So Many Appeals … Consider A Few More

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I have read with great interest the essay of Hoffmann-Schleyer-Schaefer (HSS),[1] and the named referee reports of Koch-Frenking-Bickelhaupt-Reiher (KBFR).[2] The essay and the reports deal with some fundamental issues that concern the interplay of computational chemistry and experiment in chemistry. Most of the participants felt that the time has arrived to define some standards in the reporting of computation, and even in the terminology of describing the status of a predicted new molecule (viable, fleeting, etc). One of the referees felt that this last definition was unnecessarily restrictive, and that in fact the community is well aware of the other points of appeal. I personally found the discussion to be very interesting because it reflects the important aspect of how a relatively young scientific discipline of chemistry has been carving its place among the more established experimental chemistry fields; *setting standards is one of the ways of gaining a legitimate place in the community court*. I would like to take this aspect one step further and extend the appeal to other directions as well.

Stressing the accuracy issues as in the HSS essay is like saying that our theoretical tools are necessarily accurate. But are they? Certainly, for molecules larger than 20 atoms, accuracy is still lacking. Thus, the general direction in the HSS essay overemphasizes the accuracy aspect of computations, and while this is worthy and called for, this aspect certainly does not cover the majority of the molecules, where accuracy is still unattainable. As such, the essay underemphasizes one important aspect of theory that

has already bought quantum chemistry a legitimate place alongside experimental chemistry. This aspect of quantum chemistry that used to be indispensable in the "inaccurate phase" of the discipline was the provision of new insight and new concepts; a need which Coulson has expressed long ago in his nightmare vision of the split in theoretical quantum chemistry.[3] This issue of insight appears in fact in the essay, but is hidden and is rather muted, on page 7167 of the HSS essay (middle column, top paragraph), and is alluded to by one of the referees (B). And this is my basis for an additional appeal: The technical aspects are important, but please give us also insight as beautifully put in Wigner's admonition: "*It is nice to know that the computer understands the problem. But I would like to understand it too*". This standard for a modern theoretical work is all the more important when the accuracy of the calculations is still not high, and even when it gets really high.[4]

For large molecules, the most viable and extremely useful theory is DFT. DFT calculations can be anything from highly inaccurate to highly accurate; this depends on the chemical species, the desired property, and the functional used. While the main sources of error of DFT are well recognized, the attempts to correct them has resulted in a very large number of functionals, many of which are related and differ minutely from the widely used ones, while others are significantly different. These methods are labeled by acronyms that sometimes make sense and other times are not meaningful. Some organization is sorely needed in order to avoid the outcome in the biblical story in Genesis 11, which starts as follows: "*And they said to one another… let us make brick... And they had brick for stone and slime they had for morter. And they said, let us build us a city and tower…*" and the story ends: "*And the Lord said behold… let us go down, and*

confound their language, that they may not understand one another's speech…" It appears to me that the time has arrived to organize all the rich information of functionals, to systemize the names, and to have hierarchy of accuracy and relationships. In the sense that gaining a viable place in science requires systemization in the theoretical tool, the DFT development field needs an organizing hand, like the hand of John Pople in the ab initio theory.

The issue of large molecules brings me to my third appeal that concerns the hybrid QM/MM calculations,[5] which are being increasingly done to study enzymes and other complex systems using DFT as the workhorse QM method and a variety of MM force fields. In these calculations, of e.g., an enzyme, the total system is subdivided into an inner one, which is treated by QM, and an outer one, which is rest of the protein and its additives, which are treated by MM. There are different ways to divide the system and to handle the QM-MM boundary; the treatment of the boundary is not unique and its usage varies between authors (sometimes even the same term, e.g., the "charge shift method" does not really mean the exact same procedure in different software packages). There are also different ways to account for the interaction between the two subsystems. Finally, since most QM/MM calculations start from an X-ray structure, it is customary to prepare the system by initially adding hydrogen atoms, and water molecules to solvate the protein, and by determining the protonation states of acidic and basic residues using some pK_a criteria. Subsequently, one has to run a series of short MD geometry optimizations and follow by a longer MD calculation, to equilibrate the system, and select a few snapshots for subsequent QM/MM geometry optimization or reaction path scans, etc. Here too, different authors use different approaches. The number of

combinations of the various options and procedures is very large. *This situation opens a wide door for different results for the same problem*. In the absence of proper sampling over all degrees of freedom and protonation states, what is called for is the establishment of some canonical procedures to carry out QM/MM calculations and some standardization measures of the procedures. In the language of the HSS essay, this is necessary, "to allay the skepticism of experimentalists", and to establish the legitimacy of this branch of science in chemistry.

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