Referee: 1

(a) State whether ZPE is included in E_gas or in G_gas,RRHO. I presume in the former, the latter accounting for only the thermal corrections using RRHO. (however, when I see RRHO, I automatically think it includes ZPE)

Response: E_gas is defined as the electronic energy (page 2) and does thus not contain the ZPE. I have now added the sentence “Note that G_gas,RRHO contains the zero point energy” on page 2.

(b) Recently, some have advocated calculating the gas-phase thermochemistry at an elevated pressure to simulate the decreased translational freedom encountered in solution. Does this affect the thermal and entropy corrections beyond a simple change in volume? Is this something that should be encouraged?

Response: I have not seen this in the literature and the reviewer does not provide references so I can’t comment specifically. The approach described in the paper rests on the thermodynamic cycle shown in Figure 1, where any and all condensed phase thermochemistry effects are included implicitly in the parameterization of the solvation free energies.

(c) For delta G_solv(H+), I find it very risky to compute this directly using explicit solvent molecules. Better to put the H+ on another molecule of known pKa and use continuum solvation to compute the energy difference.

Response: I agree that one obtains better error cancellation that way and I have now mentioned this on page 8. The problem is that for systems with more than one ionizable group there is no general expression for the pH-dependent binding free energy in terms of pKa values without assuming they titrate independently. Instead it must be derived for each case.

(d) Other ions: If the ion concentrations are high (experimentally), is it necessary to consider the effect of ionic strength on the activity in calculating the binding energies? Is this a consideration in the computational simulations as well?

Response: I have added a brief discussion of this issue on page 9

(e) Including more than a few explicit waters in a binding energy calculation can also mess up the entropy term, since the positions of these extra water molecules are not sampled adequately. However, this should not be a problem if only a few tightly bound waters are included. It would be good to add a comment.

Response: I already mention this potential problem on page 10: “However, adding explicit solvent molecules increases the computational cost by increasing the CPU time needed to compute energies, perform conformational searches, and compute vibrational frequencies.”

(f) Minor matters:
Pg 3: The sentence before “Molecular Thermodynamics” seems out of place. Should it be part of the previous paragraph?

Response: fixed

Pg 4: “volume of and ideal gas”

Response: fixed

Pg 6: “double-differencing” central difference of double numerical difference?

Response: fixed

Pg 6: “better to pretend that the imaginary frequency is real” – a very bad idea if the frequency is small, since the entropy blows up. Maybe better to “pretend” that it is a free rotor, which has a well defined entropy.

Response: If the reviewer is referring to Grimme’s approach then one still needs to pretend that the imaginary frequency is real to apply the switching function and compute the moment of inertia.

Pg 9: “van der Waals interactions with the solvent” -> “van der Waals and dispersion interactions with the solvent” (just so there is no misunderstanding)

Response: Dispersion is generally considered part of the van der Waals energy

Pg 10 - Eq 21 and the sentence after it: V_solv or Delta V_solv? (as in Eq 22 and 23)

Response: I have changed the notation in Eq 22 and 23 and added the sentence “ΔVsoln = ΔΔVsolv is the change in the volume of the solution on upon binding”.

Pg 11: “numerical instability”? (is this more a matter of numerical noise due to the discretization of the surface elements of the cavity leading to discontinuities in the PES that are problematic for the optimizer – a number of codes have overcome this problem)

Response: I have changed “instability” to “noise”. While this has been mostly solved for some optimizers it continues to be a problem for numerical Hessian calculations.

Pg 12: For an interesting paper on thermodynamic cycles and solution phase optimization, see DOI: 10.1039/c4cp04538f)

Response: we thank the reviewer for the kind words

Pg 15: “if protonations states”

Response: fixed

Pg 15 – 19, abstract: The first person is normally not used in scientific writing

Response: Single author papers are rare in science.

Referee: 2

1. In general, the author should go through all equations and ensure that all terms are defined.

Response: All terms should now be defined.

2. The scope of the perspective must be better defined. QM methods have been used for over 10 years for ligand binding to proteins, typically using MM/PBSA-like approaches (cf. publications and reviews by Merz, Hobza and Ryde, for example). Likewise, the author ignores attempts to using QM post-processing FEP calculations.

Response: I have now better defined the scope which is successful application of the QM+RRHO approach to computing absolute ligand-binding free energies. As far as I know, the RRHO approximation is not used in the studies the reviewer refers to. One of the points I make in the paper is that this energy component makes a huge contribution to the binding free energy and should not be neglected.

3. The introduction should start with a more general discussion of available methods to calculate ligand-binding energies and why QM is needed.

Response: It is not yet clear that QM is needed. One could equally well argue the opposite based on SAMPL4. One of the points of the paper is that to determine the importance of using QM in predicting binding free energies, we must remove or minimize other sources of error such as molecular symmetry, anharmonicity, spurious imaginary frequencies, insufficient conformational sampling, wrong or changing ionization states, errors in the solvation free energy of ions, and explicit solvent (and ion) effects that are not well-represented by continuum models.

4. Different types of QM methods should be described and it should be explained why the author concentrate on DFT and SQM methods.

Response: I concentrate DFT-D and SQM because these QM/RRHO methods have been shown by Grimme to yield accurate binding free energies. I mention that the 3-body dispersion appears to be important for accurate results and that SQM is the only practical way to compute frequencies for systems of this size. While CCSD(T) could be an alternative to DFT-D I have not seen successful absolute binding free energy predictions using this approach. The same goes for MM as an alternative to SQM.

5. What is TPSS27 (p.3)

Response: This is a perspective paper summarizing select published papers where such details can be found. A reference to TPSS27 can be found in Sure et al. 2014.

6. HF-3c should be explained

Response: This is a perspective paper summarizing select published papers (where such details can be found). HF-3c is explained in Sure & Grimme 2013.

7. “by fitting against ΔΔH_f,gas to ΔE_gas values” does not make sense to me.

Response: “against” was a mistake and has been deleted

8. Regarding the low-frequency vibrations, Grimme uses a scaling function so that there are smooth transition between vibrations and free rotation (making the actual value of the frequency unimportant below ~100 cm-1). Truhlar et al. have used a similar approach (but not for ligand binding).

Response: Yes, I mention this approach on page 5. I have also added a mention of another approach by Piccini and Sauer on the same page.

9. The prime problem with conformations is not to use Eqn. 7 but to find all low-energy conformations, including the global minimum.

Response: Yes, as I write on pg 5: “One of the main problems in computing accurate binding free energies is to identify the structures of the host, guest and (especially) the host-guest complex with the lowest free energy”

10. What is the accuracy of computationally estimated pKa values (i.e. what does “fairly accurately” mean quantitatively)? Is it enough for ligand binding?

Response: I have added a brief discussion of this issue on page 8.

11. The meaning of dG_solv(H+) should be explained and in general the difference between upper- and lower-case delta should be clarified.

Response: In hindsight, using lower case deltas was a bad decision.I have changed all lower case deltas to upper case. DG_solv(H+) is defined as the solvation free energy of the proton on page 8.

12. What do the over-bar X and L in Eqns 14 and 16, etc. signify?

Response: I have now explained this on page 8

13. It should be “van der Waals”.

Response: fixed

14. I think the selection of the reference state is primarily determined by what experimental results you want to reproduce.

Response: Yes, the reference state used the predictions has to match the reference state used in the experiments used to generate the data one wants to reproduce.

15. A short description of available CM approaches would be appropriate, referring to Table 1. I suppose you need to specify the variant of PCM also (IEF or C or what?).

Response: The kind of PCM method is now indicated in the table.

16. COSMO-RS is parametrized for many more levels of theory than BP/TZVP.

Response: That appears to be true according to the manual but only the BP/TZVP parameterization has been published.

17. References to the accuracy of solvation energies should be given. In the SAMPL competitions, appreciably worse results are typically seen.

Response: I have added a reference to Kelly *et al*. 2006 on page 11

18. I think problem with converging solution-phase optimizations is a problem special to the implementation in Gaussian. With COSMO in Turbomole, no such problems are ever seen.

Response: I have observed this problem in programs other than Gaussian

19. A recent update to Ho et al. 2010 is PCCP 2015, 17, 2859.

Response: I have now added a reference to this paper on 12

20. Since the author only considers water solvation, he should consider changing “solvation” to “hydration”.

Response: I think it would be confusing to write “hydration” and then use G_solv, which is the standard notation (or G_S) in virtually all papers on this topic.

21. What is meant by “(dispersion and free energy contributions to the binding free energy” on p.19.

Response: I have changed that to “dispersion and **RRHO** free energy contributions to the binding free energy”