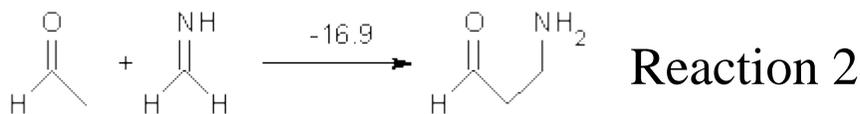
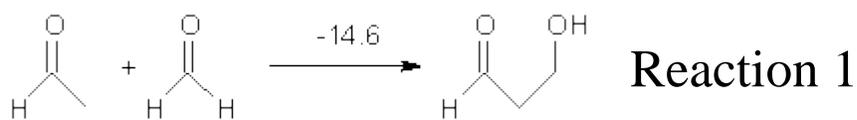
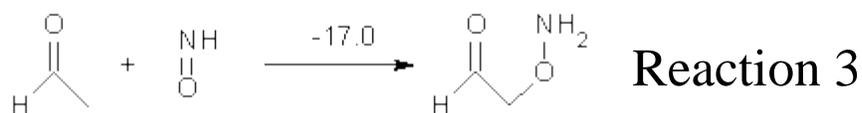


BENCHMARKING DFT FOR THE ALDOL AND MANNICH REACTIONS

Houk has performed a very nice examination of the performance of some density functionals.¹ He takes a quite different approach than what was proposed by Grimme – the “mindless” benchmarking² using random molecules. Rather, Houk examined a series of simple aldol, Mannich and α -aminoxylation reactions, comparing their reaction energies predicted with DFT against that predicted with CBQ-QB3. The idea here is to benchmark DFT performance for simple reactions of specific interest to *organic chemists*. These reactions are of notable current interest due their involvement in organocatalytic enantioselective chemistry (see my posts on the aldol, Mannich, and Hajos-Parrish-Eder-Sauer-Wiechert reaction). Examples of the reactions studied (along with their enthalpies at CBS-QB3) are Reaction 1-3.

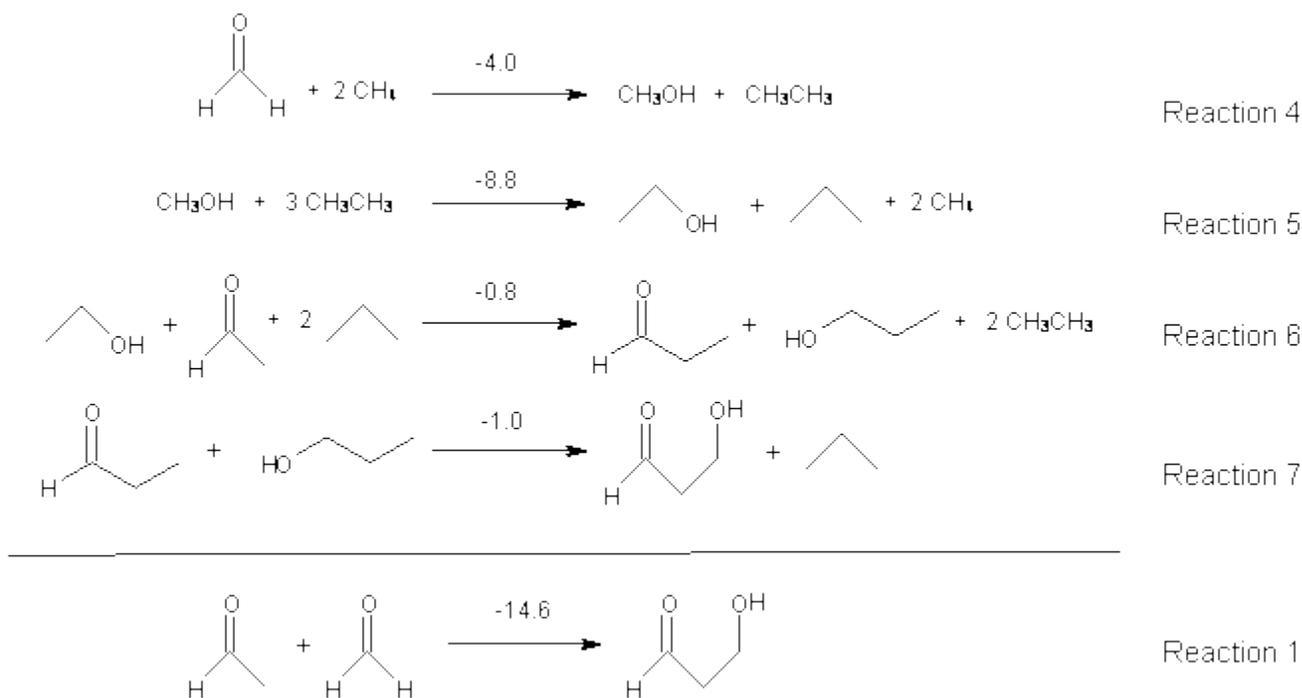




For the four simple aldol reactions and four simple Mannich reactions, PBE1PBE, mPW1PW91 and MO6-2X all provided reaction enthalpies with errors of about 2 kcal mol⁻¹. The much maligned B3LYP functional, along with B3PW91 and B1B95 gave energies with significant larger errors. For the three α -aminoxylation reactions, the errors were better with B3PW91 and B1B95 than with PBE1PBE or MO6-2X. Once again, it appears that one is faced with finding the right functional for the reaction under consideration!

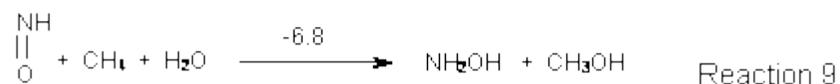
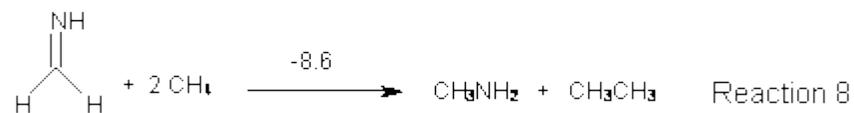
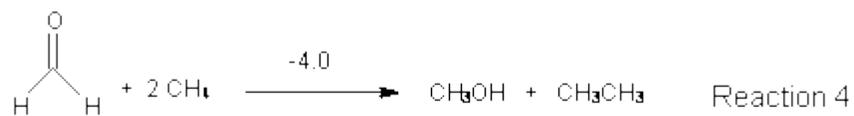
Of particular interest is the decomposition of these reactions into related isogyric, isodesmic and homodesmic reactions. So for example Reaction 1 can be decomposed into Reactions 4-7 as shown in Scheme 1. (The careful reader might note that these decomposition reactions are isodesmic and homodesmotic and hyperhomodesmotic reactions.) The errors for Reactions 4-7 are typically greater than 4 kcal mol⁻¹ using B3LYP or B3PW91, and even with MO6-2X the errors are about 2 kcal mol⁻¹.

Scheme 1.



Houk also points out that Reactions 4, 8 and 9 (Scheme 2) focus on having similar bond changes as in Reactions 1-3. And it's here that the results are most disappointing. The errors produced by all of the functionals for Reactions 4,8 and 9 are typically greater than 2 kcal mol^{-1} , and even MO2-6x can be in error by as much as 5 kcal mol^{-1} . It appears that the reasonable performance of the density functionals for the "real world" aldol and Mannich reactions relies on fortuitous cancellation of errors in the underlying reactions. Houk calls for the development of new functionals designed to deal with fundamental simple bond changing reactions, like the ones in Scheme 2.

Scheme 2



Source: <http://comporgchem.com/blog/?p=624>