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Magn. Reson. Discuss., referee comment RC2
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Comment on mr-2021-27

Anonymous Referee #2

Referee comment on "Nuclear magnetic resonance free ligand conformations and atomic resolution dynamics" by Amber Y. S. Balazs et al., Magn. Reson. Discuss., https://doi.org/10.5194/mr-2021-27-RC2, 2021

In the present manuscript Chiarparin and coworkers describe the use of the REST-MD method (replica exchange with solute tempering in explicit water, introduced by the Friesner and Bern groups in 2005) as a means to investigate the conformational preference of small molecules in order to inform drug design. While I believe that this manuscript presents solid science that would be publishable in principle (subject to minor revisions), I cannot see that it fits within the scope of Magnetic Resonance, because it does not present any advancements related to NMR. The manuscript describes a very brief case study that nicely illustrates the utility of REST-MD and the fact that NMR experiments can provide corrective results that augment the full picture during the drug design process. However, the use of NMR is limited to standard techniques to determine the rotamer populations and the rotamer barrier of a single torsion in a pair of congeneric molecules, as a means to validate results from REST-MD. In part, the manuscript reads like a review of what has been (or could be) performed in other studies in terms of using NMR data to guide REST-MD calculations and other computational approaches. It is not at all clear what is actually new in this manuscript, except the specific results for this particular set of molecules.

I would suggest that the authors expand the scope of the manuscript by incorporating a larger set of NMR data, as the authors also suggest on p. 8, and clearly show how such data can be used to curate results from REST-MD calculations, or possibly introduce NMR-based constraints to guide calculations so as to truly make the calculations 'interpret' the NMR data. At present, the manuscript merely presents a brief (but nice) illustration of the use of REST-MD, followed by validation by NMR.

Minor points:

The REST-MD simulations involve explicit water, whereas the NMR studies used DMSO as

solvent. Please comment on whether you expect deviations in rotamer populations due to the different solvents. Is it not possible to perform the NMR studies in water?

Fig. 2: Please highlight the benzylic CH group in the chemical structures to the left.

Fig. 2: Please define logD, as a service to readers outside of the medicinal chemistry field.

line 197-198: "...designing an increase in the percent bioactive conformation by restricting rotation". This sentence apparently confuses kinetics/dynamics with thermodynamics. Rotation is restricted by changing the barrier height, but this does not necessarily affect the relative populations of the two rotamer states, unless one of the two states is preferentially stabilized over the other, in which case it suffices to state just that, leaving the barrier (or restriction of rotation) out of the picture. There is similarly imprecise wording on lines 35-36.

line 207-210. I do not understand this sentence, please consider rephrasing. What is "low mode MD..."?