



SDI Review Form 1.6

Journal Name:	American Chemical Science Journal
Manuscript Number:	Ms_ACSJ_22405
Title of the Manuscript:	Papaverin. Geometrical and Electronic Structure. Acidic Force.
Type of the Article	Original Research Papers

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This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	page 1. row 6. "The first quantum-chemical calculation of the molecule papaverine" is not true as there is a lot of research done on this topic previously. See - N. Leopold, J.R. Baena , M. Bolboaca , O. Cozar, W. Kiefer, B. Lendl, Vibrational Spectroscopy 36 (2004) 47–55. - N. Leopold , J.R. Baena , M. Bolboaca, O. Cozar , W. Kiefer , B. Lendl, 60, 8–9, 2004, 2021–2028. - S. Cîntă Pînzaru, I. Pavel, N. Leopold and, W. Kiefer, Journal of Raman Spectroscopy, 35, 5, 338–346, 2004. - Fusheng Deng ; Jingling Shen ; Guangqin Wang ; Meiyan Liang, Proc. SPIE 7158, 2008 International Conference on Optical Instruments and Technology:Microelectronic and Optoelectronic Devices and Integration, 71580S (February 09,2009); doi:10.1117/12.805630 And cited there in. p 1. r 6. "AB INITIO/6-311G**". Ab initio is not the right term. Either RHF or UHF should be used.	Indeed, there are a lot of researches on this subject, but the quantum-chemical calculation of papaverine by RHF / 6-311G ** and DFT-PBE0/ 6-311G ** methods has been made for the first time.



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	p 1. r 10 “We have established that the molecule of hexoprenaline relates to the class of very weak acids ($pK_a > 14$).” The hexoprenaline structure is very different from that of papaverine, thus this statement could not be true. p 1. r 14. Where the Introduction of the text should be, instead there is a text on “Medical-biological properties and application of papaverine”. Should be revised completely. There are a lot of statements in the first part with no citations to support them. p 1. r 26-27. “in approach the insolated molecule in gas phase” . Probably “in approach the isolated molecule in gas phase”. A vital typing mistake. It is not clarified what is the role of UV-spectrum here. Who obtained this spectrum? Why is it included in the text? What is its relation to the quantum-chemically obtained structure and the aim of the article?	Thank you for your comments, we agree with it. You're right that the more accurate method we have used is RHF / 6-311G ** (closed-shell) We completely agree with the reviewer. Our article is devoted to papaverine only. This part of the article is completely redesigned Thank you for your comment. You're right. It must be "an isolated molecule in the gas phase" The spectrum has been obtained in our previous research (see References 3).
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	“Titration” is mentioned and it is not clarified what it stands for and how it is related to the topic of this article. There isn't any explanation why they needed to use quantum-chemical methods. There isn't any explanation why they used (probably) RHF and DFT methods? Why did they use PBE0 functional? There is no explanation why they use 6-311** orbital basis.	Its role is explained in the first paragraph after the table 1. "The parameters of UV spectrum of papaverine are matched ..." The aim of the article is to evaluate the acid strength of papaverine. The acid strength pKa is calculated by (1) $pK = 49.04 - 134.61q_{\max}^{H^+}$ and (2) $pK = 51.048 - 150.078q_{\max}^{H^+}$ $q_{\max}^{H^+}$ is the maximal charge on the hydrogen atom of papaverine which has been derived from the calculation by the RHF / 6-311G ** method for the formula (1) and by the DFT-PBE0 / 6-311G ** method. But the magnitude of this charge is related to the optimal electronic and geometric structure of papaverine The sentence, which used this term, was removed. The answer to this question is given in the last sentence of the introduction section
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	There is no information on what the input geometry is. Is there any conformational research done in advance? There is no explanation how they calculate Gibbs free energy changes and pK. п 3.1 66. „где“ is not an English word. It is a Russian word (meaning “where”). The text seems unrevised by its author on many levels. The results of this article doesn't seem plausible.	Due to the fact that the purpose of this manuscript is a theoretical assessment of the universal indicator of acidity (pKa), to calculate it the formulae (1) and (2) have been used, where $q_{\max}^{\text{H}^+}$ is the maximal charge on the hydrogen atom of papaverine derived from the calculation by the RHF / 6-311G ** method (see formula (1)) and by the DFT-PBE0 / 6-311G ** method in formula (2). Exactly in these methods the formulae (1) and (2) have the maximum correlation coefficient: $R = 0,97$ is for the RHF / 6-311G ** and $R = 0,95$ is for DFT-PBE0 / 6-311G **. Other methods and other bases are given by a lower correlation coefficient than the methods used in the manuscript. In this regard, pKa estimation is more accurate. That is why these methods, bases and functional have been chosen. The original geometry has been constructed by the authors on the basis of the structural formula of papaverine, which is shown in Figure 1. We don't know such researches.
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	This text doesn't correspond to basic criteria of writing an article and conducting a scientific research.	We did not calculate Gibbs free energy, pKa was calculated by formulae (1) and (2) Thank you. We agree with the comment. We tried to improve our English. The results are in reasonably good accordance with the evaluation pKa, made in The text has been significantly reworked.
<u>Minor</u> REVISION comments		
<u>Optional/General</u> comments		