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Theoretical Thermodynamics for Large Molecules: Walking the Thin Line between Accuracy and Computational Cost

TOBIAS SCHWABE AND STEFAN GRIMME*
Theoretische Organische Chemie, Organisch-Chemisches Institut der Universität Münster, Corrensstrasse 40, D-48149 Münster, Germany

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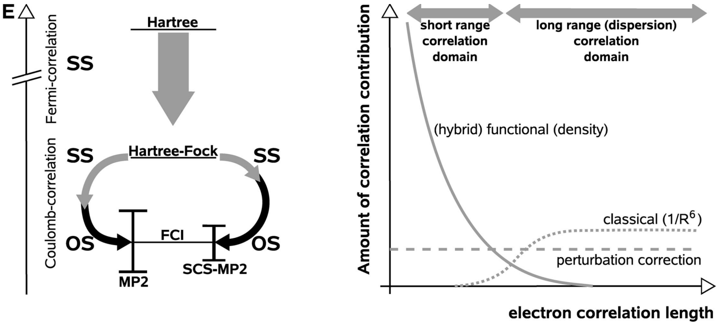

The thermodynamic properties of molecules are of fundamental interest in physics, chemistry, and biology. This Account deals with the developments that we have made in the about last five years to find quantum chemical electronic structure methods that have the prospect of being applicable to larger molecules. The typical target accuracy is about 0.5–1 kcal mol^{-1} for chemical reaction and 0.1 kcal mol^{-1} for conformational energies. These goals can be achieved when a few physically motivated corrections to first-principles methods are introduced to standard quantum chemical techniques. These do not lead to a significantly increased computational expense, and thus our methods have the computer hardware requirements of the corresponding standard treatments. Together with the use of density-fitting (RI) integral approximations, routine computations on systems with about 100 non-hydrogen atoms (2000–4000 basis functions) can be performed on modern PCs.

Our improvements regarding accuracy are basically due to the use of modified second-order perturbation theory to account for many-particle (electron correlation) effects. Such nonlocal correlations are responsible for important parts of the interaction in and between atoms and molecules. A common example is the long-range dispersion interaction that lead to van der Waals complexes, but as shown here also the conventional thermodynamics of large molecules is significantly influenced by intramolecular dispersion effects.

We first present the basic theoretical ideas behind our approaches, which are the spin-component-scaled Møller–Plesset perturbation theory (SCS-MP2) and double-hybrid density functionals (DHDF). Furthermore, the effect of the independently developed empirical dispersion correction (DFT-D) is discussed. Together with the use of large atomic orbital basis sets (of at least triple- or quadruple-ζ quality), the accuracy of the new methods is even competitive with computationally very expensive coupled-cluster methods, but they still remain routinely applicable for day-to-day chemical problems. This is demonstrated for the G3/99 benchmark set of heats of formation, 34 organic isomerization energies, and barriers for a number of pericyclic reactions. As an electronically complicated example, the relative energies of three isomeric Au_8 clusters are considered.

In general, we recommend the very robust B2PLYP-D density functional approach for heat of formation calculations and for electronically complicated situations like transition metal complexes or open-shell species. With B2PLYP-D, an unprecedented low mean absolute deviation for the G3/99 test set with a DFT approach of 1.7 kcal mol^{-1} has been achieved. For closed-shell main-group molecules and many relative energies, SCS-MP2 is the method of choice, because it completely avoids the self-interaction error problem that still plagues current DFT. In critical cases, it is recommended to apply SCS-MP2 and B2PLYP-D simultaneously, where also the comparison with standard MP2 and density functionals like B3LYP may lead to additional insight.

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1. Introduction

Thermodynamic data are of interest to every chemist. For many reasons, measuring these data is an expensive and time-consuming process. On the other hand, quantum chemistry (QC) provides an alternative access to detailed thermodynamic information about molecules. This is quite obvious, because these properties are determined by the internal energy states of a system. For "light" molecules, these states are described by quantum mechanics via the nonrelativistic Schrödinger equation and can thus be obtained by computations theoretically.[1,2]

In practice, however, one is confronted with a serious problem: even if only the electronic contributions are considered quantum mechanically (what is normally done in QC), the necessary equations will be too complex to be solved but for the simplest (one-electron) systems. As soon as a second electron enters the system, the additional interelectronic coupling leads to many-particle effects, and in QC, the phenomenon is called electron correlation. For details, we refer the reader to the very recent overview of Tew et al.[3] Nevertheless we want to emphasize here that one can distinguish two types of electron correlation: the Fermi correlation, which is related to Pauli's exclusion principle (electron spin) and is also called exchange, and the Coulomb correlation, which is due to the repulsive charge interactions between electrons. We will use the term exchange exclusively when referring to Fermi correlation and only speak of correlation when Coulomb correlation is meant to avoid ambiguity.

Because exchange and correlation cannot be computed exactly (and furthermore are not completely separable), simplifications and approximations have to be introduced to keep the mathematics treatable. In the most basic Hartree–Fock (HF) approach to a many-electron system, only exchange is accounted for. This method can be applied routinely to systems with a few hundred atoms, which is sufficient to treat many chemical compounds of interest (although large biochemical systems still represent a computational challenge). Unfortunately its underlying simplification (i.e., the neglect of electron correlation due to the product form of the wave function) leads to inaccuracies, which makes HF theory useless for most thermodynamic problems in chemistry. This forces theorists to use more sophisticated correlated approaches. These mostly rely on HF as starting point and are therefore called post-HF. However, this increases the computational requirements drastically, and for highly accurate methods (as for example the coupled-cluster treatments like CCSD(T)), the hardware and CPU-time requirements are so demanding that only systems with about 5–10 atoms heavier than hydrogen can be treated. A compromise between accuracy and computational cost that also has a broad applicability for the treatment of larger molecules is the second-order Møller–Plesset perturbation theory (MP2),[4] which forms the basis for the new approaches discussed in this Account.

Another solution to the correlation problem is offered by density functional theory (DFT).[5,6] Within its local formulation neither exchange nor correlation is treated by wave-function-type approaches. Functionals are defined instead that calculate all energy contributions based on the electron density. The exact mathematical form of these functionals is unknown, but approximative formulations have been found. Because the computational cost of DFT in its present form is much lower than that for any other method that describes correlation, it has become the most widely used quantum chemical method within the last 20 years. Roughly speaking, current DFT provides the accuracy of an MP2 treatment (or even slightly better) for the lower computational cost of a HF treatment.

Nevertheless, the accuracy of MP2, as well as of DFT, is often not sufficient in many applications. When speaking of accuracy, chemists normally think of an error of about 1 kcal mol^{-1} for relative (reaction) energies. For conformational equilibria, an even higher accuracy typically of about 0.1 kcal mol^{-1} is required. This Account summarizes the effort, which has been made in our group, to compensate for the shortcomings of DFT and simple wave function methods, while still retaining all of their desireable features, namely, to be applicable in a "black-box" manner to large molecular systems. We briefly recapitulate the underlying theory of our approaches and then present their performance for the computation of heats of formation (atomization energies) and for more commonly encountered relative energies (isomerizations). For reasons of limited space, we exclude problems regarding conformation equilibria here but want to note that according to our experience the proposed methods also work very well in this area.[7]

2. Theory of Our Approaches

As already mentioned in the Introduction, a systematic increase of the accuracy of thermodynamic computations based on ab initio methods is not feasible for large systems. For molecules with up to four nonhydrogen atoms, subkilojoule accuracy can be obtained by sequences of coupled-cluster calculations.[8] Alternatives are empirical corrections to well-established but generally too inaccurate standard methods.

The modifications should be physically motivated and of a general kind. Furthermore, only a few parameters (as few as possible) should be introduced. This avoids "overfitting" problems and increases general applicability and the chances of getting "the right answer for the right reason". Furthermore, qualities like size consistency and size extensivity should be retained as all methods presented here do.

2.1. Improving MP2: Rating Things Right. One such physically motivated correction to compute the correlation energy is the spin-component scaled MP2 (SCS-MP2) approximation.[9] Perturbation theory finds solutions to a given problem by adding an infinite series of correction terms to an unperturbed reference system, whose solutions (the HF determinant in this case) are known. In the case of MP2, the corrections are only of second-order, which represents a compromise between accuracy and computational cost.

Our approach is based on the fact that the correlation energy can be separated into contributions of electron pairs with same spin (SS, also called triplet state contribution) and opposite spin (OS, singlet state contribution), which are treated equally in the standard MP approach and add to the total correlation energy, E_C:

$$E_C = E_C^{SS} + E_C^{OS} \tag{1}$$

$$E_C^{SS} = \frac{1}{2}\sum_{ij} e_{ij} + \frac{1}{2}\sum_{\bar{i}\bar{j}} e_{\bar{i}\bar{j}} \tag{2}$$

$$E_C^{OS} = \sum_{i\bar{j}} e_{i\bar{j}} \tag{3}$$

Here, the sums run over all unique electron pairs with individual correlation energies e that are given by

$$e_{ij} = \sum_{ab}\left(T_{ij}^{ab} - T_{ij}^{ba}\right)(ia|jb) \tag{4}$$

$$e_{\bar{i}\bar{j}} = \sum_{\bar{a}\bar{b}}\left(T_{\bar{i}\bar{j}}^{\bar{a}\bar{b}} - T_{\bar{i}\bar{j}}^{\bar{b}\bar{a}}\right)(\bar{i}\bar{a}|\bar{j}\bar{b}) \tag{5}$$

$$e_{i\bar{j}} = \sum_{a\bar{b}} T_{i\bar{j}}^{a\bar{b}}(ia|\bar{j}\bar{b}) \tag{6}$$

Note, that these equations are exact as long as the exact double-excitation amplitudes T (which can be interpreted as electron collision probabilities) are inserted. At the MP2 level, these are simply computed as

$$T_{ij}^{ab} = \frac{(ia|jb)}{\epsilon_i + \epsilon_j - \epsilon_a - \epsilon_b} \tag{7}$$

where ij and ab refer to occupied and virtual spin orbitals, respectively, being of β spin when marked with a bar, $(ia|jb)$ is a two-electron integral in charge-cloud notation, and ϵ parameters represent canonical HF orbital energies.

Recently it has been shown, that a simple and plausible correction to the MP2 scheme leads to significant improvements in almost all cases where MP2 under-performs.[9] The correction is based on a different scaling of the SS and OS contributions according to

$$E_C[\text{SCS-MP2}] = p_{OS}E_C^{OS}[\text{MP2}] + p_{SS}E_C^{SS}[\text{MP2}] \tag{8}$$

where p_{OS} and p_{SS} are empirical (but theoretically well-founded) scaling factors with values of 6/5 and 1/3, respectively, which have been obtained from a fit to a set of representative reaction energies[9] (for a recent theoretical derivation of the scaling factors see ref 10). This SCS-MP2 approach differs from standard MP2, where both components contribute equally (i.e., $p_{OS} = p_{SS} = 1$). Initially it was shown, that this simple correction gives performances in reaction energies comparable to the very accurate coupled-cluster-type QCISD(T) method.[9]

The success is easily traced to the manner in which the more dynamical and short-ranged (i.e., OS) and static (i.e., SS) correlation effects are handled. In the HF method (that actually corresponds to the first-order energy (MP1) of the series), the SS electron pairs are already correlated (Fermi hole), while the OS pairs remain uncorrelated. Low (second) order perturbation theory cannot fully correct for this unbalanced starting point. Hence, the non-HF-correlated pair contribution (OS) must be scaled-up (it is underestimated in MP2), while the HF-correlated contribution (SS) must be scaled-down. This basic idea is illustrated in Figure 1, where the effects of exchange and the correlation components are shown.

Note, that the empirical scaling factors are chosen such that on average the total scaled correlation energy roughly equals its MP2 counterpart (which is often rather close to the basis set full CI limiting value) and that merely the error scatter for different systems is reduced.

The remarkable improvement of SCS-MP2 over MP2 for various chemical problems, which was already apparent from the first publication (and later verified for other problems, see, for example, refs 11–16), inspired Jung et al.[17] to move even one step further. These authors suggest to neglect the same-spin contribution completely ($p_{SS} = 0$ and an increased $p_{OS} = 1.3$), which leads (within some reasonable numerical approximations) to a method that computationally scales only with the fourth power (instead of the fifth power for MP2 and SCS-MP2) on the size of the system. The accuracy of this method, which was termed SOS-MP2, is only slightly less than that of

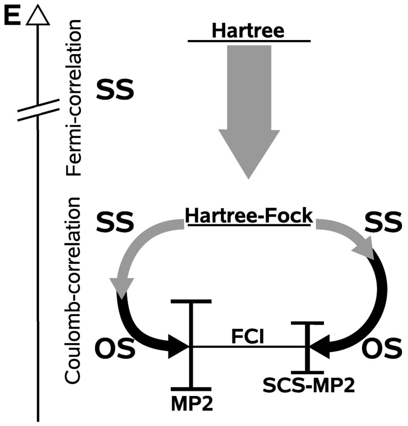


FIGURE 1. Schematic description of the contributions of exchange and correlation to molecular energies that are relevant for the SCS-MP2 method. At the Hartree level, only the classical electrostatic interactions of the electrons are considered. Including the Pauli principle leads to Fermi correlation of same spin (SS) electrons in HF theory, while the opposite spin (OS) electron pairs remain uncorrelated. This leads to a biased starting point of the MP perturbation treatment, which can be corrected by the two SCS factors. Finally, an overall more accurate (balanced) correlation energy than standard MP2 with respect to the full configuration interaction (FCI) limit is obtained. Note that, although the absolute SCS-MP2 correlation energy is similar (or even smaller) than that with MP2, on average it nevertheless yields more accurate chemically relevant relative energies.

SCS-MP2 and (although more efficient for very large systems) still superior to standard MP2.[17]

2.2. Double-Hybrid Density Functionals: Best of Both Worlds. The SCS-MP2 method is a great improvement upon MP2 and for electronically not too complicated systems a very good approximation to CCSD(T) (quantum chemists "gold standard"). We suggest to replace routinely the MP2 method by its improved successor in typical chemical applications. However, SCS-MP2 still lacks some qualities, which limits its applicability. Namely, spin-contaminated open-shell species and transition metal complexes are problematic.[18] DFT is a much more robust method for such cases.

Opposed to wave function methods, there is no clear way to improve upon existing density functionals, and this ultimately determines the accessible accuracy. However, there are some guidelines that allow one to estimate the performance of a functional, which usually improves accuracy by the way it makes use of the electron density and of the Kohn–Sham orbitals. By using the latter, one can incorporate nonlocal effects for exchange (occupied) and correlation (occupied and virtual). An improved description of exchange in current DFT is achieved by an empirical mixing of Fock exchange of the Kohn–Sham reference system with the contribution of a semilocal exchange functional. This is the famous hybrid functional approach,[19,20] which vastly extended the accuracy and applicability of DFT in chemistry. There also exists a nonempirical prescription, which introduces nonlocal correlation to DFT by a perturbation approach basically like MP2. This is known as second-order Kohn–Sham perturbation theory (KS-PT2).[21,22] The main difference from MP2 is the self-consistent way in which the correction is calculated. This leads to numerical problems on the one hand and to computational costs even larger than those of common MP2 on the other.

This was the starting point for our semiempirical approach to make use of the virtual Kohn–Sham orbitals in complete analogy to the treatment of nonlocal exchange in conventional hybrid functionals. These new functionals combine the contribution of a semilocal correlation density functional and an MP2-like second-order correction, derived from the Kohn–Sham orbitals.[23] The exchange is evaluated like in standard hybrid functionals. The exchange–correlation energy expression of such a double-hybrid density functional (DHDF) then reads

$$E_{\mathrm{XC}}^{\mathrm{DHDF}} = (1-a_{\mathrm{X}})E_{\mathrm{X}}^{\mathrm{DFT}} + a_{\mathrm{X}}E_{\mathrm{X}}^{\mathrm{HF}} + (1-a_{\mathrm{C}})E_{\mathrm{C}}^{\mathrm{DFT}} + a_{\mathrm{C}}E_{\mathrm{C}}^{\mathrm{PT2}} \quad (9)$$

where E_{X} is the exchange energy and E_{C} is the correlation energy. The perturbation correction has the usual (not spin-component scaled) MP2 form

$$E_{\mathrm{C}}^{\mathrm{PT2}} = \frac{1}{2}\sum_{ia}\sum_{jb}\frac{(ia|jb)[(ia|jb)-(ib|ja)]}{\epsilon_i+\epsilon_j-\epsilon_a-\epsilon_b} \quad (10)$$

where ϵ are the Kohn–Sham orbital energies obtained self-consistently from the hybrid-GGA part of the functional (i.e., the first three terms on the right-hand side of eq 9). It is important to mention here that only the MP2-type perturbation formula is used, but all input data come from a KS-DFT treatment. The main advantage of this procedure is that the perturbation correction is much more stable against static correlation effects in particular for open-shell species where MP2 usually breaks down. This is also the clear distinction from a related approach, where standard (HF-based) MP2 is mixed with hybrid density functionals.[24] The beneficial influence of the "correlated" KS orbitals in systems with larger static correlation contributions also explains why an SCS-type procedure for the $E_{\mathrm{C}}^{\mathrm{PT2}}$ term has only a minor effect on the accuracy and hence was not considered further (also to keep it as simple as possible).

The parameters a_{X} and a_{C} have been determined empirically. Two DHDFs have been developed so far: B2PLYP with $a_{\mathrm{X}} = 0.53$ and $a_{\mathrm{C}} = 0.27$ using the B88[25] exchange functional and mPW2PLYP[26] with $a_{\mathrm{X}} = 0.55$ and $a_{\mathrm{C}} = 0.25$ using mPW[27] exchange. Both are combined with the LYP[28] correlation functional. The two parameters have been determined empirically by a fit to a subset of the G3/05 set of heats of formantion (HOF). Compared with, for example, B3LYP with 20% Fock exchange, both DHDFs include a much larger Fock-exchange fraction, which reduces the well-known self-interaction error (which is important for transition states, for example). The unwanted effects of increased Fock exchange (e.g., incomplete account of static electron correlation effects) are compensated by the E_C^{PT2} term.

Although the accuracy of the DHDF for thermodynamical properties is remarkably higher than that of all other functionals tested so far,[26] further studies revealed that their performance could be further enhanced with an additional empirical correction for long-range dispersion effects (DFT-D approach).[7] Intramolecular van der Waals interactions are of particular importance in larger molecules, which has been overlooked for many years.[29] Although the perturbation correction should describe such effects in principle, its long-range contribution in B2PLYP and mPW2PLYP is too small (effectively about 30−40%), which was already evident from a consideration of typical van der Waals complexes.[23]

For the dispersion correction we use (in a black-box manner) the now well established and widely used approach from ref 30 that has been described before in ref 31. and is based originally on a correction for HF[32,33] (for other DFT with dispersion methods, see ref 34 and references therein). The total energy for any density functional (including DHDF) is given by

$$E_{\mathrm{DFT-D}} = E_{\mathrm{KS-DFT}} + E_{\mathrm{disp}} \tag{11}$$

where $E_{\text{KS-DFT}}$ is the usual total DFT energy and E_{disp} is an empirical dispersion correction given by

$$E_{\mathrm{disp}} = -s_6 \sum_{i=1}^{N_{\mathrm{at}}-1} \sum_{j=i+1}^{N_{\mathrm{at}}} \frac{C_6^{ij}}{R_{ij}^{\,6}} f_{\mathrm{dmp}}(R_{ij}) \tag{12}$$

Here, N_{at} is the number of atoms in the system, C_6^{ij} denotes the dispersion coefficient for atom pair ij, s_6 is a global scaling factor that only depends on the functional used, R_{ij} is an interatomic distance, and $f_{\mathrm{dmp}}(R_{ij})$ is a damping function to avoid near-singularities for small R and electron correlation double-counting effects.[30] A very appealing feature of DFT-D is that there is only one freely adjustable parameter (s_6) for each functional, which has been determined by a fit to van der Waals binding energies to be 0.55 for B2PLYP and 0.4 for mPW2PLYP, respectively.[7] The other empirical parameters of the method (which are fixed for all functionals) have been derived from computed atomic data (van der Waals radii and C_6 coefficients[30]). The remaining parameter in the damping function has intially been taken from the literature and was later slightly modified.[30] In the following, we mark the combination of any density functional with our dispersion correction by the label "-D" appended to the functional name.

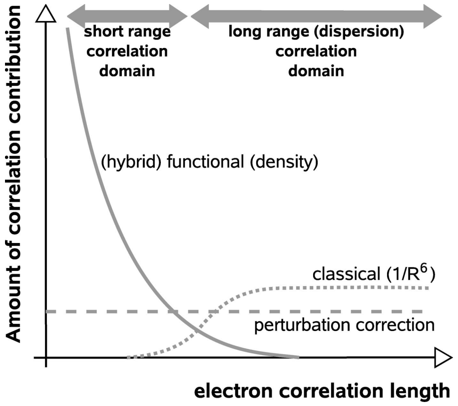


FIGURE 2. Schematic description of the dispersion-corrected double-hybrid density approach with basically different methods for different electron correlation length scales. Note that not potentials (or energies) but the methodological contributions in different regions of interelectronic coupling are shown. The use of the damping function in the dispersion correction avoids double-counting effects with the density-dependent terms already present in the conventional part of the functional.

A basic assumption of this composite approach is that electron correlation effects operate on different lengths scales that are (at least to a major extent) decoupled, and hence the contributions can be treated independently. This is illustrated in Figure 2.

Common semilocal exchange−correlation functionals account (by construction) for static and dynamic correlation effects only in relatively high-density regions, but these decay (due to the density decay) exponentially. There are, however, even in the medium distance range, nonlocal correlation effects that are related to the involved orbitals in a very system-dependent manner, as discussed in detail recently for the seemingly simple case of alkane isomerization.[35] Such effects are treated in the DHDF mainly by the perturbative part. In the long-range regime, the nonlocal correlations become less system dependent and are insignificantly influenced by quantum mechanical effects. They can therefore be treated by classical potentials, that employ the known asymptotic R^{-6} dependence of the dispersion energy for atoms and small molecules. Our approach thus tries to incorporate all relevant correlation effects in a simple but well-defined and physically well-founded manner. As already mentioned above, the only known basic deficiency of the present approach is connected to the self-interaction error of the semilocal functionals used as components. These effects are, however, alleviated by the use of relatively large amounts (∼50%) of Fock exchange.

Equipped with the basic theory, we can now go on to examine how these approaches perform for the computation of typical thermodynamic properties. All results have been obtained with a slightly modified version of the TURBOMOLE program package.[36] The Gaussian atomic orbital (AO) basis sets employed are usually very large (of heavily polarized triple- or quadruple-ζ quality) and are taken from the TURBOMOLE library[37] or from Dunning's work.[38,39] In all cases, open-shell systems have been computed with an unrestricted treatment, and if not mentioned otherwise, B3LYP optimized ground-state geometries have been used. At this point, we also want to acknowledge that SCS-MP2 as well as the DHDF strongly benefit from technical progress made earlier. In particular the formulation of density fitting techniques, also called resolution-of-the-identity (RI) approximation, speeds up MP2-type computations roughly by a factor of 10−20, which has led to some kind of renaissance of perturbation theory development and application. As a sufficient discussion would exceed the scope of this Account, we refer the interested reader to the original work.[40−43]

3. Results and Discussion

3.1. Heats of Formation: The Showcase Discipline in Thermodynamics. Among the various thermodynamic data, molecular heats of formation (HOFs) take a special place. This certainly is related to the direct comparability of experimental and theoretical gas phase data. They are most often the topic of theoretical investigations, when QC methods are benchmarked in performance tests.[44−48] It is a common belief that being good for HOF computations means also being good for everything else. We will comment on this in the next section. First we want to present results for our methods in this application.

During the years, some "gold standard" sets of molecules have been established, mainly based on the work of Curtiss et al.[44,46,49,50] who collected accurate experimental reference data. They also developed a series of theoretical schemes to compute HOF, known as Gn theories. Although these schemes are rather successful (for the development of similar approaches, see, for example, refs 51 and 52.), they are not suitable for larger molecules (with more than about a dozen non-hydrogen atoms) because they rely on sophisticated coupled-cluster-type treatments with relatively large AO basis sets.

Because of the fewer number of individual calculation steps that also have a lower computational cost, our approaches are much simpler to perform. They are explained in detail in ref 15 for SCS-MP2 and in refs 23 and 26 for DHDF. Basically the computation of a HOF requires the computation of an atomization energy. In DFT, this is typically done "brute force" without further empirical corrections, because the important core-correlation effects that occur upon atomization are accounted for by the density functional. This is very difficult in wave function theory, and therefore Gn approaches and also our SCS-MP2 computations include further terms. We use fitted corrections to atomic energies (atom-equivalent scheme)[15] to implicitely account for core-correlation, nonharmonic vibrational effects, and remaining deficiencies of the theoretical treatment with respect to the differential electron correlation between the atoms and the molecule. Furthermore, standard two-point CBS(T-Q) extrapolations for the SCS-MP2 correlation energy are performed in this case. These steps and the atomic corrections are only necessary for SCS-MP2 atomization energy computations and typically not done for more conventional reactions.

TABLE 1. Statistical Data of Different Methods for Two Heat of Formation Test Sets in kcal mol^{-1}[a]

test set		MP2[b]	SCS-MP2[b]	B3LYP[b]	mPW2PLYP	B2PLYP-D
G2/97[c]	MD	−0.4	−0.1	0.3	−0.7	0.4
	MAD	1.7	1.2	2.1	1.5	1.4
	max −min error	13.9	9.2	22.7	13.8	11.9
G3/99[d]	MD			−4.6	−1.4	0.0
	MAD			5.6	2.1	1.7
	max −min error			25.5	16.2	15.5

[a] The mean deviation (MD), mean absolute deviation (MAD), and the error spread (maximum error − minimum error) with respect to experimental data are given. [b] An atom-equivalent scheme has been applied in the computations for the G2/97 set. The values refer to a slightly modified set, that is, spin-contaminated open-shell species are removed and some main group metal compounds are added; see ref 15. The MAD values without any atomic corrections are 6.3 (MP2), 4.2 (SCS-MP2), and 5.2 (B3LYP) kcal mol^{-1}. [c] G3 theory yields a MAD of 0.92 kcal mol^{-1} for the original G2 set. [d] Without any further corrections, G3 theory yields a MAD of 1.05 kcal mol^{-1}.

For the DHDF only one single-point energy calculation with a preferably large AO basis set is necessary, and no further adjustments are made. Because of the favorable scaling behavior with respect to the system size for both approaches and because of the use of the RI approximation, we can apply large AO basis sets of quadruple-ζ quality[53] (auxiliary sets for RI from refs 54 and 55). These basis sets give results near to the basis set limit and are part of the reason for the high accuracy we can achieve.

In Table 1 some statistical quantities for two of the G-sets are listed. It is obvious that SCS-MP2 as well as the DHDF are very accurate. Even for the larger G3/99 test set[49] with 223 entries, the mean absolute deviation (MAD) is only 2.1 kcal mol^{-1} for mPW2PLYP and 1.7 kcal mol^{-1} for B2PLYP-D.

As mentioned in the theory section, we found that intramolecular dispersion effects contribute significantly to the atomi-

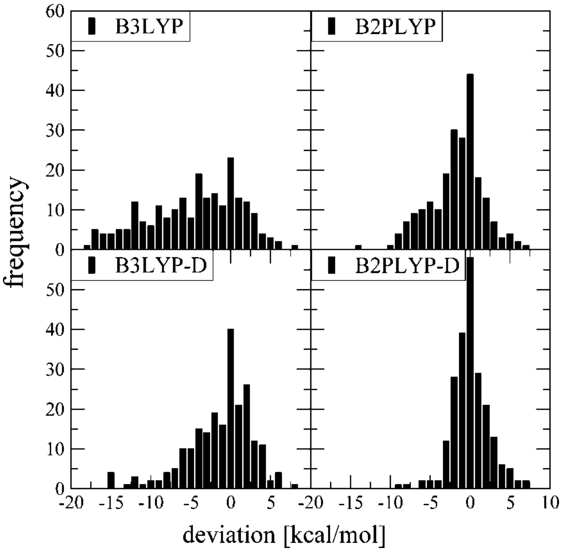


FIGURE 3. Histogram of deviations with respect to experimental data for the G3/99 set of heats of formation. The corresponding MAD values are 5.6 kcal mol^{-1} (B3LYP), 3.1 kcal mol^{-1} (B3LYP-D), 2.4 kcal mol^{-1} (B2PLYP), and 1.7 kcal mol^{-1} (B2PLYP-D).

zation energies of larger molecules.[7] This becomes even more visible when looking at the error distributions as shown in Figure 3. We compare B3LYP and B2PLYP with and without the DFT-D corrections by showing the frequency of errors (deviation = experiment − theory) in 1 kcal mol^{-1} steps. Obviously both functionals benefit from the correction. The errors become more systematic and in particular for B2PLYP-D are evenly distributed around a mean error of zero. Without the D-correction, large molecules are computed to be too unstable, which can be seen in a shift of the distributions toward negative deviations from experiment. Still B3LYP-D lacks the accuracy of the DHDFs, which emphasizes the effect of the new perturbation correction.

Because highly accurate HOF can be determined with B2PLYP-D in one step without any further empirical corrections or basis set extrapolations, we recommend this method for HOF calculations whenever more elaborate methods like coupled-cluster are not feasible.

3.2. Relative Energies: Different Requirements Favor Different Approaches. Although there is great interest in HOF, relative energies are what chemists are really concerned with. These of course can be calculated by the detour over HOF, but this is rather inefficient and generally not done in computational chemistry. When computed HOFs are based on atomization energies, all bonds are broken and (normally) a closed-shell system is converted to an atomic open-shell species. This is an extreme change in the electronic structure, which can be considered as a worst case scenario for differential electron correlation effects. On the other hand, when dealing with typical relative (reaction) energies, the reactants and products are more akin to each other, and many problems appearing in the atomization calculation are not present (as is also the case for HOF computations based on isodesmic reactions).

This is the reason why more and more benchmarks of theoretical methods are carried out with test sets of reaction energies, activation barriers, or isomerizations.[56−60] This often yields more insight, because the errors for more realistic chemical changes are considered. For example, we could show that common DFT methods are not able to correctly describe the branching of alkanes,[35] which is easily overlooked when atomization energies of individual molecules are computed. Contrary to the experimental findings, the *n*-alkanes appear to be more stable than their branched isomers with most density functionals. In a following study, we revealed that this failure also appears for substituted carbon and silicon chains.[61] Recently Schreiner summarized further problems of DFT for relative energy computations and even dissuaded DFT methods for their computation,[62] though there are some promising results[63] that indicate that these problems may be overcome.

Therefore, we made a systematic investigation of how to compute isomerization energies accurately.[64] For this, we used a set of 34 organic isomerization reactions, first introduced by Jorgensen et al.[65] We considered different basis sets as well as a broad variety of methods. One outcome of this study underlines the long-known fact, that well-balanced basis sets of triple-ζ quality including sufficient polarization functions have to be used for energy evaluations. Unfortunately this represents no established standard, and many computations in the chemical literature still suffer from too small (double-ζ) AO basis sets.

In Table 2, the top 12 methods, as well as results for B3LYP, are listed based on their root-mean-square deviation (rms) with respect to the experimental data. As can be seen by this comparison, the SCS-MP2 approach outperforms all other methods tested except CCSD(T)/cc-pVTZ. SCS-MP2 is also superior to the DFT methods, which one would not expect based on its performance in "brute-force" HOF computations. It has an rms value of 1.3 kcal mol^{-1}, which is 0.5 kcal mol^{-1} less than the best conventional density functional tested (BMK[57]). This underlines the different requirements for relative energies and for HOF computations and that the performance for one particular type of reaction cannot be transferred one-on-one to others. Note also that the dispersion correction even for this relatively small molecule containing set makes a significant contribution, such that B2PLYP-D

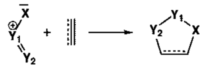
TABLE 2. Statistical Data for the Performance of Different Methods for 34 Organic Isomerization Energies in kcal mol^{-1}[a]

method	rms	MAD	max	no. outliers
CCSD(T)/cc-pVTZ	0.95	0.68	2.3	0
SCS-MP2	1.27	1.03	2.6	0
B2PLYP-D	1.50	1.01	5.3	2
BMK	1.79	1.28	4.7	4
mPW2PLYP	1.83	1.19	6.1	4
B2PLYP	1.93	1.32	6.0	4
MP2	2.04	1.45	6.2	3
PBE0	2.45	1.79	7.0	7
MPWB1K	2.47	1.89	4.9	11
PBE	2.54	1.89	7.3	6
BH-LYP	2.66	1.66	8.9	4
BP86	2.70	1.88	8.4	6
CCSD(T)/6-31G(d)	2.78	1.82	9.6	6
B3LYP	3.27	2.29	10.2	11

[a] When not noted otherwise, the computations have been performed with the TZV(2df,2pd) AO basis set. The root-mean-square deviation (rms), mean absolute deviation (MAD), maximum (unsigned) deviation (max), and the number of cases with a deviation larger than 3 kcal mol^{-1} (no. outliers) with respect to experimental values are given.

TABLE 3. Statistical Performance Data for Three Perturbative Methods and B3LYP for Different Types of Pericyclic Reactions in kcal mol^{-1}[c]

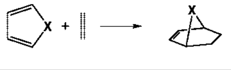
1,3-dipolar cycloadditions[a]



X : O, NH, CH_2
Y_1=Y_2: NN, H_2CNH, HCN

	ΔH‡ (0K)		ΔH (0K)	
	MD	MAD	MD	MAD
SCS-MP2	0.7	1.3	2.0	2.7
MP2	−4.5	4.5	−0.4	2.3
B2PLYP	1.5	1.5	5.1	5.1
B3LYP	3.9	3.9	7.6	7.6

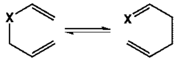
[2+4] (Diels-Alder) cycloadditions[b]



X: {none}, CH_2, NH, O, SiH_2, PH, S

	ΔH‡ (0K)		ΔH (0K)	
	MD	MAD	MD	MAD
SCS-MP2	0.2	0.4	0.0	0.6
MP2	−7.7	7.7	−3.7	3.7
B2PLYP	2.7	2.7	6.8	6.8
B3LYP	7.8	7.8	13.6	13.6

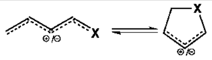
Cope and Claissen rearrangements[b]



X: CH_2, O

	ΔH‡ (0K)		ΔH (0K)	
	MD	MAD	MD	MAD
SCS-MP2	0.2	1.0	2.3	3.8
MP2	−6.4	6.4	2.8	4.2
B2PLYP	0.4	1.0	−0.9	0.9
B3LYP	2.3	2.6	−3.2	3.8

electro cyclisations[b]



X: CH_2, NH

	ΔH‡ (0K)		ΔH (0K)	
	MD	MAD	MD	MAD
SCS-MP2	0.1	0.6	−0.1	0.8
MP2	−3.4	3.6	−1.8	1.8
B2PLYP	1.4	1.9	3.4	3.4
B3LYP	3.1	3.4	6.1	6.1

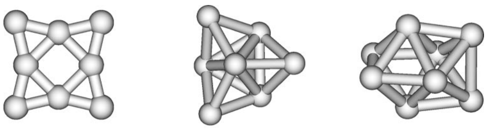
[a] The reference data refer to the CBS-QB3 level of theory. [b] The reference data refer to the G3 level of theory. [c] All computations refer to the cc-pVTZ AO basis. The mean deviation (MD) and the mean absolute deviation (MAD) for activation (Δ*H*‡(0K)) and reaction enthalpies (Δ*H*(0K)) with respect to theoretical reference values are given.

becomes the best-performing DFT approach tested with an accuracy similar to that of SCS-MP2.

Further studies that prove the high accuracy of SCS-MP2 and B2PLYP for chemically more meaningful relative energies have been performed for different pericyclic reactions.[12,66] An overview of the performance in comparison to standard MP2 and B3LYP is given in Table 3. Note that we are considering also reaction barriers here, which is not fundamentally different from the computation of a reaction energy from the theoretical point of view.

Clearly, both new methods improve over their popular precursors. The MAD for the barriers with SCS-MP2 and B2PLYP is typically less than 1−2 kcal mol^{-1} compared with 3−4 kcal mol^{-1} for MP2 or B3LYP. Similar improvements are observed for the reaction enthalpies, although B2PLYP is clearly outperformed here by SCS-MP2. Additionally in these studies[12,66] it was observed that both methods benefit from an increasing quality of the basis set, as expected for a well-behaved quantum chemical method. This does not necessarily hold for other methods, and in particular, the B3LYP results often deteriorate with increasing basis set quality.

Finally in order to explore the limits of application of our methods, we briefly want to show results for an electronically more difficult case. Molecular clusters of gold and in particular their transition from the planar two-dimensional (2D) to three-dimensional (3D) structures have been intensively studied (see ref 67 and references therein). Recently rather accurate CCSD(T) computations of the relative energies of representative types of structures for the Au_8 neutral closed-shell system have been performed by Olson and Gordon.[67] The three most important structures that are also considered here are shown in Figure 4. The system is of theoretical interest also because of the so-called "aurophilic" interaction (see ref 68 and references therein), which is regarded as a dispersion-like electron correlation phenomenon that mainly involves the completely filled but relatively polarizable d-shells of the metal (80 electrons in total). Such contributions (which are further complicated by ionic correlation contributions[68]) are difficult to account for by standard density functionals, and



1 3 6

FIGURE 4. Molecular structures of the investigated gold clusters. The numbers refer to an ordering of isomers used also in previous studies.

TABLE 4. Relative Energies (in kcal mol^{-1}) for the Three Au_8 Clusters with Planar and Three-Dimensional Structures[a]

	relative energy		
method	**1** (D_{4h})	**3** (T_d)	**6** (D_{2d})
HF	0	24.4	33.6
MP2	0	−12.3	−17.1
PBE	0	13.2	16.2
B3LYP	0	21.7	25.7
SCS-MP2	0	−1.8	−3.3
SCS-MP3	0	8.6	10.8
B2PLYP	0	8.2	8.9
CCSD(T)[b]	0	6.0	7.2

[a] The computations refer to a large def2-QZVPP[71] ([7s5p4d4f2g]) AO basis set and the Stuttgart ECP[72] with 19 valence electrons. The structures have been fully optimized at the PBE level. The numbers refer to an ordering of isomers used also in previous studies. [b] CCSD(T) results using a triple-ζ AO basis set from ref 67.

furthermore metallic systems are usually considered as the worst case scenario for MP2 and related HF-based methods.

Inspection of the results for the relative energies reveals this system as being electronically rather problematic with very strong electron correlation contributions. Note that all three isomers have a relatively large HOMO–LUMO gap and according to test calculations not much multiconfigurational character. As can be seen from Table 4, the planar form becomes much too stable at the HF level due to missing electron correlation effects. Oppositely, correlation is grossly overestimated at the MP2 level such that the more "dense" 3D-structures become more stable by 12 and 17 kcal mol^{-1} compared with the planar form. This typical problem of MP2 (overcorrelation) is alleviated by SCS-MP2, and the error with respect to the CCSD(T) result is reduced by 50%. However, the 3D-structures are still slightly more stable than structure **1**, and as can be seen by the very good SCS-MP3 result,[69] higher-order corrections (couplings between electron-pair excitations) are necessary to come close to the CCSD(T) result. This missing robustness of SCS-MP2 (and the increased computational cost of SCS-MP3) were two of the reasons for the development of the DHDF approach, which performs excellently in this example. In fact, the difference between the B2PLYP result and the CCSD(T) reference values of about 1–2 kcal mol^{-1} is within the expected basis set and geometry effects. Note that with B2PLYP (and this holds also for SCS-MP2) **3** and **6** are correctly computed to be much closer in energy. For this property and also regarding the 2D–3D transition, the B3LYP (and to a lesser extend PBE) functionals are not accurate enough.

4. Conclusion

This Account has dealt with the developments that we have made in about the last five years to find quantum chemical methods for an accurate theoretical description of the thermodynamic data even for large molecules. Because the required chemical accuracy can currently not be achieved by a systematic improvement of first principle methods because of the too demanding computational costs, we have introduced a few physically motivated corrections to existing standard quantum chemical techniques. These do not lead to a significantly increased computational expense, and thus our methods have the computer hardware requirements of a standard second-order perturbation treatment. Together with the use of density-fitting (RI) integral approximations, routine computations on systems with about 100 nonhydrogen atoms (2000–4000 basis functions) can be performed on modern PCs.

As the presented results show, our corrections dramatically improve the performance of MP2 and standard hybrid density functionals. The HOFs are typically so accurate that they can compete with experiment and can even be used to identify problematic cases for measurement. Relatively large AO basis sets are necessary to achieve this, and we strongly recommend not going below the triple-ζ level and not relying on uncontrollable error compensation. Although not discussed in detail in this Account, we would also like to underline that both SCS-MP2 and the dispersion-corrected DHDF are also very well suited for all applications that involve noncovalent interactions.[7,34]

When looking for the appropriate theoretical method for a given thermodynamic problem, we want to stress that the choice depends very much on the nature of the chemical problem at hand. We recommend the more robust B2PLYP-D functional for HOF calculations and for electronically complicated situations like transition metal complexes or open-shell species. For closed-shell main-group molecules and many relative energies, SCS-MP2 is the method of choice because it completely avoids the self-interaction error problem of current DFT. Note that 4d/5d-transition metal complexes do not represent so difficult correlation problems for SCS-MP2 as has recently been shown for the thermodynamics of the ruthenium-catalyzed olefin metathesis.[70]

It also seems important to mention that both methods are fundamentally of single-reference character and thus break down for genuine multireference cases like covalent bond breaking or metallic systems with vanishing HOMO–LUMO gap. In any case, we would also recommend applying SCS-MP2 and B2PLYP-D simultaneously in critical problems, where also the comparison with standard MP2 and density functionals like B3LYP may lead to additional insight.

Future development of the DHDF is expected to increase the accuracy further, because until now only unmodified semilocal functionals have been used as components. Work to adjust these to the presence of the perturbative and the dispersion terms are currently under way in our laboratory. However, with further improvement of the electronic contribution to the thermodynamic properties of larger molecules there will be a point where reconsideration of the vibrational contributions (in particular for atomization energies) will become essential.

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Note Added in Proof. The outstanding performance of DHDF also compared to highly parametrized density functionals has been demonstrated very recently for extensive thermodynamic and kinetic benchmark sets by Martin et al.[73]

BIOGRAPHICAL INFORMATION

Tobias Schwabe studied chemistry at the university of Münster. In his advanced courses, he focused on theoretical chemistry. He received his diploma degree for his thesis about the X2-PLYP density functionals. Now he is continuing his research in DFT development and application for a Ph.D. under the supervision of Stefan Grimme.

Stefan Grimme studied Chemistry at the TU Braunschweig and finished his Ph.D. in 1991 in Physical Chemistry on a topic in laser spectroscopy. He then moved to Bonn where did his Habilitation in Theoretical Chemistry in the group of Sigrid Peyerimoff. In 2000, he got the C4 chair for Theoretical Organic Chemistry at the University of Münster. His research interests are the development of quantum chemical methods for large systems, density functional theory, electronic spectroscopy/excited states and the properties of chiral systems.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: grimmes@uni-muenster.de. Phone: (+49)-251-8336512.

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