Faculty of Physical Chemistry Belgrade, 14. 7. 2016.

University of Belgrade

Serbia

Dear Prof. Juranić,

Thank you very much for facilitating the review of our manuscript entitled “Unrevealing mechanisms of avobenzone’s photothermal tautomerization by means of quantum chemical computations”, which we have now revised based on the reviewers’ comments. We would like to express our sincere gratitude to the referees, whose comments are very valuable. Based on the reviewers comments we decided to submit the revised version of the manuscript with title “Unrevealing mechanism of avobenzone’s thermal tautomerization by means of quantum chemical computations”. We believe the quality of the manuscript has improved substantially and provide a point-by-point response below. We hope that you’ll find the manuscript acceptable for publication in *The Journal of Serbian Chemical Society.*

Sincerely,

Mihajlo Etinski

Assistant Professor

Faculty of Physical Chemistry

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**Reviewer A:**  The authors present a computational study on mechanism of keto-enol
tautomerization of a molecule that is used in sunscreens as a UVA filter. The study appears to be carefully carried out, and results analysed. However, there are certain questions/weaknesses in the manuscript that authors need to address to be able to provide a full review.
Page 1; reference 21 is related to a model molecule, and it is not directly related to the molecule that is subject of the study

**Authors’ response**: The sentence “Chelated enol form is more stable due to the intramolecular hydrogen bond 21 although the keto tautomer is also present in a minor extent in equilibrium” is substituted with “Generally, chelated enol form of dibenzoylmethane derivatives is more stable due to the intramolecular hydrogen bond 21 although the keto tautomer is also present in a minor extent in equilibrium 22”

**Reviewer A:**    Page 1. References are needed to support the statements “although the keto tautomer is also present in a minor extent in equilibrium” and “the keto tautomer absorbs in the UVC band”

**Authors’ response**: A new reference 22 is added to support the statement “although the keto tautomer is also present in a minor extent in equilibrium” whereas the reference 15 is cited for the statement “the keto tautomer absorbs in the UVC band”.

**Reviewer A:**    There is no justification that demonstrates that the removing t-butyl group does not affect the keto-enol tautomerization, as authors clearly indicated that metoxy group (small substituent) changes its orientation in different rotamers, the effect for t-butyl group (large bulky substituent) may introduce different greater steric effects on the rotamers)

**Authors’ response**: We do not agree with the reviewer that the inclusion of the t-butyl group would significantly alter keto-enol tautomerization thermodynamics. On the other hand, the bulky t-butyl group may modify the kinetics of tautomerization. The justification of this reasoning is provided in the answer of the next question.

**Reviewer A:**    Authors have considered only one type of enol form, only oxygen O2 is considered to be as a hydroxyl group, authors did not provide justification why oxygen O1 is not considered as hydroxyl group. The absence of t-butyl may affect this.

**Authors’ response**: This question is related to the previous one. In our opinion the thermodynamics and spectral properties of avobenzone are dominated by dibenzoylmethane moiety whereas the side groups (the methoxy and t-butyl group) have a minor effect. In order to support this reasoning we computed the Gibbs energy difference between the two chelated structures in which the hydroxyl group is on the O1 and O2 atoms, respectively. If the methoxy group had a significant effect on the tautomerization than this would reflect on the free energies. The energy difference is computed to be only 0.7 kJ/mol which is much lower than the accuracy of the method. Thus, the two oxygen cites are equivalent. The explanation behind this is that the electron density in the vicinity of the oxygen atoms is similar and not significantly influenced by side groups. Also, we inserted the following text in the manuscript: “Since there are two oxygen atoms O1 and O2, there are two sets of enol conformers depending whether the hydrogen atom is bound to O1 or O2 atom. Our computation revealed that the free energy difference between the two chelated enol conformers is only 0.7 kJ/mol which is much below the accuracy of the method. Thus, we regard these conformers equivalent and consider only enol tautomers in which the hydrogen atom is bound to the O2 atom.”

**Reviewer A:**   Authors should provide an explanation why diketo form in a cis arrangements was not considered for calculation and what are ground state energies for this form?

**Authors’ response**: We added the following text: “The oxygen atoms in these structures are in trans arrangements. The cis arrangement is not stable due to a repulsion of oxygen nonbonding electrons and transforms to the trans arrangements.”

**Reviewer A:**    The aim is not clearly defined, did authors want to study keto-enol tautomerization in ground state, or keto-enol tautomerization upon photoexcitation?

**Authors’ response**: In the revised manuscript we study keto-enol tautomerization in the ground state. Also we present excited state properties of selected tautomers.

**Reviewer A:**    The details of the computational experiments are not provided, it is not clear what parameters and keywords were used to setup computations, therefore it is difficult to judge if the setup is adequate for the system studied.

**Authors’ response**: We employed the default parameters. Also, we added the following sentence: “Ultrafine grid was used for numerical integrations.”

**Reviewer A:**    Did authors consider solvent in the computations, as it is clearly indicated that whole effect is solvent dependent.

**Authors’ response**: No, we did not consider solvent effects. The solvent dependence is one of several important issues related to tautomarization mechanism but it deserves a new detail study. Particularly, hydrogen bonding with solvent molecules may alter free energies of transient tautomers. We added the following sentence in the manuscript: “All computations were performed in vacuum.”

**Reviewer A:**    Page 4. Authors state “The optimized geometry of keto d is symmetric “
which cannot be observed in figure 2, and the molecule itself is clearly asymmetric

**Authors’ response**: We corrected that statement into “The dibenzoylmethane moiety of the optimized geometry of keto *d* tautomer is symmetric while in the case of keto *s* it is characterized by twisted geometry.”

**Reviewer A:**    Page 5. Authors state “it is expected that its rotation barrier will be much smaller than in the case of the rotamer d.” This should be calculated and provided as activation energy for different rotations, as this can highly influence the pathway from one rotamer to another.

**Authors’ response**: We have tried to optimize a transition state for rotation about double bond but we failed due to problems with SCF convergence at this geometry. The problem comes from the fact that the transition state is located on a conical intersection between the ground and the S1 state. In vicinity of this intersection, two states are almost degenerate and single reference methods fail to be valid for those geometries.

**Reviewer A:**    Conclusion should indicate that the results are based on the model system

**Authors’ response**: In the revised manuscript, we indicated that the results are based on the model system.

**Reviewer A:** REPORT:
Generally, there are minor probles with the english grammar, which should be looked into after the manuscript is resubmitted The references are not clearly supporting all the statements that are in the introduction There are no references in the results and disucssion section that provide a
critical insight of the obtained results. Structures in the figure 1 are too small. In my opinion, this manuscript should: be published after major revision and additional review

**Authors’ response**: We corrected Figure 1.

**Reviewer B**: Title and the end of the Abstract are largely misleading. They suggest photochemically induced molecular transformations. Actually the ground state thermal equilibrium among several isomers is discussed, and subsequently are analyzed their spectral features. Figure 2 has to be redrawn, because the atomic labels are not clearly visible.

**Authors’ response**: We deleted atomic labels in Figures 2 and 3.

**Reviewer B**: After Figure 1 bonds are declared as single or double, but both have similar
bond-lengths (both are shorter than C-C bonds in benzene), and discussion of rotation about them is not so simple. At this point must be made clear what initiated the isomerization of avobenzone. ? Is it initiated by absorption of light quanta, or is a mere thermal rotation?

**Authors’ response**: We thank the reviewer for indicating us that the C1-C2 bond is shorter than C-C bonds in benzene. This was a typo that we corrected. The correct C1-C2 bond length is 1.43 Å which is close to the length of a single bond. In the revised manuscript, we indicated that the tautomerization has a thermal origin.

**Reviewer B**: The relative energies of keto and enol forms are calculated for molecules in
vacuum. Presence of water molecule(s) can stabilize intermolecular hydrogen bonding. It can make the scission of intramolecular H-bonding less unfavorable.

**Authors’ response**: We agree with the reviewer. In our opinion, the tautomerization with solvent molecules deserves its own study.

**Reviewer B**: In ‘classical’ photochemistry, rotation around double bond is attributed
to triplet state of ππ\*. It is obvious that triplet state can have dominant role in isomerization of (quasi)double bonds. If the photoisomerization is the central issue in this work, then the triplet state should be seriously discussed.

**Authors’ response**: In the revised manuscript the thermal tautomerization is the central issue. Nevertheless, we discuss the lowest excited triplet state.

**Reviewer B**: Low symmetry of these molecules indicates high probability of intersystem
crossing, and it should be major issue in discussion of the destiny of vibrationally relaxed S1 state.

**Authors’ response**: The probability of intersystem crossing largely depends on the orbital type of the initial and final electronic states. We already discussed intersystem crossing probability: “Since all these triplet states have the same orbital character as the S1 state, it is not expected that intersystem crossing from the S1 to triplet states will be fast.”

**Reviewer B**: It is hard to see the need for lengthy discussion of S1 state geometry,
except for the estimation of fluorescence of enol isomer. All the rest has little meaning. For rotamer and diketone, optimization must be done for S2 and S3 states, because these are primarily populated by photoexcitation.

**Authors’ response**: We shortened the discussion of the S1 state geometries and spectra. Although initially populated, higher singlet excited states have very short lifetimes since they are coupled to other states. Thus, the photochemistry mainly proceeds from the S1 or T1 states. In addition, it is very difficult to optimize the S2 and S3 states with a single reference method due to the above mentioned reason.

**Reviewer B**: Still, the study of photochemical transformation needs to involve triplet
states, because they have larger life-times, and can undergo chemical change. The main flaw in the manuscript is that the connection between light
absorption and chemical transformation is not demonstrated.

**Authors’ response**: We discuss the triplet states in the revised manuscript.

**Reviewer B**: In my opinion, the article has to be more consistently (re)written and
submitted for new review.

REPORT: In my opinion, the article has to be more consistently (re)written and submitted for new review. In my opinion, this manuscript should: be published after major revision and additional review