

Computational nanochemistry study of the molecular structure and properties of ethambutol

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Abstract The M06 family of density functionals was employed to calculate the molecular structure and properties of the ethambutol molecule. Besides determination of molecular structures, UV–vis spectra were computed using TD-DFT in the presence of a solvent and the results compared with available experimental data. The chemical reactivity descriptors were calculated through conceptual DFT. The active sites for nucleophilic and electrophilic attacks have been chosen by relating them to Fukui function indices. A

comparison between the descriptors calculated through vertical energy values and those arising from Koopmans' theorem approximation were performed in order to check the validity of the latter procedure.

Keywords Ethambutol · DFT · M06 density functionals · TD-DFT · Conceptual DFT · Molecular structure · Molecular properties

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Introduction

Isoniazid, rifampin, pyrazinamide, and ethambutol (EMB) are the front-line agents recommended by World Health Organization (WHO) for the treatment of tuberculosis (TB). EMB is a simple diamine molecule that was synthesized by reacting 1,2-dihaloethane with chirally pure (S)-2-amino 1-butanol, and is primarily a bacteriostatic antituberculosis agent. EMB targets the arabinosyl transferases responsible for arabinogalactan biosynthesis—a key component of the unique mycobacterial cell wall. Despite modest antituberculosis activity, EMB is used in combination with other front-line antituberculosis agents mainly owing to its synergy with other drugs and low toxicity [1].

Nanoscale chemistry (nanochemistry) is an exciting area of chemical science and technology where the physical and chemical properties of the considered systems depend on their sizes and shapes [2, 3]. The size can range from a single molecule of about 1–2 nm to many thousands of molecules with almost macroscopic properties. Indeed, chemical properties at the nanoscale differ from those at the macroscopic scale. We use the term computational nanochemistry to describe the process of computational calculation of the properties of systems at the nanoscale, as in this case, for the EMB molecule.

Density functional theory (DFT) [4], especially since the work of Kohn and Sham [5], is based entirely on the exchange and correlation density functional. Using hybrid meta-generalized gradient approximation (GGA) has made it possible to calculate binding energies with chemical precision, i.e., such that the predictions made are comparable to experimental results. Included in this last family are the functionals developed at the University of Minnesota by Truhlar et al., known as M05, M05-2X, M06, M06L, M06-2X, and M06-HF [6–8]. Except for the local functional M06L, these functionals are hybrid meta-GGAs; they incorporate varying degrees of Hartree-Fock (HF) exchange, which were determined by adjusting their predictions to match the experimental values for several properties. However, because these functionals are approximations of the unknown exact energy density functional, the process of determining which functional should be used for a given system and the properties predicted by it requires one to perform calculations for each system and property and then compare them with experimental results [9].

In computational nanochemistry and molecular modeling, research is conducted using what is called a “model chemistry”. A model chemistry combines a density functional with a basis set, and, when a solvent is included, the parameters for its simulation must also be considered. The aim of this work was to test the performance of the M06 family of density functionals [6–8] for the prediction of the infrared (IR) and ultraviolet-visible (UV-vis) spectra, and the chemical reactivity descriptors that arise from conceptual density functional theory (DFT) [4, 10] for the EMB molecule. A comparison between the descriptors calculated through vertical energy values and those arising from the Koopmans’ theorem approximation will be performed in order to check for the validity of the last procedure within DFT. The results will be compared with the empirical evidence available in the literature.

Computational details

All computational studies were performed with the Gaussian 09 [11] 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 computing analytical frequencies on the stationary points obtained after optimization to check for true minima. The basis set used in this work was MIDIY, which is the same basis set as MIDI! with a polarization function added to the hydrogen atoms. The MIDI! basis is a small double-zeta basis with polarization functions on N, F, Si, Cl, Br, and I [12–17].

To calculate the molecular structure and properties of the studied systems, we chose the hybrid meta-GGA density functionals M06, M06L, M06-2X and M06HF [6], which consistently provide satisfactory results for several structural and thermodynamic properties [6–8]. Solvation energies were computed by the Integral Equation Formalism-Polarizable Continuum Model (IEF-PCM) [18], including the UAKS model and water as a solvent.

Calculation of the ultraviolet (UV-vis) spectra of the studied systems was performed by solving the time-dependent DFT (TD-DFT) equations according to the method implemented in Gaussian 09 [14, 19–21]. The equations were solved for ten excited states.

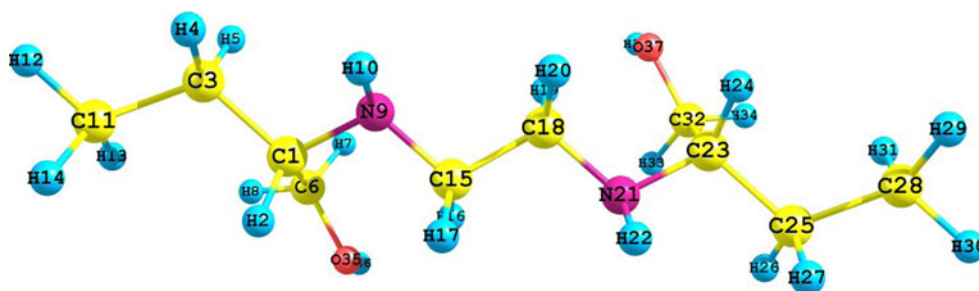
IR and UV-vis spectra were calculated using the Swizard program [22, 23] and visualized with Gabedit [24]. In all cases the displayed spectra show the calculated frequencies and absorption or emission wavelengths.

The highest-occupied molecular orbital (HOMO) and lowest-unoccupied molecular orbital (LUMO) were extracted from the calculations and visualized using the Chemcraft Program Version 1.6 [25].

Results and discussion

The molecular structure of EMB was pre-optimized by starting with the readily available PDB structure, and finding the most stable conformer by means of the Conformers module of Materials Studio through a random sampling with molecular mechanics techniques and consideration of all the torsional angles. The structure of the resulting conformer was then optimized with the M06, M06L, M06-2X and M06-HF density functionals in conjunction with the MIDIY and DGDZVP basis sets. As stated in the “Computational details”, these optimizations, as well all the remaining calculations, were performed by resorting to

Fig. 1 Optimized molecular structure of the ethambutol (EMB) molecule



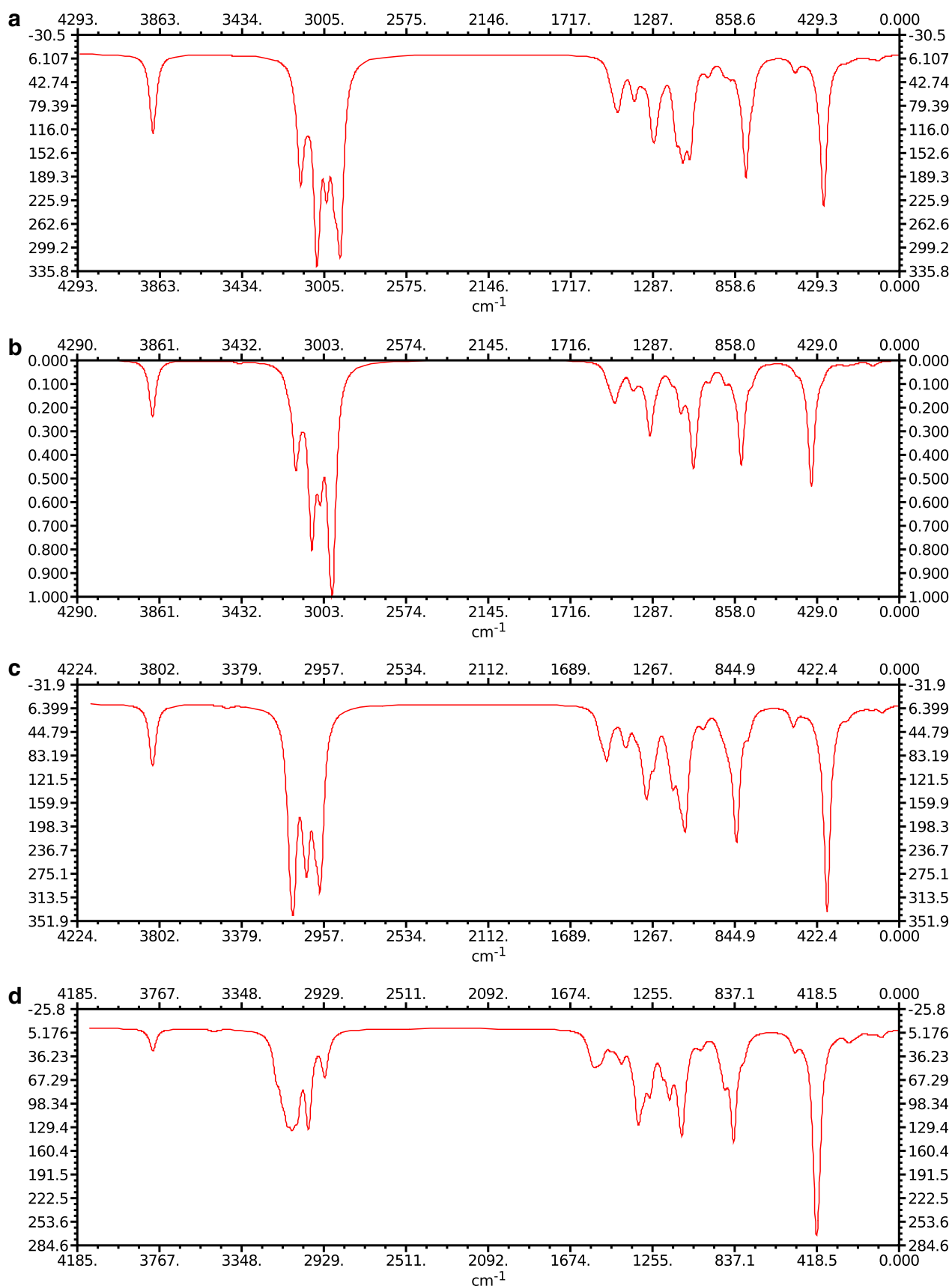


Fig. 2 Infra-red (IR) spectra of the EMB molecule calculated with the M06, M06L, M06-2X and M06-HF density functionals and the MIDIY basis set

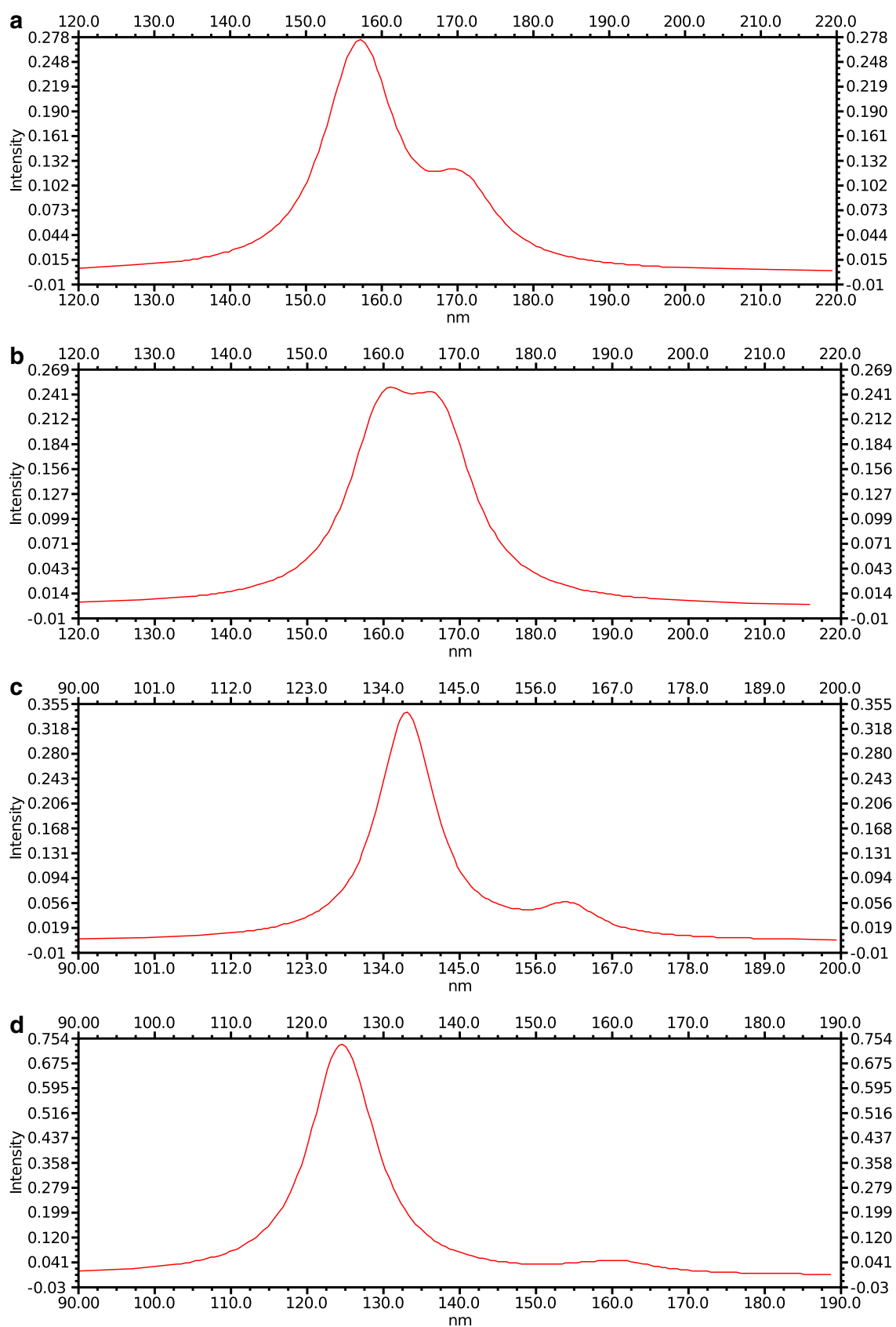


Fig. 3 Absorption spectra of the ethambutol molecule calculated with the M06, M06L, M06-2X and M06-HF density functionals and the MIDIY basis set

the IEF-PCM [18], including the UAKS model and water as a solvent.

The optimized molecular structure of the EMB molecule (with the M06 density functional) is shown in Fig. 1, while the bond distances (in Å) and the bond angles (in degrees) calculated with the M06, M06L, M06-2X and M06-HF functionals in conjunction with the MIDIY basis set are presented in Tables A1 and A2 of the Supplementary Material, respectively. It is not the objective of this study to analyze in detail the results predicted by the different functionals for the optimized structure of the EMB molecule. However, a comparison of the results by superimposing the structures revealed no important differences between them. This is not surprising because modern density functionals are able to predict molecular structures with a good degree of accuracy and using low-cost basis sets.

The IR spectra of the EMB molecule calculated with the M06, M06L, M06-2X and M06-HF density functionals and the MIDIY basis set are shown in Fig. 2. None of the IR spectra display an imaginary frequency, meaning that the structures predicted by all the functionals are a minimum on the potential energy surface. The experimental IR spectrum of EMB [26] shows a sharp peak at 1,055 cm⁻¹ and a broad peak at 3,200–3,400 cm⁻¹ related to the primary alcohol group. There is also a band at 1,620 cm⁻¹ due to N–H bending. Although they are present in the calculated spectra, there is a shift that indicates the need for a scaling factor different to that used for these model chemistries.

The absorption UV–vis spectra of EMB calculated with the M06, M06L, M06-2X and M06-HF density functionals and the MIDIY basis set are presented in Fig. 3. The results of the displayed absorption spectra and the associated orbital transition assignments help explain why it is not possible to detect ethambutol directly by colorimetry and why it is necessary to complex it with nickel or copper or to use an additional reagent such as ninhydrin, which is used to detect ammonia or primary and secondary amines. Indeed, this happens because the ethambutol molecule does not have a chromophore group.

The transition assignments for the TD-DFT calculation of the UV–vis spectra of EMB with the M06, M06L, M06-2X and M06-HF density functionals and the MIDIY basis set are presented in Tables A3, A4, A5 and A6 of the Supplementary Material.

Within the conceptual framework of DFT [4, 10], the chemical potential μ , which measures the escaping tendency of electron from equilibrium, is defined as:

$$\mu = \left(\frac{\partial E}{\partial N} \right)_{v(\vec{r})} = -\chi \quad (1)$$

where χ is the electronegativity.

The global hardness η can be seen as the resistance to charge transfer:

$$\eta = \frac{1}{2} \left(\frac{\partial^2 E}{\partial N^2} \right)_{v(\vec{r})} \quad (2)$$

Using a finite difference approximation and Koopmans' theorem [14–17], the above expressions can be written as:

$$\mu \approx -\frac{1}{2}(I + A) \approx \frac{1}{2}(\varepsilon_L + \varepsilon_H) \quad (3)$$

$$\eta \approx \frac{1}{2}(I - A) \approx \frac{1}{2}(\varepsilon_L - \varepsilon_H) \quad (4)$$

where ε_H and ε_L are the energies of the HOMO and LUMO, respectively. However, within the context of DFT, the above inequalities are justified in light of the work of Perdew and Levy [27], who commented on the significance of the highest occupied Kohn–Sham eigenvalue, and proved the ionization potential theorems for the exact Kohn–Sham DFT of many-electron systems.

The electrophilicity index ω represents the stabilization energy of systems saturated by electrons coming from the surroundings:

$$\omega = \frac{\mu^2}{2\eta} \approx \frac{(I + A)^2}{4(I - A)} \approx \frac{(\varepsilon_L + \varepsilon_H)^2}{4(\varepsilon_L - \varepsilon_H)} \quad (5)$$

The validity of the Koopmans' theorem within the DFT approximation is controversial. However, it has been shown [28] that although KS orbitals may differ in shape and

Table 1 Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ , total hardness η , and global electrophilicity ω of the ethambutol (EMB) molecule calculated with the M06, M06L, M06-2X and M06-HF density functionals and the MIDIY basis set. The upper part of the table shows the results derived assuming the validity of Koopmans' theorem and the lower part shows the results derived from the calculated vertical I and A

Property	M06	M06L	M06-2X	M06-HF
HOMO	6.018	4.874	7.970	10.113
LUMO	2.687	2.517	3.390	4.293
χ	4.3525	3.6955	5.6800	7.2030
η	1.6655	1.1785	2.2900	2.9100
ω	2.8437	2.8971	3.5221	4.4573
I	6.025	5.555	6.643	7.253
A	2.299	2.020	2.428	2.698
χ	4.1620	3.7875	4.4455	4.9755
η	1.8630	1.7675	2.1075	2.2775
ω	2.3245	2.0290	2.3443	2.7174

Table 2 Electrophilic f^- and nucleophilic f^+ condensed Fukui functions and Δf over the atoms of the EMB molecule calculated with the M06, M06L, M06-2X and M06-HF density functionals and the MIDIY basis set. The actual values have been multiplied by 100 for easier comparison

Atom	M06			M06L			M06-2X			M06-HF		
	f^+	f^-	Δf	f^+	f^-	Δf	f^+	f^-	Δf	f^+	f^-	Δf
1C	1.14	-0.50	-1.64	1.16	-0.37	-1.53	1.52	-0.64	-2.16	2.06	-0.51	-2.56
2H	3.02	4.01	0.99	2.84	6.27	3.34	3.32	4.46	1.14	3.27	2.48	-0.79
3C	0.06	-0.98	-1.04	0.06	-1.30	-1.36	0.06	-0.97	-1.03	0.06	-0.41	-0.47
4H	0.00	7.83	7.83	0.00	9.18	9.18	0.00	7.35	7.35	0.01	3.91	3.90
5H	0.13	3.11	2.98	0.12	2.61	2.49	0.15	2.87	2.72	0.16	2.10	1.94
6C	0.89	-0.40	-1.29	0.76	2.96	2.20	0.91	-0.62	-1.53	1.18	-2.57	-3.75
7H	0.26	1.78	1.52	0.21	0.12	-0.19	0.33	1.96	1.63	0.44	5.95	5.51
8H	0.47	5.76	5.29	0.49	2.87	2.38	0.30	5.58	5.28	0.19	6.98	6.79
9 N	36.42	0.98	-35.45	36.40	0.93	-35.47	35.83	1.04	-34.79	33.41	0.71	-32.70
10H	0.95	10.16	9.91	1.03	8.40	7.37	0.95	10.87	9.92	0.82	8.74	7.92
11C	0.05	-2.11	-2.16	0.04	-1.60	-1.64	0.05	-2.01	-2.06	0.07	-1.29	-1.36
12H	0.02	4.13	4.11	0.02	3.44	3.42	0.02	3.54	3.52	0.04	2.12	2.08
13H	0.00	3.84	3.84	0.00	3.23	3.23	0.00	3.61	3.61	0.00	2.44	2.44
14H	0.01	3.73	3.72	0.01	4.14	4.13	0.01	3.57	3.57	0.02	1.75	1.73
15C	1.75	0.19	-1.56	1.62	0.85	-0.77	2.23	-0.10	-2.33	4.15	-1.06	-5.21
16H	0.38	0.71	0.33	0.36	0.13	-0.23	0.32	1.04	0.72	0.24	3.91	3.67
17H	3.31	6.72	3.41	3.19	5.99	2.80	3.53	7.46	3.93	3.74	6.60	2.86
18C	1.75	0.19	-1.56	1.62	0.85	-0.77	2.23	-0.10	-2.33	4.15	-1.06	-5.21
19H	0.38	0.71	0.33	0.36	0.13	-0.23	0.32	1.04	0.72	0.24	3.91	3.67
20H	3.31	6.72	3.41	3.19	5.99	2.80	3.53	7.46	3.93	3.74	6.60	2.86
21 N	36.42	0.98	-35.44	36.40	0.93	-35.47	35.83	1.04	-35.81	33.41	0.71	-32.70
22H	0.95	10.16	9.25	1.03	8.40	7.37	0.95	10.87	9.92	0.82	8.74	7.92
23C	1.14	-0.50	-1.64	1.16	-0.37	-1.53	1.52	-0.64	-2.16	2.06	-0.51	-2.57
24H	3.02	4.01	0.99	2.84	6.27	3.47	3.32	4.46	1.14	3.27	2.48	-0.79
25C	0.06	-0.98	-1.04	0.06	-1.30	-1.36	0.06	-0.97	-1.03	0.06	-0.41	-0.47
26H	0.13	3.11	2.98	0.12	2.61	2.49	0.15	2.87	2.72	0.16	2.10	1.94
27H	0.00	7.83	7.83	0.00	9.18	9.18	0.00	7.35	7.35	0.01	3.91	3.90
28C	0.05	-2.11	-2.16	0.04	-1.60	-1.64	0.05	-2.01	-2.06	0.07	-1.29	-1.36
29H	0.01	3.73	3.72	0.01	4.14	4.13	0.01	3.57	3.56	0.02	1.75	1.73
30H	0.02	4.13	4.11	0.02	3.44	3.42	0.02	3.54	3.52	0.04	2.12	2.08
31H	0.00	3.84	3.84	0.00	3.23	3.23	0.00	3.61	3.61	0.00	2.44	2.44
32C	0.89	-0.40	-1.29	0.76	2.96	2.20	0.91	-0.62	-1.53	1.18	-2.57	-3.75
33H	0.26	1.78	1.52	0.21	0.12	-0.19	0.33	1.96	1.63	0.44	5.95	5.51
34H	0.47	5.76	5.29	0.49	2.87	2.38	0.30	5.58	5.28	0.19	6.98	6.79
35O	1.12	0.35	-0.77	1.68	0.87	-0.81	0.46	0.29	-0.17	0.12	-0.01	-0.13
36H	0.02	0.67	0.65	0.01	1.28	1.27	0.01	0.72	0.71	0.01	8.17	8.16
37O	1.12	0.35	0.77	1.68	0.87	-0.81	0.46	0.29	-0.17	0.12	-0.01	-0.13
38H	0.02	0.67	0.65	0.01	1.28	1.27	0.01	0.72	0.71	0.01	8.17	8.16

energy from HF orbitals, their combination produces conceptual DFT reactivity descriptors that correlate quite well with the reactivity descriptors obtained through HF calculations. Thus, it is worth calculating the electronegativity, global hardness and global electrophilicity for the studied systems using both approximations in order to verify the quality of the procedures.

The HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ , total hardness η , and global electrophilicity ω of the EMB molecule calculated with the M06, M06L, M06-2X and M06-HF density functionals and the MIDIY basis set are presented in Table 1. The upper part of the table shows the results derived assuming the validity of

Koopmans' theorem and the lower part shows the results derived from the calculated vertical I and A.

It can be concluded from the results shown in Table 1 that the assumed equivalence between the HOMO and LUMO and the ionization potential I and electron affinity A only holds with fair accuracy for the M06 calculations. Also, for the results obtained using this density functional, there is a good agreement between both types of calculation for the chemical reactivity descriptors χ , η and ω .

The condensed Fukui functions can also be employed to determine the reactivity of each atom in the molecule. It is possible to evaluate condensed Fukui functions from single-points calculations directly, without resorting to additional calculations involving the systems with $N-1$ and $N+1$ electrons:

$$f_k^+ = \sum_{a \in k} \left[c_{ai}^2 + c_{ai} \sum_{b \neq a} c_{bi} S_{ab} \right] \quad (\text{where } i = \text{LUMO}) \quad (6)$$

and

$$f_k^- = \sum_{a \in k} \left[c_{ai}^2 + c_{ai} \sum_{b \neq a} c_{bi} S_{ab} \right] \quad (\text{where } i = \text{HOMO}) \quad (7)$$

with c_{ai} being the LCAO coefficients and S_{ab} the overlap matrix. The condensed Fukui functions are normalized, thus $\sum_k f_k = 1$ and $f_k^0 = [f_k^+ + f_k^-]/2$.

The condensed Fukui functions were calculated using the AOMix molecular analysis program [23, 29] starting from single-point energy calculations. We have presented, discussed and successfully applied the described procedure in our previous studies on different molecular systems [30–32].

The condensed dual descriptor has been defined as $\Delta f_k = f_k^+ - f_k^-$ [33, 34]. From the interpretation given to the Fukui function, one can note that the sign of the dual descriptor is very important to characterize the reactivity of a site within a molecule toward a nucleophilic or an electrophilic attack. That is, if $\Delta f_k > 0$, then the site is favored for a nucleophilic attack, whereas if $\Delta f_k < 0$, then the site may be favored for an electrophilic attack [33–35].

The electrophilic f^- and nucleophilic f^+ condensed Fukui functions and Δf over the atoms of the EMB molecule calculated with the M06, M06L, M06-2X and M06-HF density functionals and the MIDIY basis set are shown in Table 2. The actual values have been multiplied by 100 for easier comparison.

The results from this Table clearly indicate that, in light of the values of Δf_k over all the atoms, the sites for the electrophilic attack are the nitrogens N9 and N21, and the same behavior is predicted by the four density functionals considered in this work.

The electron donating (ω^-) and electron accepting (ω^+) powers have been defined as [36]:

$$\omega^- = \frac{(3I + A)^2}{16(I - A)} \quad (8)$$

and

$$\omega^+ = \frac{(I + 3A)^2}{16(I - A)} \quad (9)$$

It follows that a larger ω^+ value corresponds to a better capability of accepting charge, whereas a smaller value of ω^- value of a system makes it a better electron donor. In order to compare ω^+ with $-\omega^-$, the following definition of net electrophilicity has been proposed [37]:

$$\Delta\omega^\pm = \omega^+ - (-\omega^-) = \omega^+ + \omega^- \quad (10)$$

that is, the electron accepting power relative to the electron donating power.

The electron donating (ω^-) and electron accepting (ω^+) powers and net electrophilicity $\Delta\omega^\pm$ of the ethambutol molecule calculated with the M06, M06L, M06-2X and M06-HF density functionals and the MIDIY basis set are presented in Table 3. The upper part of the table shows the results derived assuming the validity of Koopmans' theorem and the lower part shows the results derived from the calculated vertical I and A.

The results from Table 3 clearly indicate that EMB is an electron-donating molecule, with the same result predicted by all the four density functionals considered in this study. However, only the results obtained through the calculations with the M06 density functionals are in fair agreement between those from vertical calculations of I and A and those coming from the assumption of the validity of the Koopmans' theorem in DFT.

Table 3 Electrodonating (ω^-) and electroaccepting (ω^+) powers and net electrophilicity $\Delta\omega^\pm$ of the EMB molecule calculated with the M06, M06L, M06-2X and M06-HF density functionals and the MIDIY basis set. The upper part of the table shows the results derived assuming the validity of Koopmans' theorem and the lower part shows the results derived from the calculated vertical I and A

Property	M06	M06L	M06-2X	M06-HF
ω^-	8.0717	7.7892	10.1704	12.8799
ω^+	3.7192	4.0937	4.4904	5.6769
$\Delta\omega^\pm$	11.7909	11.8829	14.6608	18.5568
ω^-	6.9629	6.1727	7.4116	8.2073
ω^+	2.8009	2.3852	2.8761	3.2318
$\Delta\omega^\pm$	9.7638	8.5579	10.2877	11.4391

Conclusions

Combining all the results presented in this contribution, it can be clearly demonstrated that the sites of interaction of the EMB molecule can be predicted using DFT-based reactivity descriptors such as the hardness, softness, and electrophilicity, as well as Fukui function calculations. These descriptors were used in the characterization and successful description of the preferred reactive sites and provide a solid explanation for the reactivity of the EMB molecule.

The M06 family of density functionals (M06, M06L, M06-2X and M06-HF) used in the present work leads to the same qualitatively and quantitatively similar description of the chemistry and reactivity of the EMB molecule, yielding reasonable results. For the case of the particular M06 functional, the agreement is fairly good between the results obtained through energy calculations and those that assume the validity of Koopmans' theorem.

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