Response letter

**A DFT study of the chemical reactivity of thiobencarb and its oxidized derivatives in aqueous phase.**

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Reviewer 1

*1. Why have author changed basiset for calculating reactivity parameters? justification needed.*

Answer:

Our apologizes by this mistake, in all cases the level of theory is the specified in the methodology section i.e. wB97XD/6-311++G(2d,2p). We have corrected this mistake in the mansucript.

*2. Section” Experimental “would be altered as Computational*

Answer:

We agree, we have done the correction.

*3. PCM Model – aqueous phase descriptors are not available.*

Answer:

In fact, all chemical descriptors were determined in aqueous phase. For sake of clarity we have done the modification of the description of Table I as:

Table I. Global reactivity descriptors evaluated for TB and its dechlorinated forms at the wB97XD/6-311++G(2d,2p) level of theory in the aqueous phase, employing the PCM solvation model, according to the equations (1), (3) and (4).

*4. E(N - 1) description not given*

Answer:

We agree, we have added the description of E(N - 1). Now it is possible to read on page 8, last paragraph.

…………………….where E(N - 1) corresponds to the energy of the cationic configuration……………………..

*4. No emphasis on toxicity is made with reference to the studied parameters.*

Answer:

We agree, we have done an analysis of the toxicity in function of the electrophilicity index. Thus, new equations were considered, now it is possible to read on page 4.

From this reactivity index it is possible to define the electrodonating (**-) and electroaccepting (**+) powers as:32

 (5)

 (6)

where

 (7)

and,

 (8)

The discussion of the toxicity employing these reactivity descriptors is found in the last paragraph in page 9. Now it is possible to read.

Here, it is interesting to mention that the origin of toxicity is supposed to be governed by the possible charge transfer between a toxin and a biosystem,43 for example electrophilic substances can form covalent bonds to proteins and DNA, resulting in reactive toxicity and according diseases such as dermal or respiratory sensitization and mutagenicity.44 In this sense, the origin of the toxicity may be attributed to the electron accepting nature,43 which may be evaluated through equation (6).45 In Table II are reported the values of **+ for the compounds analyzed in the present work. Observe that DTB exhibit a lower value of **+ in comparison to TB suggesting a major toxicity by DBT. Indeed this result is coincident with the reported experimentally because DBT is more toxic than TB.8 Also, note that the **+ value of DTBSu is lower than the obtained for TBSu, suggesting that the first one is more toxic than the second one. In the case of DTBS and TBS, these compounds show similar **+ values, indicating a similar toxicity. According to the last results, the more toxic thiobencarb derivatives are DTB and DTBSu.

Table II. Electroaccepting (**+) powers evaluated at the wB97XD/6-311++G(2d,2p) level of theory in the aqueous phase, employing the PCM solvation model, according to the equation (6).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **  / eV |  |  | **  / eV |
| TB | 0.0195 |  | DTB | 0.0158 |
| TBS | 0.0201 |  | DTBS | 0.0202 |
| TBSu | 0.0204 |  | DTBSu | 0.0167 |

And new references were added.

43. A. Poland, D. Palen, E. Glover, *Nature* **300** (1982) 271

44 D. Wondrousch, A. Böhme, D. Thaens, N. Ost, G. Schüürmann, *J. Phys. Chem. Lett.* **1(10)** (2010) 1605

45. A. U. Orozco-Valencia, A. Vela, *J. Mex. Chem. Soc.* **56(3)** (2012) 294

*5. The magnitude of isosurfaces plotted is not given*

Answer:

We agree, we have added this data in the Figure captions.

*6. Electrostatic potential map will provide more insight on reactivity they can refer the following paper 1. Density functional theory investigation of cocaine water complexes Journal of molecular modelling, 2013.*

Answer:

We agree, we have done an analysis employing electrostatic map potentials. Now, it is possible to read on page 17,

Additional to the global and local reactivity descriptors we analyzed the reactivity of TB, TBS, and TBSu and their dechlorinated forms through maps of the electrostatic potential. This kind of maps may provide insight on reactivity.47 In these maps a reactive site is a particularly charged region of a molecule that has an affinity for interacting with charged particles. Thus, a region of very low potential energy would have a very strong influence on positively charged particles or regions of particles nearby. In Figure 1S (see supplementary material), areas of low potential (red color), are characterized by an abundance of electrons while areas of high potential, (blue color), are characterized by a relative absence of electrons. Note that the oxygen atoms have the lowest values of potential in comparison to the other atoms; consequently have a higher electron density around them.

Also the Figure IS was added in supplementary material.

|  |  |  |
| --- | --- | --- |
| 1. TB | 1. TBS | 1. TBSu |
|  |  |  |
| 1. DTB | 1. DTBS | 1. DTBSu |
|  |  |  |

Figure 1S. Mapping of the electrostatic potentials evaluated at the wB97XD/6-311++G(2d,2p) level of theory employing the PCM solvation model, onto a density isosurface (value =0.002 e/a.u.3) for a) TB, b) TBS, c) TBSu, d) DTB, e) DTBS and f) DTBSu.

and a new reference was added

47. L. Senthilkumar, P. Umadevi, K.N. Nithya, P. Kolandaivel, *J. Mol. Model.* **19(8)** (2013) 3411.

*7.For fukui functions, chemical hardness authors may cite 1. Study of effective hardness and condensed Fukui functions using AIM, ab initio, and DFT methods Molecular physics, 2005. 2. Post Hartree–Fock and density functional theory studies on tautomerism of 6-thioxanthine in gas phase and in solution Journal of Molecular Structure: THEOCHEM, 2003*.

Answer:

We have revised the references provided by the reviewer 1, however the references indicated in these papers for the global and local reactivity descriptors are coincident with the reported in the original manuscript. Therefore, we have kept the original references where the Fukui Functions and hardness equations appeared for the first time.

Reviewer 2

1. *Which is the reason for use theoretical model wB97XD/6-311++G(2d,2p) level of theory? If author compared calculations performed on wB97XD/6-311++G(2d,2p) level of theory with some another level of theory so these data must be add in manuscripth for comparation.*

Answer:

Our apologizes by this mistake, in all cases the level of theory is the specified in the methodology section i.e. wB97XD/6-311++G(2d,2p). We have corrected this mistake.

*2. N,N- in the IUPAC name must be in italic.Check out this.*

Answer:

We agree, we have done the correction.

*3. And final, for readers are necessary and very important that author attach cartesian coordinates for all optimized structures in Electronic supporting materijal.*

Answer:

We agree, we have added these data as supplementary material, see Tables IS-VIS.

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