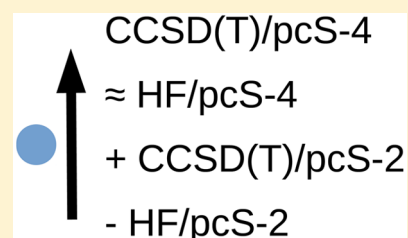# Approximating CCSD(T) Nuclear Magnetic Shielding Calculations Using Composite Methods

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S *Supporting Information*

ABSTRACT: A series of composite method approximations for the computationally efficient calculation of NMR shieldings has been developed. These approximations utilize basis sets from the pcS-*n* series, which is shown to converge rapidly toward experimental gas-phase shieldings at CCSD(T). The possibility of using HF, B3LYP, KT3, or MP2 shieldings to approximate results at CCSD(T) was then examined. It was determined that using HF in conjunction with MP2 significantly reduces the CPU time of calculations while having a minimal impact on the accuracy of the predicted shieldings.

CCSD(T)/pcS-4
≈ HF/pcS-4
+ CCSD(T)/pcS-2
- HF/pcS-2

1. INTRODUCTION

NMR spectroscopy is one of the most important tools in chemistry and biological chemistry for determining the structure of molecules. Since NMR can detect hydrogens and can be applied to molecules in solution, it eliminates many of the difficulties associated with X-ray crystallography. However, NMR spectra and structural parameters are not directly linked. Moreover, in the case of large systems, overlapping peaks hinder interpretation.

Theoretical calculations can thus play a significant role in the resolution of spectroscopic ambiguities and in confirmation of proposed structures. However, to be of practical use in assigning spectral peaks, calculations of NMR shielding constants must be highly accurate. Previous studies show that the accurate prediction of NMR parameters depends heavily on the treatment of electron correlation.[1−4] The second-order Møller−Plesset perturbation method (MP2)[5,6] and some density functional methods (such as KT3)[7] yield NMR shieldings with moderate accuracy. However, more reliable results are obtained using the coupled cluster method with single and double excitations and perturbative treatment of triple excitations [CCSD(T)][8] with large basis sets. Unfortunately, the CCSD(T) approach requires a computation time that scales as the seventh power of the number of basis functions, N_{basis}^7. This means that CCSD(T)/large-basis-set calculations are not feasible for molecules with any more than approximately 10 atoms heavier than hydrogen.[9]

If highly accurate calculations of NMR shielding constants for large organic and biological molecules are to be performed, then it is necessary to develop methods to circumvent this scaling problem. In previous papers, we have presented two such methods: systematic molecular fragmentation by annihilation (SMFA) and locally dense basis sets. SMFA was shown to replace the NMR calculation for large molecules with calculations on relatively small fragments, without significant loss of accuracy.[10] Moreover, a systematic approach for assigning local basis sets was developed.[11] In this approach, a large basis set is allocated only to the functional group that contains the nuclei for which NMR parameters are required. Atoms in adjoining groups have smaller basis sets, and more distant atoms have even smaller basis sets. Again, this reduction in the size of the whole basis set does not significantly reduce the accuracy of the calculated NMR parameters while substantially reducing the computation time.

In this article, we introduce a third method for reducing the computation time for NMR calculations: composite sequences of calculations using different levels of *ab initio* theory and basis sets. Such composite methods are common in *ab initio* calculations of molecular energies (as used in the G2 and G3 methods, for example).[12,13] In the context of NMR parameter calculations, such composite methods have also been explored to a more limited extent.[14,15]

Here, we demonstrate that the pcS-*n* basis sets developed by Jensen[16] provide a very convenient, rapidly converging series of basis sets for NMR parameters and produce results comparable to the results obtained with large basis sets from Dunning's correlation-consistent basis-set families.[17−20] In addition, we show that NMR shielding constants calculated at CCSD(T)/pcS-*n* are in good agreement with experimental values for molecules in the gas phase for large *n*. We then examine the accuracy of two composite methods that accurately reproduce these CCSD(T)/large-basis-set results.

The next section describes the composite methods. Results are presented in Section 3, and the article finishes with some concluding remarks.

2. METHODS

2.1. Composite Methods. The simplest form of composite method is

$$L_{high}/B_{large} \approx L_{low}/B_{large} - L_{low}/B_{small} + L_{high}/B_{small} \quad (1)$$

where L_{high} and L_{low} are two levels of theory, with L_{high} providing the more accurate treatment of correlation; B_{large} and B_{small} are two basis sets, with B_{large} being the largest; and L/B represents the NMR shielding constant obtained at that model chemisty. For all calculations in this work, L_{high} represents CCSD(T) and B_{large} represents the pcS-4 basis set.

The rationale behind eq 1 is that the basis set correction for a high level of *ab initio* theory, $L_{high}/B_{large} - L_{high}/B_{small}$, is approximately the same as the basis set correction for a lower level of *ab initio* theory. The computation time for the high level of *ab initio* theory scales much more rapidly with N_{basis} than does the time for the low level of theory. The right-hand side of eq 1 is much faster to compute than the left-hand side because the high level of *ab initio* theory is evaluated only with the smaller basis set.

In addition, it is possible to add a further, intermediate level of theory/basis set such that the approximation becomes

$$L_{high}/B_{large} \approx L_{low}/B_{large} - L_{low}/B_{medium}$$
$$+ L_{intermediate}/B_{medium} - L_{intermediate}/B_{small} + L_{high}/B_{small} \tag{2}$$

This form of composite method is referred to in this work as a double composite. The rationale behind eq 2 is that the intermediate level of theory with a medium-sized basis set should account for electron correlation reasonably well and that the change in the basis set size used for the low level of theory is reduced, which reduces the error associated with use of this low level of theory. As we will see, eq 2 may also allow the size of B_{small} to be reduced such that the calculation at the high level of theory can be performed with a smaller basis set and without significant loss of accuracy. In this work, MP2 is used exclusively as $L_{intermediate}$.

2.2. Computational Details. The accuracy of eqs 1 and 2 was investigated using a test set of 27 molecules, for which very large basis set CCSD(T) calculations of the shielding constant have been reported in Table 2 of ref 4. These molecules are listed in the Supporting Information. The geometries of these 27 molecules were optimized at CCSD(T)/aug-cc-pVTZ in ref 4. Each molecule contains no more than 3 heavy atoms. This gives a total of 20 carbon, 37 hydrogen, 8 nitrogen, 15 oxygen, 10 fluorine, 2 phosphorus, 3 silicon, 3 aluminum, and 2 lithium atoms.

To compare calculated shieldings with experimental results, we have considered a subset of the 27 molecules for which reliable gas-phase values are available. These molecules contained a total of 6 carbon, 21 hydrogen, 6 nitrogen, and 4 oxygen atoms. These molecules are also listed in the Supporting Information. Calculations have been carried out at the Hartree–Fock (HF), MP2, and CCSD(T) levels of theory and using density functional theory with the B3LYP and KT3 functionals. We have used the Dalton[21] and CFOUR[22] program packages. In all cases, the GIAO[23−25] technique was utilized to ensure gauge invariance.

2.3. ZPE Correction. Theoretical calculations of a shielding constant are normally carried out with a molecule in its minimum energy geometry. However, even at zero kelvin, a molecule has zero-point energy (ZPE) and occupies a distribution of configurations, given by the ground-state nuclear wave function. Hence, even at zero kelvin, there is a difference between the value of the shielding constant at the minimum energy geometry and the value of the shielding constant in the ground state. Calculation of this zero-point vibrational

correction, $\delta\sigma_{ZPE}$, to the shielding constant is a computationally demanding task,[26] but it has been reported in ref 4 at B3LYP/aug-cc-pCVTZ. Subtracting $\delta\sigma_{ZPE}$ from the experimental value of the shielding constant gives an empirical shielding estimate of the value of the shielding constant at the minimum energy geometry. Note that the experimental shielding constants have been measured at temperatures well above absolute zero. Thermal excitations will result, therefore, in additional shifts to the NMR shielding constant. Accounting for these shifts is a computationally demanding task and has not been attempted in this work.

3. RESULTS

Prior to discussing results, it is necessary to define the criteria for accurate shieldings, as this depends on the nuclei under consideration. Hydrogen shieldings typically occur over 10 parts-per-million (ppm) range and require calculated shielding predictions to within about 0.1 ppm to distinguish between nuclei in similar chemical environments. Heavier nuclei, conversely, vary over a much larger range, with carbon shieldings typically occurring between 0 and 200 ppm and other nuclei varying over an even larger scale. Hence, we consider shieldings to be accurate for carbon if the absolute calculation error is less than 1 ppm and on the order of 1−2 ppm for heavier nuclei such as nitrogen, oxygen, and fluorine.

3.1. Comparison with Experiment. Before considering the utility of composite methods, it is useful to establish the convergence of theoretical approaches to experimental data. The experimental values of the NMR shielding constant for various nuclei in gas-phase molecules are presented in Table 2 of ref 4. The Supporting Information lists the nuclei and molecules for which gas-phase experimental values of the shielding constant have been considered herein.

Figure 1 presents the mean absolute deviation (MAD) of the empirical shieldings from the values calculated at the minimum
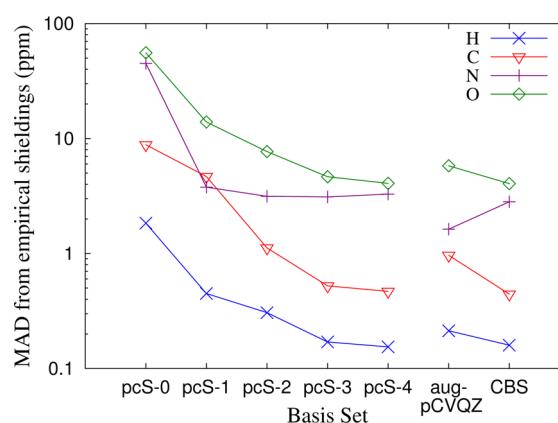

Figure 1. MADs from empirical shieldings at CCSD(T) with various basis sets in the pcS-n series and for CCSD(T) results from ref 4.

energy geometry using the CCSD(T) method with various basis sets.

The results on the right-hand side of Figure 1 use the data from ref 4 obtained with the Dunning type basis, aug-cc-pCVQZ, and results extrapolated to the basis set limit using a sequence of Dunning-type basis sets.[27,28] We note that the MAD in this extrapolated limit is on the order of 0.15 ppm for hydrogen nuclei, 0.4 ppm for carbon, 3 ppm for nitrogen, and 4 ppm for oxygen. For carbon, the MAD is within acceptable

limits, it is nearly so for hydrogen, and it is larger than desired for nitrogen and oxygen. For nitrogen, the calculated shieldings appear to worsen slightly as the size of the basis set is increased beyond pcS-2. This behavior is consistent between the pcS-n and Dunnings basis sets, suggesting that there is some cancellation of error between basis set incompleteness and, possibly, level of theory. Moreover, shieldings for the oxygen nuclei appear to improve less rapidly than they do for the other nuclei, suggesting that achieving accurate results for oxygen is a more computationally demanding task.

The residual MAD may be due to a number of factors, including the neglect of thermal effects, the approximate nature of B3LYP for the treatment of the ZPE correction, and, possibly, the inadequacy of the CCSD(T) method. Nonetheless, the reliability of the CCSD(T) method with large basis sets is reasonable. Importantly, Figure 1 also shows that the pcS-n sequence of basis sets converges to the extrapolated basis set limit very well by pcS-4. Moreover, pcS-3 values are very close to the basis set limit results, and even pcS-2 values are reasonable. Hence, in developing composite methods, we have used CCSD(T)/pcS-4 shieldings as the L_{high}/B_{large} "target" method and smaller pcS-n basis sets as B_{small} and B_{medium} in eqs 1 and 2.

It is also notable that the results reported in ref 4 at aug-cc-pCVQZ are in between those obtained at pcS-2 and pcS-3 in terms of MADs, although the basis set is roughly equivalent to pcS-4 in terms of the number of primitives. This demonstrates that, despite having been originally designed for use with DFT, the pcS-n basis sets converge rapidly toward the basis set limit at post Hartree–Fock levels of theory and represents a sensible choice of basis set at these levels.

3.2. Basic Composites. The mean absolute deviation (MAD) of the left- and right-hand side of eq 1 is displayed in Table 1 for various combinations of L_{low} and B_{small}, with CCSD(T) as L_{high} and pcS-4 as B_{large}. With HF, B3LYP, and KT3 as L_{low}, the MADs begin to approach the required accuracy criteria by the time B_{small} reaches pcS-2, although, for all nuclei aside from carbon, the errors are not below these criteria until pcS-3 is reached. Even for the pcS-2 and pcS-3

basis sets, there is considerable variation in the errors between levels of theory and nuclei. HF has a MAD that is marginally lower than those for B3LYP and KT3 for hydrogens, but it is clearly higher for carbons, nitrogens, and oxygens and is roughly comparable for fluorine. Interestingly, KT3 does not appear to provide a significant advantage over B3LYP in terms of MADs for the majority of nuclei considered here, even though the KT3 functional was developed specifically for NMR shielding calculations.[7]

Unsurprisingly, the lowest MADs are achieved using MP2 as L_{low}. This is likely due to the relative similarity in the treatment of electron correlation between MP2 and CCSD(T), as compared with the lack of correlation in HF and the semiempirical approach used in the two DFT methods. At MP2, the MADs with pcS-1 as B_{small} are approximately equivalent to those obtained with pcS-2 at the other levels of theory. The required accuracy for hydrogen and carbon nuclei is already achieved at this level.

Based solely on MADs, there appears to be little clear advantage to using B3LYP or KT3 over the less expensive HF method. The preferred method would depend on the type of nuclei under consideration. While HF and DFT are considerably cheaper than MP2, this advantage is offset by the fact that a larger basis set is required for B_{small} in order to attain a similar accuracy. This, in turn, means [see the right-hand side of eq 1] that a larger basis set will be required for the CCSD(T) calculation and thus the composite calculation is more expensive (and less feasible) overall. A possible means for achieving similar results while avoiding these expensive CCSD(T) calculations is to employ a double composite method.

3.3. Double Composites. From the results in Table 1, the most appropriate double composite methods would be those in which the lower basis set provides satisfactory results when used with MP2 and the medium basis set provides satisfactory results with HF or DFT. Thus, pcS-1 is used exclusively as B_{small}, whereas pcS-2 and pcS-3 are explored as possibilities for B_{medium}. HF and B3LYP are explored for L_{low}, with $L_{intermediate}$ kept at MP2. The results are shown in Table 2.

Table 1. Mean Deviations of Basic Composite Methods from CCSD(T)/pcS-4 Shieldings for All Hydrogen, Carbon, Nitrogen, Oxygen, and Fluorine Atoms in the Test Set[a]

L_{low}	B_{small}	H	C	N	O	F
HF	pcS-0	0.327	12.999	55.501	119.474	12.982
	pcS-1	0.309	2.787	9.172	14.804	5.120
	pcS-2	0.136	1.259	3.999	4.511	2.452
	pcS-3	0.024	0.171	0.389	0.593	0.315
B3LYP	pcS-0	0.367	3.732	13.216	39.497	20.007
	pcS-1	0.256	1.660	6.728	11.062	8.056
	pcS-2	0.141	0.729	2.004	3.869	1.986
	pcS-3	0.022	0.118	0.311	0.518	0.230
KT3	pcS-0	0.329	5.300	2.928	21.388	27.788
	pcS-1	0.296	2.524	6.363	9.698	12.297
	pcS-2	0.150	0.845	1.098	2.900	3.037
	pcS-3	0.024	0.089	0.180	0.523	0.273
MP2	pcS-0	0.123	3.220	41.239	101.006	6.887
	pcS-1	0.039	0.169	2.256	4.815	1.441
	pcS-2	0.010	0.119	1.057	1.787	0.728
	pcS-3	0.002	0.024	0.126	0.126	0.100

[a]Results are presented for various combinations of L_{low} and B_{small}.

Table 2. Mean Deviations of Double Composite Methods from CCSD(T)/pcS-4 Shieldings for All Hydrogen, Carbon, Nitrogen, Oxygen, and Fluorine Atoms in the Test Set[a]

L_{low}	B_{medium}	H	C	N	O	F
B3LYP	pcS-2	0.169	0.791	1.536	2.253	2.665
	pcS-3	0.061	0.215	2.236	4.372	1.483
HF	pcS-2	0.164	1.290	3.337	6.132	2.481
	pcS-3	0.063	0.241	2.160	4.366	1.254

[a]Results are presented for various combinations of L_{low} and B_{medium}.

Comparing the entries in Tables 1 and 2, we see that the MADs labeled by HF and pcS-2 are comparable for all nuclei except oxygens. For this case, eqs 1 and 2 imply

$$\text{CCSD(T)/pcS-4} \approx \text{HF/pcS-4} - \text{HF/pcS-2} + \text{CCSD(T)/pcS-2} \tag{3}$$

and

$$\text{CCSD(T)/pcS-4} \approx \text{HF/pcS-4} - \text{HF/pcS-2} + \text{MP2/pcS-2} - \text{MP2/pcS-1} + \text{CCSD(T)/pcS-1} \tag{4}$$

The computational advantage of eq 4 over eq 3 is that CCSD(T) calculations are performed only with the small pcS-1 basis set, although this comes at the cost of requiring MP2/pcS-2 calculations. From Table 2, we see that eq 4 provides shielding constants close to the desired accuracy for all atoms other than oxygen. The MADs are further reduced if pcS-3 is substituted for pcS-2 in eq 4:

$$
\begin{aligned}
\text{CCSD(T)/pcS-4} \approx{} & \text{HF/pcS-4} - \text{HF/pcS-3} + \text{MP2/} \\
& \text{pcS-3} - \text{MP2/pcS-1} + \text{CCSD(T)/pcS-1}
\end{aligned}
\tag{5}
$$

Previous studies[10,11,15,29,30] have shown that accurate shielding constant calculations for oxygen atoms are more demanding in terms of level of theory and basis sets than they are for carbon, nitrogen, and hydrogen. It is, therefore, fortunate that spectra for hydrogen, carbon, and nitrogen are more commonly measured and used for structural analysis than are spectra for oxygen. As in Table 1, the MADs for B3LYP in Table 2 are not significantly superior to those for HF. Moreover, the fact that the MADs for nitrogen and oxygen become larger for B3LYP as the basis set is improved suggests that the results for B3LYP with pcS-2 may have been fortuitous.

The average CPU times for the composite methods in eqs 3−5 are compared to the CCSD(T)/pcS-4 CPU times in Table 3. From Table 3, it can be seen that the employment of composite methods reduces the CPU time by approximately a factor of 15 when compared to that of CCSD(T)/pcS-4.

Table 3. CPU Time (in Hours) for Several Composite Methods and the CCSD(T)/pcS-4 Calculation, Averaged over All of the Molecules in the Test Set

composite method	CPU time
basic composite (eq 3)	2.308
double composite (eq 4)	2.297
double composite (eq 5)	2.537
CCSD(T)/pcS-4	34.019

For the molecules in this test set, the three recommended methods differ little in terms of computational expense. This is because the CPU time is dominated by the HF/pcS-4 calculation, which accounts for 90% of the CPU time even in the method represented by eq 5. For larger molecules, this will not be the case, as the N^5 and N^7 scaling of MP2 and CCSD(T), respectively, will ensure that these components of the composite method will become expensive more rapidly than the HF component.

4. CONCLUSIONS

We have shown that the pcS-n family provides a convenient sequence of basis sets that rapidly converge CCSD(T) calculations of the chemical shielding constant to the results of large Dunning-type basis sets and to gas-phase experimental data. We have then used these pcS-n basis sets to evaluate composite methods of the type shown in eqs 1 and 2.

Calculations on a moderately large test set of molecules have then demonstrated that the composite methods of eqs 3−5 approximate the CCSD(T)/pcS-4 shielding constants to acceptable accuracy. The recommended composite methods are outlined in eqs 3 and 4. While eqs 4 and 5 require only CCSD(T)/pcS-1 calculations, this is at the expense of requiring MP2/pcS-2 and MP2/pcS-3 calculations, respectively. For the majority of systems, this will prove to be a worthwhile trade-off,

owing to the N^7_{basis} scaling of CCSD(T), although this will depend on the size of the system and the required accuracy.

In many cases, the cost of the MP2/pcS-2 calculations in eq 4 and the MP2/pcS-3 calculations in eq 5 could be substantially reduced using the local basis set method.[11] The cost of the HF/pcS-4, HF/pcS-3, and HF/pcS-2 calculations could also be reduced using local basis sets. Furthermore, the application of systematic fragmentation, as outlined in ref 10, would limit the size of fragments for which calculations would be required and could thus extend the size of systems for which composite methods could be applied.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jctc.5b00546.

> Lists of the molecules and nuclei for which calculations were performed in the composite method benchmarking and the comparisons with experiment (PDF).

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Notes
The authors declare no competing financial interest.

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