

The S66 Non-Covalent Interactions Benchmark Reconsidered Using Explicitly Correlated Methods Near the Basis Set Limit*

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The S66 benchmark for non-covalent interactions has been re-evaluated using explicitly correlated methods with basis sets near the one-particle basis set limit. It is found that post-MP2 ‘high-level corrections’ are treated adequately well using a combination of CCSD(F12*) with (aug-)cc-pVTZ-F12 basis sets on the one hand, and (T) extrapolated from conventional CCSD(T)/heavy-aug-cc-pV{D,T}Z on the other hand. Implications for earlier benchmarks on the larger S66×8 problem set in particular, and for accurate calculations on non-covalent interactions in general, are discussed. At a slight cost in accuracy, (T) can be considerably accelerated by using sano-V{D,T}Z+ basis sets, whereas half-counterpoise CCSD(F12*)(T)/cc-pVDZ-F12 offers the best compromise between accuracy and computational cost.

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Introduction

Non-covalent interactions (NCIs) play crucial roles in supra-molecular chemistry and molecular biology, for they are critical in maintaining the three-dimensional structure of large molecules, such as proteins and nucleic acids, and involved in many biological processes in which large molecules bind specifically but temporarily to one another.^[1,2]

Significant effort has been devoted to the study and benchmarking of various non-covalently-bonded systems using experimental as well as computational methods (see, e.g., refs [3–10] for recent reviews). However, experimental data are not available in sufficient quantity or in isolation from environmental or dynamical effects, and thus cannot easily be used for the parametrization of approximate methods such as molecular mechanics force fields or semi-empirical methods.^[11–13] For this reason, wave function *ab initio* calculations represent a viable alternative for obtaining highly accurate NCIs.

Where it comes to bond dissociation energies or reaction barrier heights, ‘chemical accuracy’ is typically defined somewhat arbitrarily as ± 1 kcal mol⁻¹ (1 kcal mol⁻¹ = 4.184 kJ mol⁻¹), while the goal of ‘benchmark accuracy’ is more ambitiously defined at ± 0.24 kcal mol⁻¹ (1 kJ mol⁻¹).^[14] These correspond to relative errors of $\sim 1\%$ or less, as typical bond dissociation energies are on the order of 10^2 kcal mol⁻¹. Non-covalent interactions, however, are on a much smaller energy scale (an average of 5.5 kcal mol⁻¹ for the dimers considered in the present study),

and a relative accuracy of 1% thus corresponds to approximately ± 0.05 kcal mol⁻¹. Such levels of accuracy are, at present, just barely within the reach of wave function *ab initio* methods.^[15–18]

Over the past decades, density functional theory (DFT) has become the most widely used electronic structure method in computational quantum chemistry owing to its attractive accuracy-to-computational cost ratio. It is well established that the performance of DFT can vary for different types of chemical transformations: generally speaking, the accuracy of a given exchange-correlation (XC) functional should increase as larger molecular fragments are conserved on the two sides of the reaction owing to an increasing degree of error cancellation between reactants and products. (For an important caveat, see ref. [19].) This means that the performance of DFT is better for chemical transformations in which NCIs are disrupted, compared with transformations in which covalent bonds are broken. That being said, even the best density functional methods are still an order of magnitude less accurate than what is achievable through wave function *ab initio* calculations: two massive survey studies^[20,21] on the performance of DFT methods have appeared very recently. As semilocal DFT correlation functionals are intrinsically ‘near-sighted’, dispersion (which is intrinsically a long-range effect^[22]) typically requires either a long-range dispersion correction (see refs [23,24] for a review) or a fifth-rung^[25] functional^[26] such as DSD-PBEP86^[27,28] or dRPA75.^[29,30] All the most successful functionals for NCIs

*Dedicated to Graham S. Chandler on the occasion of his 80th birthday.

require parametrization of either the dispersion correction, or the underlying functional, or both: as a rule of thumb, we advocate that parametrization or validation data should be approximately an order of magnitude more accurate than the method being parametrized or validated, lest one be merely ‘fitting to noise’.

It is well known (e.g. ref. [31]) that second-order Møller–Plesset perturbation theory (MP2) is an adequate starting approximation for NCIs (the same cannot be said, however, for molecular atomization energies or reaction barrier heights). Hence, a consensus strategy has emerged in which MP2 interaction energies, obtained using fairly large basis sets, are combined with high-level corrections (HLCs = CCSD(T) – MP2) calculated using smaller sets.

However, for interaction energies between biomolecules and additional realistic-sized systems of interest, the computational cost of HLCs becomes prohibitive even when quite modest basis sets are used. Therefore, many studies have been devoted to assessing the performance of less-costly density functional methods (with and without dispersion corrections) and low-cost wave function methods for standardized NCI benchmarks.

Two popular, and interrelated, such benchmarks are the S66 and S66×8 datasets developed by Hobza and coworkers.^[32,33] Both datasets are based around 66 non-covalent dimers, generated from combinations of 14 different monomers, which had been selected based on their frequency as motifs or functional groups in the most commonly found biomolecules. These complexes participate in a wide variety of NCIs, including electrostatic-dominated interactions (hydrogen bonding), dispersion-dominated interactions (π stacking, aromatic–aliphatic interactions, and aliphatic–aliphatic interactions), and mixed-influence interactions, and are therefore representative of NCIs one might see in biomolecules.

The reference geometries for the S66×8 dataset were obtained by first optimizing each dimer structure at the RI-MP2/cc-pVTZ level,^[32,33] then multiplying the intermonomer distances (r_e) by factors of {0.9,0.95,1.0,1.05,1.10,1.25,1.50,2.00} while keeping the intramonomer geometries frozen – thus generating 8-point unrelaxed ‘dissociation curves’ for each of the 66 monomers. The original S66×8 reference data were computed at the MP2/haV{T,Q}Z level plus an HLC correction computed at the CCSD(T)/AVDZ level, with full counterpoise (CP) correction. Hobza and coworkers then carried out quartic interpolation to the {0.9,0.95,1.0,1.05,1.10} points of each curve and determined the minimum of each polynomial, then used those as the reference geometries for the S66 set. That is to say, although the intramolecular geometry in S66 is still MP2/haVTZ level, the intermolecular part is approximately CCSD(T)/CBS. Although for many systems (e.g. (H₂O)₂, system 1), the difference between S66 and S66×8@1.0 r_e is very small, there are quite substantial differences for the π stacking systems such as benzene parallel-displaced dimer (system 24) and stacked uracil dimer (system 26). (These reference geometry differences can give rise to confusion during benchmark calculations if one is not careful.)

Quite recently, the reference values for S66×8 were revised^[17] by our group using explicitly correlated MP2 and coupled-cluster methods; the revised data were then used for a comprehensive evaluation of many conventional and double-hybrid density functionals.^[17] However, owing to the rather large size of some of the systems in the above datasets (e.g. the uracil dimer), we were unable to obtain HLCs using a basis set larger than cc-pVDZ-F12 for the whole set of 528 dimer

structures: this might actually be considered the Achilles’ heel of our study.

Meanwhile, we published a family of diffuse function-augmented basis sets for explicitly correlated calculations, aug-cc-pVnZ-F12 (in short aVnZ-F12).^[34] Those were originally developed with anionic systems in mind, but turned out to be beneficial for NCIs as well, particularly hydrogen bonds.

Now, we were finally able to perform for the whole S66 dataset, at great computational expense, full CCSD(T)-F12b and CCSD(T)(F12*) calculations, as well as CCSD(F12*)/aug-cc-pVTZ and conventional CCSD(T)/heavy-aug-cc-pVTZ (haVTZ for short) calculations. In addition, we were able to treat a subset of 18 systems with still larger cc-pVQZ-F12 and haVQZ basis sets. For both sets of calculations, appropriate CP corrections were also obtained. Thus, firm and robust HLCs for this dataset that allow assessing the performance of lower-level HLCs are finally within our reach; results and conclusions for such an assessment will therefore be reported in the present work.

Computational Details

All calculations at the Weizmann Institute of Science were carried out on the Faculty of Chemistry’s Linux cluster ‘chemfarm’, whereas those at University of Western Australia (UWA) were carried out on the Linux cluster of the Karton group and at the National Computational Infrastructure (NCI) National Facility. Most wave function-based *ab initio* calculations were carried out using *MOLPRO 2015.1*,^[35] whereas *ORCA*^[36] was used for CCSD(2)_{F12},^[37] calculations, and *TURBOMOLE*^[38] for some additional CCSD(F12)^[39] and CCSD[F12]^[40,41] calculations.

Conventional, orbital-based, *ab initio* calculations were performed using correlation-consistent^[42–45] basis sets. In general, we used the combination of diffuse function-augmented basis sets aug-cc-pVnZ (where n = D,T,Q,5) on non-hydrogen atoms and the regular cc-pVnZ basis sets on hydrogen. For short, this is denoted as haVnZ. In addition, we considered the augmented ano-pVnZ+ and semi-augmented sano-pVnZ+ atomic natural orbital basis sets of Valeev and Neese.^[46]

For the explicitly correlated MP2-F12, CCSD-F12b,^[47,48] and CCSD(F12*)^[40,41] (a.k.a. CCSD-F12c) calculations, the correlation-consistent cc-pVnZ-F12 basis sets of Peterson et al.^[49] were used in conjunction with the appropriate auxiliary basis sets for JKfit^[50] (Coulomb and exchange), MP2fit^[51,52] (density fitting in MP2), and OptRI^[53,54] (complementary auxiliary basis set, CABS) basis sets. For the largest F12-optimized orbital basis set, cc-pV5Z-F12,^[55] we employed Weigend’s aug-cc-pV5Z/JKFIT basis set^[56] for the Coulomb and exchange elements and Hättig’s aug-cc-pwCV5Z/MP2FIT basis set^[57] for both the RI-MP2 parts and for the CABS; the latter was recommended in ref. [55], a brute-force alternative, for want of an optimized OptRI. We also employed the aug-cc-pVnZ-F12 basis sets developed in our group;^[34] the issue of the appropriate CABS basis set is investigated in detail in ref. [58] (see also ref. [59]).

For the purposes of basis set extrapolation, we employed a two-point expression of the form

$$E_\infty = E(L) + [E(L) - E(L-1)] / \left[\left(\frac{L}{L-1} \right)^\alpha - 1 \right],$$

in which the cardinal number L of the basis set is the highest angular momentum in the basis set, $E(L)$ is the total energy for

that value of L , E_∞ is the infinite basis limit and α is taken from table 2 of ref. [17]. The notation MP2-F12/V{T,Q}Z-F12, for instance, indicates a value extrapolated using this expression with the appropriate $\alpha = 4.3548$ taken from there. For the aV{T,Q}Z-F12 pair, no exponent is given there, and we optimized $\alpha = 4.6324$ by the same procedure as described in ref. [60]; for aV{D,T}Z-F12, we found $\alpha = 3.1458$.

As suggested in ref. [60], geminal exponents $\beta = 0.9$ were set for the cc-pVDZ-F12 basis set, $\beta = 1.0$ was set for cc-pVTZ-F12 and cc-pVQZ-F12 basis sets; for cc-pV5Z-F12, as specified in ref. [55], $\beta = 1.2$ was used. CABS correction was used to improve the SCF component.^[47,61] For aug-cc-pVnZ-F12, following ref. [34], we used the same geminal exponents as for the underlying cc-pVnZ-F12 basis sets.

Similarly to our previous work,^[17] three different corrections were considered for the (T) term obtained using explicitly correlated methods:

- (1) CCSD(T*)-F12b: the Marchetti–Werner approximation,^[62,63] in which the (T) contribution is scaled by the $E_{\text{corr}}[\text{MP2-F12}]/E_{\text{corr}}[\text{MP2}]$ correlation energy ratio.
- (2) CCSD(T(b/c))-F12(b/c): (T) is scaled by the respective $E_{\text{corr}}[\text{CCSD-F12(b/c)}]/E_{\text{corr}}[\text{CCSD}]$ ratios.
- (3) CCSD(Ts)-F12b:^[55] (T) contributions are multiplied by constant scaling factors of 1.1413, 1.0527, and 1.0232 for cc-pVDZ-F12, cc-pVTZ-F12, and cc-pVQZ-F12 respectively (table 3 in ref. [55]).

Options (1) and (2) are not strictly size-consistent, but can be rendered so by applying the dimer $E_{\text{corr}}[\text{MP2-F12}]/E_{\text{corr}}[\text{MP2}]$, $E_{\text{corr}}[\text{CCSD-F12(b/c)}]/E_{\text{corr}}[\text{CCSD}]$ ratios also to the monomers: this is indicated by the notation CCSD(T*_{sc}) and CCSD(T(b/c)_{sc}), respectively.

The treatment of basis set superposition error (BSSE), and in particular the balance between the countervailing forces of BSSE and intrinsic basis set insufficiency (IBSI), has been discussed in ref. [64] and references therein. Unless basis sets are very close to the one-particle basis set limit, half-CP (i.e. the average of raw and CP-corrected interaction energies) has been found to yield fastest basis set convergence for both conventional and explicitly correlated interaction energy calculations.^[7,64]

Finally, reference geometries were downloaded from BEGDB (<http://www.begdb.com>; accessed 10 January 2018)^[65] and used verbatim.

Results and Discussion

MP2-F12 Limit

We were able to perform RI-MP2-F12 calculations with the cc-pV5Z-F12 basis set for the entire S66 set, both with and without CP corrections. Unfortunately, the very large auxiliary basis sets that these calculations entail cause a large number of numerical problems owing to near-linear dependence: with the aug-cc-pwCV5Z/OptRI CABS basis set, one data point (47, T-shaped benzene dimer) even yielded a plainly absurd result. With the aug-cc-pVQZ/OptRI CABS basis set, we were able to obtain a complete set of data: although of course this CABS basis set does not match the orbital basis set, we recently found^[58] (for the S66 dataset at the MP2-F12 level) that CABS basis sets are fairly transferable between similar-sized orbital basis sets.

With the aug-cc-pVQZ-F12 basis set, no numerical problems were encountered except for the need^[34] to delete the diffuse f

function from carbon atoms to avoid near-linear dependence in the benzene-containing systems. The root mean square (RMS) CP correction over the S66 set can be taken as a gauge for remaining basis set incompleteness: for aVQZ-F12, that amounts to 0.014 kcal mol⁻¹ at the MP2-F12 level, of which 0.011 kcal mol⁻¹ comes from the correlation contribution. This is considerably better than 0.042 and 0.034 kcal mol⁻¹ respectively, with the cc-pVQZ-F12 basis set, and actually similar to 0.012 kcal mol⁻¹ (both criteria) obtained with the larger cc-pV5Z-F12 basis set.

Another option is cc-pV{T,Q}Z-F12 basis set extrapolation. For this, the RMS difference between raw and CP-corrected extrapolated values is 0.022 kcal mol⁻¹: this drops to 0.006 kcal mol⁻¹ for cc-pV{Q,5}Z-F12, with the caveat that cc-pV5Z-F12 was obtained using an aug-cc-pVQZ/OptRI CABS.

At any rate, the MP2-F12 component is clearly not the accuracy-limiting factor: indeed, Hobza's^[33] best estimated CP-corrected MP2 limits differ from CP-corrected RI-MP2-F12/cc-pVQZ-F12 by just 0.009 kcal mol⁻¹ RMS, which increases to 0.017 kcal mol⁻¹ relative to aV{T,Q}Z-F12 extrapolation (Table 1).

HLC Part 1: CCSD–MP2 Difference

The largest basis set for which we were able to perform CCSD (F12*) calculations for the whole set turned out to be aug-cc-pVTZ-F12. The RMS CP correction for that, again used as a gauge for basis set incompleteness, was found to be 0.013 kcal mol⁻¹, comparable with the remaining amount for MP2-F12/aug-cc-pVQZ-F12. Intriguingly, the regular cc-pVTZ-F12 yields a functionally equivalent RMS CP of 0.012 kcal mol⁻¹: the improvement from the diffuse functions seems to play out primarily at the MP2-F12 level.

For a subset of 18 systems, we were able to perform CCSD (F12*)/cc-pVQZ-F12 calculations, and achieved a reduction of the RMS CP to 0.008 kcal mol⁻¹. This improvement is clearly not commensurate with the immensely greater computational expense (approximately an order of magnitude more CPU time, aside from much greater memory and I/O requirements). This holds especially true in view of the residual uncertainty in the MP2 part.

The CCSD–MP2 difference appears to have stabilised at the CCSD(F12*)/cc-pVQZ-F12 level. As justified at great length in ref. [64] for explicitly correlated calculations with medium and larger basis sets, and in ref. [7] for conventional calculations with sufficiently large basis sets, we have chosen the half-CP values as our ‘gold standard’ reference – by construction, these are equidistant from raw and CP-corrected cc-pVQZ-F12 values, by 0.004 kcal mol⁻¹ RMS (Table 2).

Obviously, cc-pVQZ-F12 is not a realistic option for the entire S66 set. CCSD-F12b/cc-pVTZ-F12 clocks in at 0.015 kcal mol⁻¹ RMSD (root mean square deviation) raw or half-half, and 0.017 kcal mol⁻¹ with full CP. That drops insignificantly to 0.010 kcal mol⁻¹ for CCSD(F12*)/cc-pVTZ-F12. With the small cc-pVDZ-F12 basis set, however, CCSD(F12*) has a definite edge over CCSD-F12b, the RMSDs being 0.014 and 0.043 kcal mol⁻¹ respectively. This is consistent with what we found in ref. [17] and applied there for the revised S66×8 dataset. At the CCSD(F12*)/cc-pVDZ-F12 level, raw results have marginally smaller RMSD than half-CP (0.015) and more noticeably smaller than full CP (0.021 kcal mol⁻¹). This is consistent with our findings in

Table 1. RMSD (kcal mol⁻¹) for the MP2-F12 limits of the S66 set^A
REF, reference

	Relative to cc-pV{Q,5}Z-F12 half-CP			Relative to aV{T,Q}Z-F12 half-CP		
	Raw	CP	Half	Raw	CP	Half
cc-pVDZ-F12	0.083	0.148	0.042	0.085	0.145	0.040
cc-pVTZ-F12	0.066	0.052	0.014	0.068	0.050	0.015
cc-pVQZ-F12	0.029	0.014	0.009	0.032	0.011	0.011
cc-pV5Z-F12	0.007	0.006	0.002			
cc-pV{T,Q}Z-F12	0.023	0.005	0.012	0.025	0.006	0.015
cc-pV{Q,5}Z-F12	0.003	0.003	REF			
aVDZ-F12	0.088	0.092	0.030	0.091	0.090	0.031
aVTZ-F12	0.038	0.019	0.011	0.040	0.017	0.014
aVQZ-F12	0.008	0.007	0.003	0.011	0.005	0.004
aV{D,T}Z-F12	0.040	0.009	0.024	0.043	0.011	0.027
aV{T,Q}Z-F12	0.007	0.003	0.004	0.004	0.004	REF
MP2/CBS ^B		0.019			0.017	

^AIn this and subsequent tables, cells are ‘heatmapped’ from low to high values on a green–yellow–red spectrum.

^BMP2 basis set limit used by Hobza and coworkers for S66 dataset.

Table 2. RMS deviations (kcal mol⁻¹) for the CCSD–MP2 components from the basis set limit values of S66 interaction energies as calculated with various basis sets
REF, reference

	Relative to GOLD ^A reference (for 18 systems)			Relative to SILVER ^B reference (for complete S66 set)		
	Raw	CP	Half	Raw	CP	Half
CCSD-F12b–MP2-F12						
cc-pVDZ-F12	0.043	0.063	0.052	0.042	0.051	0.044
cc-pVTZ-F12	0.015	0.017	0.015	0.019	0.017	0.017
cc-pVQZ-F12	0.005	0.006	0.004			
CCSD-(F12*)–MP2-F12						
cc-pVDZ-F12	0.014	0.021	0.015	0.015	0.020	0.014
cc-pVTZ-F12	0.010	0.007	0.006	0.011	0.007	0.007
cc-pVQZ-F12	0.004	0.004	REF			
aVDZ-F12	0.016	0.015	0.006	0.029	0.020	0.009
aVTZ-F12	0.010	0.005	0.007	0.006	0.006	REF
CCSD–MP2						
haVDZ	0.074	0.098	0.080	0.093	0.183	0.133
haVTZ	0.018	0.063	0.036	0.020	0.088	0.044
haV{D,T}Z	0.018	0.066	0.039	0.031	0.060	0.025
haVQZ	0.014	0.053	0.022			
sano-pVDZ+	0.138	0.145	0.137	0.210	0.267	0.237
sano-pVTZ+	0.085	0.067	0.055	0.071	0.113	0.074
sano-pVQZ+	0.048	0.057	0.022			
AVDZ ^C		0.096			0.179	

^AGOLD: CCSD(F12*)–MP2-F12/cc-pVQZ-F12 half-CP (for subset of 18 out of 66 systems).

^BSILVER: CCSD(F12*)–MP2-F12/aVTZ-F12 half-CP (for complete S66 set).

^CLevel of theory used by Hobza and coworkers in original S66 dataset.

ref. [64], where for small basis sets, uncorrected results consistently agreed better with the basis set limit than CP-corrected ones. (For intermediate basis sets, half-CP works best, whereas for large basis sets, the choice is largely immaterial as the BSSE corrections are so small.)

The CP-corrected [CCSD-MP2]/AVDZ used in the S66 \times 8 paper^[32] here has an RMSD of 0.096 kcal mol⁻¹, compared with 0.066 kcal mol⁻¹ for the CP-corrected [CCSD-MP2]/haV{D,T}Z used in the S66 paper, and just 0.018 kcal mol⁻¹ for the corresponding *raw* values.

What about the various approximations to CCSD-F12? For the cc-pVDZ-F12 basis set, we were able to obtain full CCSD (F12) values using *TURBOMOLE* for 64 out of 66 systems (the two uracil dimers proved too large to converge). The RMSD from these values at the CCSD(F12*) level is just 0.001 (!) kcal mol⁻¹, making it clear that CCSD(F12*) is, at least for this type of problem, as good an approximation as we can hope for. At the CCSD-F12b level, we incur an error of 0.039 kcal mol⁻¹ RMS, which increases to 0.067 kcal mol⁻¹ at the CCSD-F12a level (Table S1, Supplementary Material). (The often-proffered claims, e.g. ref. [66], that CCSD-F12a is superior to CCSD-F12b for small basis sets rest on an error compensation between basis set incompleteness and CCSD-F12a's tendency to overbind.^[16]) The CCSD[F12] level, which includes all third-order cross terms from CCSD(F12) but omits the fourth-order terms, clocks in at 0.027 kcal mol⁻¹. Using the CCSD(2)_{F12} implementation in *ORCA 4*, we obtain 0.022 kcal mol⁻¹.

It had earlier been suggested to us by reviewers of refs [16,55] that the gap between CCSD-F12b and CCSD(F12*) might be closed by evaluating the CABS terms in the projector, which occurs in the dominant CCSD-F12 coupling terms and which are neglected in standard CCSD-F12b. (Their evaluation can be forced by setting IXPROJ = 1 in *MOLPRO*.) With the larger cc-pVTZ-F12 basis set, F12b and F12b(IXPROJ = 1) are both \sim 0.02 kcal mol⁻¹ RMS from CCSD(F12*): In the cc-pVDZ-F12 basis set, however, a larger benefit is observed: RMSD = 0.018 kcal mol⁻¹ from full CCSD(F12) is actually better than CCSD[F12] (see above). We noted previously for the water clusters^[16] that the projector terms do converge very rapidly with the basis set.

HLC Part 2: Triples (T) Term

This term does not benefit from F12, although various approximate scaling techniques have been proposed (see below).

It was previously found for water clusters^[16] as well as for main-group atomization energies^[67] that (T) is best obtained from conventional CCSD(T) calculations. We will attempt to do so here.

For a subset of 18 systems, we were able to do CCSD(T)/haV{T,Q}Z extrapolation: the RMS CP correction to (T) is just 0.004 kcal mol⁻¹: this suggests the extrapolated value is very close to the one-particle infinite basis set limit, where said difference should vanish. It also means that these values should be an acceptable benchmark for lower-level approaches.

Intriguingly, for CCSD(T)/sano-V{T,Q}Z+, the RMS CP correction increases to 0.010 kcal mol⁻¹, even though atomic natural orbital basis sets should (in principle) minimize basis set superposition error. Extrapolation of raw and CP-corrected (T)/haV{T,Q}Z contributions to the interaction energy led to nearly identical results, the RMS difference between both sets of results being a negligible 0.007 kcal mol⁻¹ (Table 3). The same remark as in the previous paragraph applies to the extrapolated value.

Table 3. RMS deviations (kcal mol⁻¹) for the (T) term of conventional CCSD(T) calculated for S66 interaction energies with various basis sets

	For 18 subsystems			For complete S66 set		
	Raw	CP	Half	Raw	CP	Half
haV{T,Q}Z	0.002	0.002	REF ^A			
haV{D,T}Z	0.007	0.011	0.008	0.007	0.007	REF ^B
haVQZ	0.005	0.019	0.012			
haVTZ	0.011	0.047	0.028	0.022	0.052	0.026
haVDZ	0.035	0.137	0.081	0.086	0.172	0.089
sano-pV{T,Q}Z+	0.010	0.007	0.007			
sano-pV{D,T}Z+	0.022	0.041	0.027	0.026	0.057	0.039
sano-pVQZ+	0.020	0.043	0.030			
sano-pVTZ+	0.047	0.095	0.069	0.073	0.132	0.102
sano-pVDZ+	0.128	0.226	0.176	0.199	0.312	0.254
AVDZ ^C		0.115			0.134	

^AGOLD: [CCSD(T)-CCSD]/haV{T,Q}Z half-CP (for subset of 18 out of 66 systems).

^BSILVER: [CCSD(T)-CCSD]/haV{D,T}Z half-CP reference (for complete S66 set).

^CLevel of theory used by Hobza and coworkers in original S66 dataset.

We have somewhat arbitrarily chosen the average of both values – mathematically equivalent to ‘half-CP’ – as our ‘gold standard’ reference value.

The (T)/haV{D,T}Z does remarkably well, at an RMSD relative to half-CP (T)/haV{T,Q}Z of just 0.011 kcal mol⁻¹ without CP and 0.008 kcal mol⁻¹ with half-CP. The (T) for uracil dimer still takes over 1 week wall time on 16 cores, though: with the smaller sano-V{D,T}Z+ basis sets, the calculation time can be halved, at the expense of increasing RMSD to 0.022 kcal mol⁻¹ (raw) and 0.027 kcal mol⁻¹ (half-CP). Thus, sano-V{D,T}Z may be a viable option where haV{D,T}Z is computationally too expensive and various F12 scaling schemes with (aug-)cc-pVDZ-F12 basis sets too inaccurate.

What about the various scaling schemes for the triples? With the cc-pVTZ-F12 basis set, which is similar in cost, RMSDs over the small 18-system set are smallest for (Ts) with half-CP (0.006 kcal mol⁻¹), (T*_{sc}) with full CP (0.007 kcal mol⁻¹), or unscaled (T) without CP correction (0.012 kcal mol⁻¹, similar to (T_{sc}) half-CP) (Table 4). For VQZ-F12, very low RMSDs are obtained for (Ts) with half-CP, (T_{sc}) or (T*_{sc}) with full CP, or unscaled raw (T).

We now turn to the cc-pVDZ-F12 basis set, where recovery of the (T) term represents a challenge on account of the small basis set. With either the CCSD(F12*) or the CCSD-F12b ansatz, half-CP is clearly superior over the two other choices, particularly CCSD(T_{sc}) and CCSD(T*_{sc}).

HLC Considered as a Whole

The best level of HLC we can afford, and that only for a subset of 18 systems, would be what we could term GOLD: [CCSD(F12*)-MP2-F12]/cc-pVQZ-F12 half-CP combined with (T)/haV{T,Q}Z. The next level down we term SILVER: CCSD(F12*)/aug-cc-pVTZ-F12 half-CP combined with (T)/haV{D,T}Z, which we were able to complete for all 66 systems. (By far

Table 4. RMS deviations (kcal mol^{-1}) for the (T) term of explicitly correlated CCSD(T)-F12x calculated for S66 interaction energies with various basis sets

	Raw (T*)	Raw (T)	Raw (T _{b_{sc}})	Raw (T* _{sc})	Raw (T _s)	CP (T*)	CP (T)	CP (T _{b_{sc}})	CP (T* _{sc})	CP (T _s)	Half (T*)	Half (T)	Half (T _{b_{sc}})	Half (T* _{sc})	Half (T _s)
Relative to GOLD ^A reference (for 18 subsystems)															
F12b/cc-pVQZ-F12	0.022	0.006	0.020	0.025	0.016	0.010	0.019	0.003	0.003	0.007	0.015	0.008	0.009	0.013	0.005
F12b/cc-pVTZ-F12	0.042	0.012	0.037	0.045	0.030	0.017	0.046	0.015	0.007	0.021	0.027	0.024	0.012	0.020	0.006
F12b/cc-pVDZ-F12	0.066	0.046	0.045	0.061	0.033	0.044	0.132	0.067	0.053	0.077	0.038	0.088	0.018	0.013	0.027
(F12*)/cc-pVDZ-F12	0.057	0.055	0.039	0.050	0.025	0.051	0.141	0.074	0.063	0.086	0.036	0.097	0.024	0.015	0.037
(F12*)/aVDZ-F12	0.055	0.043	0.045	0.058	0.032	0.035	0.117	0.048	0.037	0.060	0.036	0.079	0.013	0.017	0.020
Relative to SILVER ^B (for complete S66 set)															
F12b/cc-pVTZ-F12	0.062	0.018	0.066	0.079	0.057	0.019	0.054	0.010	0.012	0.015	0.039	0.023	0.032	0.044	0.023
F12b/cc-pVDZ-F12	0.085	0.044	0.096	0.122	0.080	0.048	0.167	0.064	0.044	0.076	0.041	0.103	0.029	0.047	0.022
(F12*)/cc-pVDZ-F12	0.069	0.058	0.084	0.103	0.063	0.061	0.181	0.074	0.058	0.092	0.036	0.118	0.023	0.032	0.026
(F12*)/aVDZ-F12	0.080	0.032	0.121	0.142	0.102	0.035	0.140	0.036	0.028	0.049	0.045	0.081	0.055	0.072	0.040

^AGOLD: [CCSD(T)–CCSD]/haV{T,Q}Z half-CP (for subset of 18 out of 66 systems).

^BSILVER: [CCSD(T)–CCSD]/haV{D,T}Z half-CP reference (for complete S66 set).

Table 5. RMS deviations (kcal mol^{-1}) for the high-level corrections (HLC = [CCSD(T)-F12x – MP2-F12]/cc-pVnZ-F12) components of the S66 interaction energies

	Raw HLC (T*)	Raw HLC (T)	Raw HLC (T _{b_{sc}})	Raw HLC (T* _{sc})	Raw HLC (T _s)	CP HLC (T*)	CP HLC (T)	CP HLC (T _{b_{sc}})	CP HLC (T* _{sc})	CP HLC (T _s)	Half HLC (T*)	Half HLC (T)	Half HLC (T _{b_{sc}})	Half HLC (T* _{sc})	Half HLC (T _s)
Relative to GOLD ^A reference (for 18 subsystems)															
F12b/cc-pVQZ-F12	0.019	0.003	0.018	0.023	0.013	0.014	0.014	0.005	0.009	0.004	0.016	0.007	0.011	0.015	0.007
F12b/cc-pVTZ-F12	0.039	0.009	0.035	0.043	0.028	0.020	0.055	0.026	0.021	0.032	0.023	0.029	0.012	0.018	0.012
F12b/cc-pVDZ-F12	0.039	0.082	0.024	0.031	0.027	0.089	0.184	0.122	0.110	0.133	0.048	0.132	0.063	0.051	0.075
(F12*)/cc-pVDZ-F12	0.057	0.058	0.043	0.053	0.032	0.061	0.153	0.087	0.077	0.100	0.036	0.103	0.034	0.026	0.046
(F12*)/aVDZ-F12	0.067	0.031	0.060	0.073	0.047	0.042	0.130	0.062	0.052	0.074	0.036	0.079	0.016	0.020	0.023
Relative to SILVER ^B (for complete S66 set)															
F12b/cc-pVTZ-F12	0.068	0.025	0.075	0.088	0.066	0.021	0.057	0.022	0.024	0.026	0.041	0.024	0.039	0.051	0.032
F12b/cc-pVDZ-F12	0.058	0.072	0.078	0.102	0.065	0.074	0.196	0.103	0.087	0.115	0.035	0.132	0.050	0.053	0.055
(F12*)/cc-pVDZ-F12	0.073	0.054	0.092	0.112	0.072	0.069	0.190	0.087	0.071	0.103	0.034	0.119	0.032	0.039	0.035
(F12*)/aVDZ-F12	0.105	0.035	0.149	0.170	0.130	0.044	0.158	0.053	0.041	0.067	0.048	0.078	0.061	0.078	0.047

^AGOLD: half-CP-corrected [CCSD(F12*)–MP2-F12]/cc-pVQZ-F12 combined with half-CP-corrected [CCSD(T)–CCSD]/haV{T,Q}Z.

^BSILVER: half-CP-corrected [CCSD(F12*)–MP2-F12]/aVTZ-F12 combined with half-CP-corrected [CCSD(T)–CCSD]/haV{D,T}Z.

the most CPU-intensive step was the CCSD(T)/haVTZ calculations, which took over 2 weeks on a 16-CPU machine for uracil dimer.)

The RMS difference between GOLD and SILVER for the 18 systems where we have the former available is just $0.006 \text{ kcal mol}^{-1}$; hence, we are probably justified using SILVER as a standard. For comparison, full-CP [CCSD(T)–MP2]/haV{D,T}Z as used for the Hobza S66 reference values has an RMSD = $0.053 \text{ kcal mol}^{-1}$ from SILVER, and $0.054 \text{ kcal mol}^{-1}$ from GOLD.

As unlike for the MP2-F12 part, there seems to be comparatively little effect of the extra diffuse functions on the [CCSD(F12*)–MP2-F12] part, we also considered a lower-cost STERLING level (i.e. silver–copper alloy) in which

[CCSD(F12*)–MP2-F12]/aug-cc-pVTZ-F12 is combined with (T)/sano-V{D,T}Z+. Deviation from GOLD is just $0.022 \text{ kcal mol}^{-1}$ RMS over the 18-system subset; from SILVER, it is $0.026 \text{ kcal mol}^{-1}$ over the whole S66 set. As the most expensive calculation step for the largest systems in S66 has now been reduced to ‘just’ 5 days on a 16-core machine, this may be a viable option for larger benchmarks if greater accuracy is needed.

Can we avoid having to do the (T) in a triple-zeta basis altogether? This pretty much implies using some form of scaling scheme. From Table 5, it would seem that CCSD(F12*)(T_{sc})/cc-pVDZ-F12 with half-CP would be the lowest-cost option. According to Table 5, this deviates by just $0.032 \text{ kcal mol}^{-1}$ RMS from SILVER, and hence becomes our new BRONZE (or BRONZEnew) option.

Table 6. Systems in the S66 dataset and final recommended dissociation energies (kcal mol⁻¹) obtained in the present work

Systems	GOLD ^A	SILVER ^B
01 Water ... Water	4.979	4.982
02 Water ... MeOH	5.666	5.666
03 Water ... MeNH ₂	6.985	6.986
04 Water ... peptide		8.183
05 MeOH ... MeOH	5.824	5.822
06 MeOH ... MeNH ₂	7.625	7.617
07 MeOH ... peptide		8.307
08 MeOH ... water	5.065	5.064
09 MeNH ₂ ... MeOH	3.088	3.087
10 MeNH ₂ ... MeNH ₂	4.189	4.184
11 MeNH ₂ ... peptide		5.436
12 MeNH ₂ ... water	7.354	7.349
13 Peptide ... MeOH		6.251
14 Peptide ... MeNH ₂		7.516
15 Peptide ... peptide		8.689
16 Peptide ... water		5.180
17 Uracil ... uracil (BP)		17.407
18 Water ... pyridine		6.927
19 MeOH ... pyridine	7.464	7.467
20 AcOH ... AcOH	19.364	19.361
21 AcNH ₂ ... AcNH ₂	16.468	16.474
22 AcOH ... uracil		19.736
23 AcNH ₂ ... uracil		19.420
24 Benzene ... benzene (π - π)		2.685
25 Pyridine ... pyridine (π - π)		3.751
26 Uracil ... uracil (π - π)		9.672
27 Benzene ... pyridine (π - π)		3.300
28 Benzene ... uracil (π - π)		5.517
29 Pyridine ... uracil (π - π)		6.629
30 Benzene ... ethene	1.348	1.358
31 Uracil ... ethene		3.291
32 Uracil ... ethyne		3.651
33 Pyridine ... ethene	1.790	1.779
34 Pentane ... pentane		3.741
35 Neopentane ... pentane		2.582
36 Neopentane ... neopentane		1.745
37 Cyclopentane ... neopentane		2.376
38 Cyclopentane ... cyclopentane		2.967
39 Benzene ... cyclopentane		3.488
40 Benzene ... neopentane		2.824
41 Uracil ... pentane		4.761
42 Uracil ... cyclopentane		4.052
43 Uracil ... neopentane		3.652
44 Ethene ... pentane		1.973
45 Ethyne ... pentane		1.696
46 Peptide ... pentane		4.215
47 Benzene ... benzene (TS)		2.801
48 Pyridine ... pyridine (TS)		3.472
49 Benzene ... pyridine (TS)		3.260
50 Benzene ... ethyne (CH- π)	2.839	2.828
51 Ethyne ... ethyne (TS)	1.526	1.519
52 Benzene ... AcOH (OH- π)		4.691
53 Benzene ... AcNH ₂ (NH- π)		4.376
54 Benzene ... water (OH- π)		3.267
55 Benzene ... MeOH (OH- π)		4.139
56 Benzene ... MeNH ₂ (NH- π)		3.174
57 Benzene ... peptide (NH- π)		5.222
58 Pyridine ... pyridine (CH-N)		4.189
59 Ethyne ... water (CH-O)	2.912	2.905
60 Ethyne ... AcOH (OH- π)	4.925	4.917
61 Pentane ... AcOH		2.876
62 Pentane ... AcNH ₂		3.491

(continued)

Table 6. (Continued)

Systems	GOLD ^A	SILVER ^B
63 Benzene ... AcOH		3.709
64 Peptide ... ethene		2.967
65 Pyridine ... ethyne		4.064
66 MeNH ₂ ... pyridine		3.930

^AGOLD: MP2-F12/aV{T,Q}Z-F12 half-CP + [CCSD(F12*)-MP2-F12]/cc-pVQZ-F12 half-CP + [CCSD(T)-CCSD]/haV{T,Q}Z half-CP.^BSILVER: MP2-F12/aV{T,Q}Z-F12 half-CP + [CCSD(F12*)-MP2-F12]/aVTZ-F12 half-CP + [CCSD(T)-CCSD]/haV{D,T}Z half-CP.

The same level of HLC without CP was used in the S66 \times 8 revision paper, and alas incurs RMS = 0.096 kcal mol⁻¹, even though the deviation from GOLD for the 18-system subset is just 0.044 kcal mol⁻¹. The difference between raw CCSD(F12*) (T_{cc})/cc-pVDZ-F12 and its half-CP counterpart can indeed be non-trivial, reaching a maximum of 0.2 kcal mol⁻¹ for system 26 (stacked uracil dimer).

Final Reference Data and Overall Performance

Our final reference data are given in Table 6, while Fig. 1 graphically represents the errors for the entire S66 set compared with SILVER references. The Hobza S66 reference values are actually quite close to SILVER: unfortunately, the CCSD(T)/haVTZ step they entail makes them essentially as expensive as SILVER itself. Aside from a few outliers (acetic acid and acetamide dimers), STERLING performs quite well and might be a viable option for a recalculation of S66 \times 8. BRONZEnew would be the next best solution, and is computationally much less expensive: the extra cost compared with our published S66 \times 8 revision is essentially that of the CCSD(F12*)(T)/cc-pVDZ-F12 CP steps. Considering that this cuts the interquartile range of the errors approximately in half, we believe that the fairly modest extra cost is well justified.

Finally, the ‘old S66’ level of theory, at which Hobza and coworkers calculated the S66 set, clearly has an inadequate HLC (just CCSD(T)/AVDZ with full CP), as noted previously in ref. [17].

CP-corrected [CCSD(T)-MP2]/AVDZ, as used in the S66 \times 8 paper, clearly does benefit from some error compensation between CCSD-MP2 and (T), as the RMSD relative to the 66-system silver standard is *substantially* smaller than the RMSDs on the two constituent components.

A Preliminary Update of S66 \times 8

It is computationally quite feasible to re-evaluate all of S66 \times 8 at our new BRONZE level. These data are presented in Table 7.

Differences with our previously published revision are small at equilibrium and stretched distances (0.053 kcal mol⁻¹ RMS), but more significant at compressed distances (0.108 kcal mol⁻¹ RMS). The largest differences are seen for dimers involving uracil. We attempted aug-cc-pVDZ-F12 half-CP as well, but spot-checking against SILVER results for a small subset of systems (20, 21, 24) suggests that any calculation in which (T) is not evaluated with at least a haVTZ basis set needs to be considered with caution for the compressed distances. Such a re-evaluation is presently in progress, but will take time owing to its formidable computational cost for, particularly, the uracil dimers.

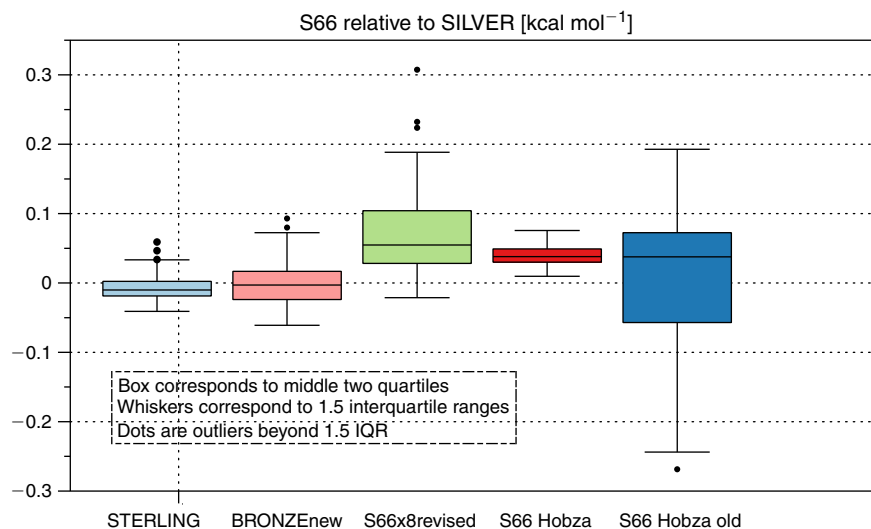


Fig. 1. Box plot of errors in S66 association energies compared with SILVER values (kcal mol^{-1}).

Table 7. Preliminary re-evaluation of the S66 \times 8 dataset at our new BRONZE level (kcal mol^{-1})

	$0.9r_e$	$0.95r_e$	$1.0r_e$	$1.05r_e$	$1.1r_e$	$1.25r_e$	$1.5r_e$	$2.0r_e$
01 Water ... water	4.610	4.912	4.915	4.739	4.462	3.460	2.108	0.871
02 Water ... MeOH	5.232	5.578	5.589	5.396	5.086	3.947	2.385	0.952
03 Water ... MeNH ₂	6.530	6.897	6.894	6.660	6.291	4.916	2.973	1.140
04 Water ... peptide	7.666	8.076	8.089	7.851	7.465	5.991	3.828	1.437
05 MeOH ... MeOH	5.328	5.727	5.773	5.599	5.299	4.147	2.526	1.010
06 MeOH ... MeNH ₂	7.006	7.497	7.558	7.346	6.971	5.497	3.342	1.273
07 MeOH ... peptide	7.689	8.186	8.255	8.051	7.680	6.190	3.649	1.099
08 MeOH ... water	4.629	4.985	5.023	4.867	4.601	3.595	2.201	0.908
09 MeNH ₂ ... MeOH	2.813	3.037	3.029	2.889	2.680	1.970	1.097	0.394
10 MeNH ₂ ... MeNH ₂	3.671	4.068	4.127	3.985	3.730	2.777	1.302	0.388
11 MeNH ₂ ... peptide	4.922	5.334	5.387	5.221	4.926	3.204	1.402	0.457
12 MeNH ₂ ... water	6.777	7.224	7.259	7.036	6.659	5.217	3.149	1.195
13 Peptide ... MeOH	5.725	6.149	6.213	6.053	5.762	4.615	2.952	1.308
14 Peptide ... MeNH ₂	6.860	7.379	7.478	7.310	6.978	5.611	3.552	1.492
15 Peptide ... peptide	8.085	8.590	8.673	8.485	8.131	6.677	4.426	1.782
16 Peptide ... water	4.740	5.097	5.146	5.006	4.758	3.805	2.458	1.136
17 Uracil ... uracil (base pair)	16.042	17.190	17.432	17.078	16.352	13.263	8.410	3.357
18 Water ... pyridine	6.453	6.853	6.872	6.653	6.294	4.939	3.013	1.189
19 MeOH ... pyridine	6.855	7.366	7.451	7.263	6.911	5.490	3.385	1.336
20 AcOH ... AcOH	17.793	19.070	19.328	18.923	18.106	14.657	9.246	3.595
21 AcNH ₂ ... AcNH ₂	15.185	16.242	16.441	16.085	15.386	12.485	8.022	3.009
22 AcOH ... uracil	18.241	19.470	19.732	19.358	18.581	15.243	9.907	4.161
23 AcNH ₂ ... uracil	18.011	19.157	19.419	19.094	18.391	15.309	10.276	4.672
24 Benzene ... benzene (π - π)	-0.030	1.905	2.634	2.739	2.546	1.543	0.499	0.067
25 Pyridine ... pyridine (π - π)	1.063	2.997	3.716	3.788	3.543	2.360	0.974	0.241
26 Uracil ... uracil (π - π)	7.693	9.396	9.765	9.406	8.688	6.110	3.138	1.013
27 Benzene ... pyridine (π - π)	0.463	2.523	3.265	3.338	3.096	1.976	0.735	0.151
28 Benzene ... uracil (π - π)	3.278	5.041	5.588	5.475	5.034	3.296	1.380	0.260
29 Pyridine ... uracil (π - π)	3.460	5.990	6.698	6.513	5.936	3.876	1.796	0.543
30 Benzene ... ethene	0.048	0.977	1.310	1.333	1.210	0.678	0.176	-0.008
31 Uracil ... ethene	2.424	3.130	3.300	3.181	2.921	1.981	0.937	0.257
32 Uracil ... ethyne	2.628	3.442	3.649	3.528	3.247	2.213	1.045	0.275
33 Pyridine ... ethene	0.699	1.487	1.764	1.762	1.621	1.013	0.367	0.047
34 Pentane ... pentane	2.789	3.569	3.734	3.581	3.278	2.223	1.050	0.273
35 Neopentane ... pentane	1.817	2.466	2.590	2.467	2.240	1.491	0.699	0.187
36 Neopentane ... neopentane	1.428	1.713	1.753	1.667	1.524	1.042	0.504	0.136
37 Cyclopentane ... neopentane	1.574	2.225	2.384	2.306	2.122	1.458	0.705	0.191
38 Cyclopentane ... cyclopentane	2.199	2.811	2.971	2.839	2.578	1.705	0.791	0.207
39 Benzene ... cyclopentane	2.013	3.135	3.496	3.420	3.135	2.062	0.903	0.194

(continued)

Table 7. (Continued)

	$0.9r_e$	$0.95r_e$	$1.0r_e$	$1.05r_e$	$1.1r_e$	$1.25r_e$	$1.5r_e$	$2.0r_e$
40 Benzene ... neopentane	1.753	2.597	2.839	2.767	2.544	1.703	0.773	0.191
41 Uracil ... pentane	3.732	4.624	4.792	4.569	4.064	2.451	0.986	0.220
42 Uracil ... cyclopentane	2.963	3.910	4.094	3.895	3.526	2.298	1.026	0.253
43 Uracil ... neopentane	2.807	3.560	3.678	3.478	3.142	2.055	0.932	0.235
44 Ethene ... pentane	1.589	1.918	1.948	1.830	1.648	1.078	0.490	0.121
45 Ethyne ... pentane	0.997	1.526	1.669	1.616	1.473	0.958	0.418	0.097
46 Peptide ... pentane	3.673	4.144	4.195	4.009	3.700	2.615	1.190	0.290
47 Benzene ... benzene (T-shaped)	1.549	2.513	2.823	2.790	2.590	1.772	0.839	0.230
48 Pyridine ... pyridine (T-shaped)	2.444	3.248	3.492	3.426	3.202	2.294	1.188	0.378
49 Benzene ... pyridine (T-shaped)	1.992	2.975	3.280	3.229	3.004	2.103	1.060	0.339
50 Benzene ... ethyne (CH- π)	1.784	2.585	2.822	2.764	2.563	1.785	0.895	0.274
51 Ethyne ... ethyne (TS)	1.183	1.449	1.506	1.449	1.335	0.930	0.462	0.135
52 Benzene ... AcOH (OH- π)	3.895	4.523	4.661	4.519	4.228	3.121	1.705	0.558
53 Benzene ... AcNH ₂ (NH- π)	3.763	4.247	4.346	4.216	3.961	2.974	1.651	0.486
54 Benzene ... water (OH- π)	2.710	3.139	3.212	3.089	2.869	2.090	1.153	0.417
55 Benzene ... MeOH (OH- π)	3.316	3.941	4.106	4.005	3.760	2.786	1.529	0.521
56 Benzene ... MeNH ₂ (NH- π)	2.376	2.983	3.153	3.062	2.823	1.939	0.941	0.264
57 Benzene ... peptide (NH- π)	3.620	4.866	5.220	5.105	4.759	3.419	1.818	0.626
58 Pyridine ... pyridine (CH-N)	2.890	3.887	4.194	3.921	3.474	2.199	1.025	0.281
59 Ethyne ... water (CH-O)	2.573	2.844	2.883	2.788	2.618	1.994	1.177	0.460
60 Ethyne ... AcOH (OH- π)	4.295	4.788	4.863	4.692	4.385	3.248	1.769	0.557
61 Pentane ... AcOH	2.642	2.852	2.839	2.697	2.488	1.775	0.784	0.171
62 Pentane ... AcNH ₂	3.079	3.442	3.458	3.283	3.013	2.102	1.041	0.276
63 Benzene ... AcOH	2.574	3.483	3.715	3.591	3.296	2.226	1.024	0.265
64 Peptide ... ethene	2.528	2.893	2.945	2.820	2.605	1.846	0.878	0.191
65 Pyridine ... ethyne	3.647	4.002	4.065	3.948	3.727	2.870	1.684	0.623
66 MeNH ₂ ... pyridine	3.357	3.803	3.907	3.803	3.582	2.697	1.502	0.497

Conclusions

We have re-evaluated the S66 benchmark for NCIs at the highest *ab initio* level that is currently feasible. Obtaining reliable MP2-F12 basis set limits does not appear to represent a serious challenge: our aug-cc-pV{T,Q}Z-F12-extrapolated values are probably as reliable as can be achieved, and are only a minor factor in the cost of the overall benchmark calculations.

We can define three tiers of accuracy for the CCSD(T)-MP2 ‘high-level correction’:

- ‘GOLD’ combining [CCSD(F12*)-MP2-F12]/cc-pVQZ-F12 half-CP with (T)/haV{T,Q}Z half-CP
- ‘SILVER’ combining [CCSD(F12*)-MP2-F12]/aug-cc-pVTZ-F12 half-CP with (T)/haV{D,T}Z half-CP
- ‘BRONZE’, i.e. half-CP CCSD(F12*)(T_{sc})/cc-pVDZ-F12.

In addition, we can identify a reduced-cost variant of SILVER, which we will call

- ‘STERLING’ combining [CCSD(F12*)-MP2-F12]/cc-pVTZ-F12 half-CP with (T)/sano-PV{D,T}Z+ raw.

SILVER is available for the entire set: for a subset of 18 systems where GOLD was feasible, SILVER deviates from it by less than 0.01 kcal mol⁻¹ RMS.

STERLING sacrifices ~0.02 kcal mol⁻¹ RMS in accuracy, but cuts overall computation time in half thanks to the smaller ‘semi-augmented’ basis sets used for the (T) component.

BRONZE deviates by just over 0.03 kcal mol⁻¹ RMS from SILVER, but at drastically reduced cost (over an order of magnitude) and is a viable option for larger systems and more extensive benchmarks.

The revised S66 benchmark of the Hobza group stands up well under scrutiny: the fairly inexpensive CCSD(T)/AVDZ HLCs used in their S66×8 study are inadequate, but still do benefit from error compensation. The revised S66×8 values from our group could still have been improved further by adding half-CP corrections to the HLC. We have presented such values in the present work; however, we recommend that they be treated with caution, particularly at compressed distances. A more thorough re-evaluation is in progress.

Note Added in Proof

After acceptance of the present manuscript, we managed to perform a CCSD(T)/saug-ano-pVQZ calculation on the most problematic system of the set (26, stacked uracil dimer). This calculation took eight days wall clock time running in parallel on 96 CPUs with a total of 1.5 TB RAM and 18 TB of solid state scratch disk. The CP calculation required the same amount of scratch space but under two days wall clock time. The (T) correction thus obtained, in kcal mol⁻¹, is 1.809 CP, 1.889 raw, and 1.849 half-CP. Extrapolation from saug-ano-pV{T,Q}Z yields 1.936 CP, 1.967 raw, and 1.951 kcal mol⁻¹ half-CP. Combined with the MP2-F12/aug-cc-pV{T,Q}Z-F12 half-CP value of 11.177 kcal mol⁻¹ and the [CCSD(F12*)-MP2-F12]/aug-cc-pVTZ-F12 correction of -3.434 kcal mol⁻¹, we obtain a ‘14-carat GOLD’ reference value of 9.694 kcal mol⁻¹, slightly higher than the SILVER value of 9.672 kcal mol⁻¹ in Table 6. This value is considerably higher than the 9.312 kcal mol⁻¹ obtained by Schmitz and Hättig^[68] using a localized pair natural orbital CCSD(F12*)(T) approach, but in quite good agreement with the 9.67 kcal mol⁻¹ (raw) or 9.57 kcal mol⁻¹ (CP) obtained

by Ma and Werner^[69] in a paper documenting their PNO-LCCSD(T)-F12 approach. Our CCSD limit is 7.743 kcal mol⁻¹, which agrees reasonably well with the 7.92 ± 0.02 kcal mol⁻¹ obtained by Valeev and coworkers^[70] considering their slightly different reference geometry (1.0r_e from the S66×8 set); our calculated energy difference between the two geometries is 0.053 kcal mol⁻¹ at the CCSD(F12*)/aug-cc-pVTZ-F12 level, leading to an adjusted CCSD limit of 7.80 kcal mol⁻¹. We thank Professor Edward F. Valeev (Virginia Tech) for helpful discussions and for bringing ref. [70] to our attention.

Supplementary Material

An Excel spreadsheet containing calculated total energies and interaction energies for the S66 dataset at the levels of theory considered is available on the Journal's website.

Conflicts of Interest

The authors declare no conflicts of interest.

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