Response letter

A DFT Study of the Chemical Reactivity of Cimetidine A, C and D in Gas, H_2O, MeOH and EtOH solvents.

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We thank anonymous referee for evaluating and reviewing our manuscript. We are especially grateful for the many constructive comments and suggestions. We address the referee's comments in the following point by point response.

Referee comments: 1. Line 30: Better choice of keywords should be made.

Answer: We agree, we have changed the original keywords, now it is possible to read on page 1, line 30

Keywords: cimetidine; reactivity; solvent; HSAB; Fukui; DFT

Referee comments: 2. Line 93: Formula should be written properly

Answer: We agree, we have corrected the equation (1), now it is possible to read on page 3, line 93.

$$\mu = \left(\frac{\partial E}{\partial N} \right)_{v(r)} = -\frac{1}{2}(I + A) \qquad (1)$$

Referee comments: 3. Lines 137-139: This is already described in the methodology. I think thisis an unnecessary repetition.

Answer: We agree; we have deleted lines 137-139 according to the referee's suggestion.

Referee comments: 4. Lines 137-139: I think that this statement is incorrect.

Answer: Please, see previous answer. We have deleted lines 137-139 according to the referee's suggestion.

Referee comments: 5. Lines 160-161: Value correction factor 0.953 is not taken from reference40. The authors should explain how they got this value.

Answer: We agree, our apologies by this mistake, we have corrected the scaling factor value and the reference. Now, it is possible to read on page 7, lines 156-158, first paragraph

……In the present case, the scaling correction factor was obtained via the Reduced Scale Factor Optimization Model described by Alecu et al. This factor is 0.950 for the case when the wB97XD/def2TZVP level of theory is employed.[40]

Also, the right reference related to this scaling correction factor is reported in the reference section,

40. I. M. Alecu, J. Zheng, Y. Zhao, D. G. Truhlar, J. Chem. Theory Comput. 6 (2010) 2872.

Referee comments: Generally speaking,good agreement between theoretical IR spectra in different solvents was expected. I really do not understand the chemical sense of comparative studies IR spectra in different solvents. Why isn't theoretical IR spectra compared with the experimental IR spectra?

Answer: We agree with this referee comment, generally, a good agreement between theoretical IR spectra in different solvents is obtained. But in the present case, in water solvent it was identified and additional vibration to those observed at MeOH and EtOH. We considered that this information may become useful as a reference, for possible experimental studies to be reported in the future by other researchers. Also, a direct comparison between theoretical and experimental IR spectra was not possible, because, to the best of our knowledge, there is not any report of IR spectra of pure cimetidine compounds A, C and D in the different solvents analyzed in the present work. Unfortunately, the IR spectra available have been obtained only in solid state.

Referee comments: In line 197 the similarity between the experimental and the theoretical spectrum is mentioned, while inline 198 they reference 6 is cited for experimental IR spectra. I strongly recommend that the authors change or delete this part of discussion.

Answer: We agree we have deleted line 197-198 in the original manuscript, according to the referee's suggestion.

*Referee comments:*6. Lines 185: A typing error "si" should be replaced with "is"

Answer: We agree we have corrected the typo.

Referee comments:7 Lines 189: In Table 1 column 4 is unnecessary because the sum of columns 3and 4 gives result in column 2.

Answer: We agree we have deleted the column 4 in Table 1, according to the referee's suggestion.

Referee comments: 8. Lines 210-216: This part of the text should be written clarified. The quality of Fig 5 should be improved. Similar figures for structures in polar solvents should be presented in the supplementary material.

Answer: We agree we have clarified the text in lines 210-216, now it is possible to read on page 8, lines 204-214, and last paragraph

…….....The *s* colored isosurfaces for CimA, CimC and CimD are reported in Figure 3, where the red color represents stabilizing interactions, while the white color suggests a destabilization. In Figure 3a, note that the hydrogen bonds correspond to the stabilizing interactions, while the hydrogen–hydrogen interactions are destabilizing. Also, it is possible to observe that the folded structure in CimA is caused by intramolecular interactions among imidazole nitrogen and hydrogen atoms. In the case of CimC, the structure is extended. It is probably because there is not any hydrogen bond in the center of the molecule, see Figure 3b. In Figure 3c, are depicted the intramolecular interactions in CimD, note the presence of guanidine nitrogen-hydrogen interactions which are causing its folded structure. Similar results were obtained in the solvents H_2O, MeOH, and EtOH, see Tables 5S, 6S and 7S in supplementary material…….

Also, the quality of Figure5 was improved. We consider that the quality of the new Figure 5 is better in comparison to the previous one. Similar figures for structures in

polar solvents have been added in the supplementary material as Tables 5S, 6S and 7S.

Referee comments: 9. Generally speaking, there are a lot of figures in the paper. Figures 6-8 should be converted into a single figure. Alternatively, Figures 7 and 8 could be moved to Supplementary material.

Answer: We agree with the referee´s comment. Thus, the corresponding figures in polar solvents are reported as supplementary material. Figures 7 and 8 were moved to supplementary material. Also, the original the Figures 3 and 4, corresponding to the IR spectra in the original manuscript were moved to supplementary material