers, optically nonlinear polymers and biomaterials contain heterocyclic structures [8]. Thiadiazoles, the nitrogen containing analogs of thiophene, and their derivatives are the structural basis of some of these polymeric materials [9,10].

Quantitative structure property relationships (QSPR) and, when applied to biological activity, quantitative structure activity relationships (QSAR) are methods for determining properties due to very sophisticated mechanisms purely by a curve fit of that property to aspects of the molecular structure. This allows a property to be predicted independent of having a complete knowledge of its origin [11]. Thus, structure–activity relationships (SARs) are widely used in the pharmaceutical industry to understand how the various features of biologically active molecules contribute to their activity [12]. Thiadiazoles and their derivatives have applications in medicinal chemistry as pharmacophores. Some examples are the use of 1,2,4-thiadiazole derivatives as novel cathepsin inhibitors [13] and in the design of inhibitors targeting the cysteine residues of proteins [14]. A recent review has been published on therapeutic applications of 1,2,4-thiadiazole heterocycles [15]. QSAR studies have been attempted for thiadiazoles. A recent example involves the exploration of QSAR of thiadiazole derivatives as human adenosine $A_1$and A_3receptor antagonists [16,17]. Another examples include QSAR studies of thiadiazole derivatives as nonsteroidal anti-inflammatory drugs [18] and as anti-tuberculosis compounds [19].

The complete basis set (CBS) theories are model chemistries that arose from the observation that certain levels of theory with certain basis sets tended always to give results with systematic

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errors for the equilibrium geometries of main group compounds. The procedure for obtaining these results consist of running a series of calculations with different basis sets and levels of theory and then correcting the resulting energies for systematic errors so they are closer to the exact energy than with any of the individual methods [11].

As a further step in the study of the chemical reactivity of the thiadiazoles, some results are presented in this paper on the calculation of such molecular descriptors for the four unsubstituted isomeric thiadiazole molecules by using the CBS-QB3 model chemistry [20,21].

2. Theory and computational details

All computational studies were performed with the Gaussian 03W [22] series of programs with ab initio and 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 CBS-QB3 model chemistry [20,21] was employed for the calculation of the molecular structures and for the determination of all the molecular descriptors of the four unsubstituted thiadiazoles. For a complete description of the method, look at Refs. [20,21,23].

3. Results and discussion

The results of the calculation of the molecular structure of 1,2,5-thiadiazole (25T), 1,3,4-thiadiazole (34T), 1,2,3-thiadiazole (23T) and 1,2,4-thiadiazole (24T) have been already presented earlier [24]. As the first step in the CBS-QB3 model is an optimization at the B3LYP/CBSB7 level of theory, the values of bond distances and angles will be the same as those calculated in that paper and will be not be repeated here. The interested reader is referred to the original work [24]. They are related to the molecular structures displayed in Fig. 1 a–d.

In Table 1, we present the values of several molecular descriptors for the four thiadiazoles obtained with the CBS-QB3 model chemistry. They are the total energy at 0 K, the total energy at 298 K, the enthalpy at 298 K, the free energy at 298 K, the entropy at 298 K, the HOMO energy, the LUMO energy, the vertical ionization potential and electron affinity calculated by two methods, the dipole moment, the average polarizability, and those parameters derived from conceptual density functional theory, as the electronegativity, the total hardness and the global electrophilicity, the three of them also established by the application of two different methods.

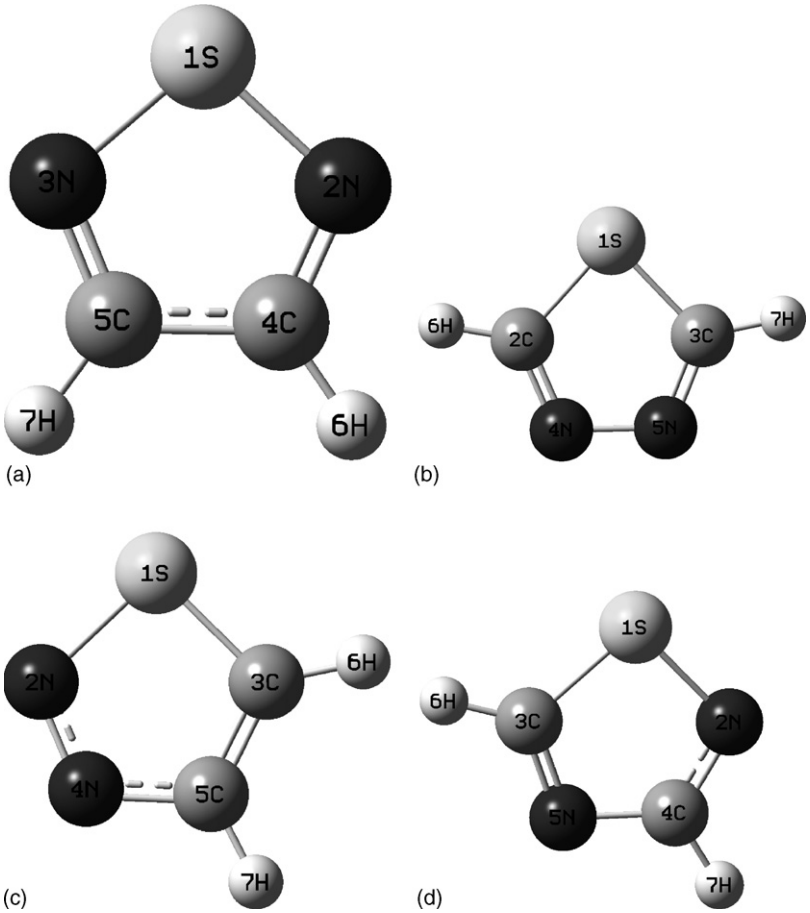

Fig. 1. Molecular structure of (a) 1,2,5-thiadiazole (25T), (b) 1,3,4-thiadiazole (34T), (c) 1,2,3-thiadiazole (23T) and (d) 1,2,4-thiadiazole (24T), calculated with the CBS-QB3 model chemistry.

Table 1
Molecular descriptors for 1,2,5-thiadiazole (25T), 1,3,4-thiadiazole (34T), 1,2,3-thiadiazole (23T) and 1,2,4-thiadiazole (24T) molecules, calculated with the CBS-QB3 model chemistry

Molecular descriptor[a]	25T	34T	23T	24T
Total energy$_{0K}$(a.u.)	−584.362	−584.341	−584.335	−584.366
Total energy$_{298K}$(a.u.)	−584.358	−584.337	−584.331	−584.362
Enthalpy$_{298K}$ (a.u.)	−584.357	−584.336	−584.330	−584.361
Free energy$_{298K}$ (a.u.)	−584.388	−584.367	−584.362	−584.393
Entropy$_{298K}$ (cal/mol K)	65.2	65.2	67.3	67.3
HOMO energy (eV)	−10.068	−10.775	−10.202	−10.421
LUMO energy (eV)	1.007	1.088	0.927	1.061
Ionization potential$_{\Delta}$ (eV)	10.134	9.904	9.823	10.204
Ionization potential$_{HOMO}$ (eV)	10.068	10.775	10.202	10.421
Electron affinity$_{\Delta}$ (eV)	0.027	0.381	0.381	0.218
Electron affinity$_{LUMO}$ (eV)	1.007	1.088	0.927	1.061
Dipole moment (Debye)	1.525	3.239	3.515	1.523
Polarizability (a.u.)	45.185	45.870	46.426	45.113
Electronegativity$_{\Delta}$ (eV)	5.067	5.143	5.102	5.211
Electronegativity$_{Koopmans}$ (eV)	4.538	5.932	5.565	5.741
Total hardness$_{\Delta}$ (eV)	5.054	4.762	4.721	4.993
Total hardness$_{Koopmans}$ (eV)	4.531	4.844	4.638	4.572
Global electrophilicity$_{\Delta}$ (eV)	2.540	2.777	2.757	2.720
Global electrophilicity$_{Koopmans}$ (eV)	3.384	3.632	3.339	3.604

[a] See text for explanation of symbols.

The total energies at 0 and 298 K (in a.u.), the enthalpy at 298 K (in a.u.) and the free energy at 298 K (in a.u.) can be extracted from the output of the calculation, while the entropy at 298 K (in cal/mol K) has been determined from those results using standard formulas.

The HOMO and LUMO energies (in eV) are also extracted from the output file. The vertical ionization potential is calculated in two ways: (a) the ionization potential Δ (in eV), and (b) the ionization potential HOMO (in eV). The last result comes from Koopmans theorem, namely $I_{HOMO} = -E_{HOMO}$, while the first is determined as the difference of energy between the positively charged and the neutral molecule, both at the geometry of the neutral species. The same idea applies for the electron affinity calculation: (a) the electron affinity Δ (in eV) is the difference between the neutral molecule and the negatively charged species, and (b) the electron affinity LUMO (in eV) is obtained through Koopmans theorem as $A_{LUMO} = E_{LUMO}$. The ionization potential calculated for the thiadiazoles by the two methods are similar, while the A_{LUMO} are two to four times larger than the A_{HOMO}.

The dipole moment and the polarizability are common electrostatic descriptors used in QSAR and QSPR [11]. Both the dipole moment (in Debye) and the polarizability (in a.u.) result from the outcome of the calculation. As the dipole moments that arise from a CBS-QB3 calculation are essentially based on a frequency calculation at the B3LYP/CBSB7 level of theory, the results are the same as those presented previously [26], and are included in Table 1 for the sake of completeness.

Finally, we present in Table 1 the results for those concepts coming from density functional theory [2], namely the electronegativity (in eV), the chemical hardness (in eV) and the global electrophilicity (in eV) [25]. The electronegativity Δ or χ_{Δ}, the electronegativity$_{Koopmans}$or $\chi_{Koopmans}$, the total hardness Δ or η_{Δ}, the total hardness$_{Koopmans}$ or $\eta_{Koopmans}$, the global electrophilicity Δ or ω_{Δ} and the global electrophilicity$_{Koopmans}$ or $\omega_{Koopmans}$, have been calculated as follows:

$$\chi_{\Delta} = \frac{I_{\Delta} + A_{\Delta}}{2} \tag{1}$$

$$\chi_{Koopmans} = \frac{E_{HOMO} + E_{LUMO}}{2} \tag{2}$$

$$\eta_{\Delta} = \frac{I_{\Delta} - A_{\Delta}}{2} \tag{3}$$

$$\eta_{Koopmans} = \frac{E_{HOMO} - E_{LUMO}}{2} \tag{4}$$

$$\omega_{\Delta} = \frac{\chi_{\Delta}^2}{2\eta_{\Delta}} \tag{5}$$

$$\omega_{Koopmans} = \frac{\chi_{Koopmans}^2}{2\eta_{Koopmans}} \tag{6}$$

The results for the electronegativity and total hardness are similar in both type of calculations, but for the global electrophilicity there are marked differences between the Δ and Koopmans results. This considerations should be taken into account when these molecular descriptors are incorporated in a QSAR or QSPR study of thiadiazoles and their derivatives.

4. Conclusions

In this work, the results of the calculation of several molecular descriptors of isomeric thiadiazoles through the CBS-QB3 model chemistry have been presented. The results could be useful in quantitative structure–activity relationship (QSAR) or quantitative structure–property relationship (QSPR) studies of derivatives of the nitrogen-containing analogs of thiophene, specially for applications in medicinal chemistry.

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