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Interactive comment on "Extending the applicability of P3D for structure determination of small molecules" *by* Alain Ibáñez de Opakua and Markus Zweckstetter

Anonymous Referee #2

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This manuscript reports extensive testing of simulations of RDC data by a software program, P3D, particularly as applied to data collected in lyotropic liquid crystal alignment media used in diastereomeric characterization of small molecules. Much effort is being expended in the development of new alignment media for small molecules, often with the goal of enantiomeric identification. The later is not achievable when only RDC and RCSA data are used. Prospects are much better if molecular characteristic of solute – alignment interactions can be included. This is what the P3D software attempts to do. The extensive testing presented here, on several solutes and several recently introduced alignment media takes a step toward realizing this goal. Some useful observations, include the fact that predictions work well when solutes depart from a near

spherical structure or when electrostatic interactions are strong and asymmetric. Also, the program appears to be useful in modeling systems having multiple conformations having individual alignment tensors. There are, however, some additional issues that could be discussed. While potential reasons for failure associated with solutes of high symmetry are well discussed, less attention is given to reasons for failure of about half the media tested on a well-behaved solute. Also, there are presumably factors associated with the nature of the RDC sets (number of measurements and degeneracy of dipole orientations). Some comments regarding these could be added. There are some discrepancies in the sucrose data that should be clarified. In figure 5 the numbering of the sucrose structure (a) and the notations in the table (b) don't agree. CH vectors with numbers 1,2,3 and 4 in the structure displayed are nearly parallel and should have very similar RDCs. The data appear to come from the Ndukwe reference, which does show this trend. In the manuscript table RDCs with the Ndukwe values are numbered 5,9, 10 and 11. Also, it is not clear where the populations are coming from. These appear to be fitted parameters? The text seems to suggest that the populations are consistent with free ender estimates on line 315. They are not. Also, some comment might be made in comparison to water MD simulations (Case) where only M1 and M2 are highly populated with a difference of only 0.3kcal, something more in line with populations. There are a few places that the text could be improved for clarity: Line 31 – not clearly worded. Maybe: "alignment requires a minimum concentration of lyotropic medium and then often aligns strongly at this concentration, resulting in .." line 87: RQ might be defined here as opposed to much later.

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