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# Systematic Study of Locally Dense Basis Sets for NMR Shielding Constants

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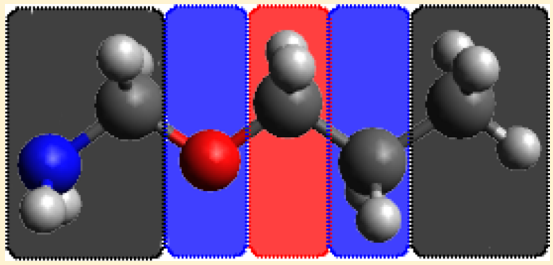
Supporting Information

**ABSTRACT:** This paper presents a systematic study of partitioning schemes for locally dense basis sets in the context of NMR shielding calculations. The partitionings explored were based exclusively on connectivity and utilized the basis sets from the pcS-*n* series. Deviations from pcS-4 shieldings were calculated for a set of 28 organic molecules at the HF, B3LYP, and KT3 levels of theory, with the primary goal being the determination of an efficient scheme that achieves maximal deviations of 0.1 ppm for $^{1}$H and 1 ppm for $^{13}$C. Both atom based and group based divisions of basis sets were examined, with the latter providing the most promising results. It is demonstrated that for the systems studied, at least pcS-1 is required for all parts of the molecule. This, coupled with pcS-3 on the group of interest and pcS-2 on the adjacent groups, is sufficient to achieve the desired level of accuracy at a minimal computational expense. In addition, the suitability of the pcS-*n* basis sets for post-SCF methods was confirmed through a comparison with other standard basis sets at the MP2 level.



## 1. INTRODUCTION

NMR spectroscopy provides an attractive alternative to X-ray crystallography for structural resolution. Among its significant advantages are its ability to resolve hydrogens and its applicability to molecules in solution—which not only provides a more accurate representation of the naturally occurring structure but also eliminates the need for crystallization (an often difficult to realize goal). In contrast to X-ray crystallography, however, NMR spectra and structural parameters are not directly linked, and in the case of large systems, overlapping peaks hinder interpretation.[1] To this end, theoretical calculations can greatly aid in the resolution of ambiguities and confirmation of proposed structures.

Theoretical calculations, however, have similar limitations for larger systems. The (at least) $N^4$ formal scaling of computer resources with system size, coupled with the additional expense associated with second order property calculations, limits quantitative predictions to systems with no more than several heavy atoms.[2] Avenues for decreasing the cost associated with calculations while maintaining their accuracy are thus of vital importance.

Among the most effective approaches for reducing the computational cost of property calculations for large molecules are linear scaling algorithms. These include the Fragment Molecular Orbital (FMO) method and the recently developed fragmentation methods, whereby large molecules are decomposed into molecular fragments and properties of the whole molecule are given by a sum over the corresponding values for the fragments.[3−8] NMR shielding constants can be approximated using both FMO and fragmentation.[9−11] As the molecular fragments generated by these decompositions typically contain at least several heavy atoms, the accurate calculation of NMR parameters is demanding even for these fragments. This necessitates further reductions in the computational cost; especially since a molecule containing thousands of atoms is decomposed into many (hundreds) of fragments.

The accurate prediction of NMR parameters depends heavily on the treatment of electron correlation.[2,12−14] Previous calculations[12] indicate that the second order Møller−Plesset (MP2) method and the KT3 density functional approach[15] yield NMR shieldings in reasonable agreement with those obtained using the very reliable coupled cluster with single and double excitations and perturbative account of triple excitations [CCSD(T)] method.

Another consideration that has historically been a central concern for the prediction of NMR parameters is the choice of basis set. In early years, this was due to the gauge origin problem,[16] though even since its effective resolution[17−25] it has been noted that large basis sets are required for reliable predictions.[26,27] In particular, NMR parameters, being predominantly local properties,[28] benefit from tighter Gaussians than those provided by the standard, energy optimized, basis functions.[29−39] The development of separately optimized basis sets for NMR parameters therefore reduces the computational cost associated with attaining a desired level of accuracy.

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For chemical shieldings, one such specifically optimized basis set series is pcS-*n*, developed by Jensen.[30] While these basis sets were designed for the purpose of rapid convergence at the Density Funtional Theory(DFT) level, they have found additional use in post-Self Consistent Field(SCF) methods.[12,40] The rate of convergence at post-SCF levels has, however, not been investigated.

The local nature of shieldings has also prompted the suggestion that large basis sets are only required in the vicinity of the nuclei under study, and that significant computational savings can be made by utilizing smaller basis sets elsewhere in the molecule. This locally dense basis set (LDBS) approximation was first explored by Chesnut and Moore[41] and has been in common usage since.[42,43] While it has been noted that chemically intuitive partitionings yield better results,[44] to the best of our knowledge no systematic study of partitioning schemes to determine the requirements for accurate shieldings has been performed.

The goals of this work are thus 2-fold: to compare basis set convergence of the pcS-*n* series with other standard basis sets at post-SCF levels of theory, represented here by MP2, and to conduct a systematic study of partitioning schemes for the LDBS approximation.

## 2. METHOD

Calculations of NMR shielding constants have been carried out at the SCF, MP2, B3LYP, and KT3 levels of theory using the *GAUSSIAN09*[45] and *DALTON2011*[46] program packages. In all cases, the GIAO technique was utilized to ensure gauge independence. Since this study is concerned with convergence of shielding constants with basis set size, the molecular geometries employed are not particularly significant. All calculations have been carried out at the HF/cc-pVDZ equilibrium geometry. The geometries of all molecules studied are presented in the Tables S1−39 of the Supporting Information. No vibrational or thermal averaging of the shielding constants has been undertaken, although this would be necessary for comparison with experimental values.

**2.1. Basis Set Convergence for MP2.** The rate of convergence of MP2 shielding constants with the number of basis functions was examined for several common types of basis set: Jensen's pcS-*n* and aug-pcS-*n* bases with $n = 0-4$;[30] Dunning's cc-pV*x*Z,[47] aug-cc-pV*x*Z[48] and cc-pCV*x*Z[49] with $x$ = D, T, Q, 5 bases; the Pople style bases STO-3G, 6-31G** and 6-311G(2df,2pd);[50] and Ahlrich's SVP,[51] TZV,[52] and QZVP[53] bases. Basis sets not featured in the standard implementation for each program package were obtained from EMSL.[54] Given the high computational cost of these MP2 calculations, shielding constants were evaluated for all atoms in a test set of relatively small molecules: $NH_3$, $H_2O$, HF, $CH_4$, $C_2H_4$, $C_2H_2$, HCN, $CH_3F$, $F_2$, CO, and $N_2$. Aside from ensuring tractability, these molecules were chosen for possessing lone pairs and/or multiple bonds (methane being the sole exception), and thus representing cases for which correlation might be important. Given that Jensen's pcS-*n* and aug-pcS-*n* basis sets have been shown to provide rapid convergence for shielding constants at DFT levels, the largest basis set (aug-pcS-4) has been taken to represent the basis set limit. Hence, all shielding constants are presented relative to the MP2/aug-pcS-4 value.

**2.2. Locally Dense Basis Sets.** All calculations with locally dense basis sets have been carried out using the HF, B3LYP, and KT3 methods, and the pcS-*n* basis sets on the following molecules: 2-methoxyethylamine, 1,2-diaminoethane, methylethylamine, diethylamine, 1,3-diaminopropane, 3-hydroxy-1-aminopropane, azetidine, pyrollidine, *n*-propylamine, cyclopropylamine, isopropylamine, cyclobutylamine, propylene imine, allylamine, *n*-butylamine, *n*-propanol, i-propanol, *n*-butanol, i-butanol, *s*-butanol, *t*-butanol, 2-chloroethanol, isobutylamine, ethandiol, 2-aminoethanol, allyl alcohol, *sec*-butylamine, and *tert*-butylamine. Coordinates for this test set can be found in Tables S12−39 of the Supporting Information. These molecules are within a size range of 4−5 heavy atoms and are thus small enough that uniform pcS-4 calculations are feasible, though large enough to contain functional groups with $\alpha$, $\beta$, and more distant substituent groups. There are a total of 244 hydrogen and 126 heavy atoms in these molecules, which are used to evaluate mean absolute deviations (MADs) of shielding constants. The largest basis set (pcS-4) has been taken to represent the convergence limit, with all shielding constants presented as deviations from the corresponding HF, B3LYP, and KT3 values obtained with the pcS-4 basis set on all atoms in the molecule.

The partitioning schemes in this work were based on connectivity rather than distance. This was for two reasons: first, the molecules examined do not display significant through space intramolecular interactions and would thus present a poor test set for examining distance related effects, and second, this allowed the effect of each atom to be studied more systematically.

Atoms are considered connected if the distance between them is less that the sum of their covalent radii (plus a small tolerance of 0.4 Å). This criteria was chosen to reproduce the ordinary chemical assignment of bonds. Two different schemes to partition the basis set throughout the molecule were considered.

(i) The atom-based partition: An atom is chosen for which the shielding constant is calculated. This is henceforth referred to as the "focus" atom. The basis set for this atom is denoted pcS*x*. All atoms bonded to the focus atom are assigned a common basis, denoted pcS*y*. All other atoms in the molecule are assigned a common basis, denoted pcS*z*. The complete basis set is then denoted as pcS*x*/pcS*y*/pcS*z*.

(ii) The group based partition: The bonded atoms are assigned to groups containing a single heavy atom and any hydrogens bonded to it. A group is chosen for which the shielding constants are calculated. This will henceforth be referred to as the "focus" group. The common basis set for each atom in this group is denoted pcS*x*. All atoms in groups that are bonded to the focus group are assigned a common basis, denoted pcS*y*. All other atoms in the molecule are assigned a common basis, denoted pcS*z*. The complete basis set is then denoted as pcS*x*/pcS*y*/pcS$z^G$.

This basis is locally dense if

$$x > y > z$$

## 3. RESULTS AND DISCUSSION

**3.1. MP2 and Uniform Basis Set Calculations.** Prior to discussing data, it is important to note that the criteria for satisfactory results depends on the nuclei under consideration. The chemical shift scale for $^{13}C$ is more than an order of magnitude larger than for $^{1}H$, while heavier nuclei such as $^{15}N$


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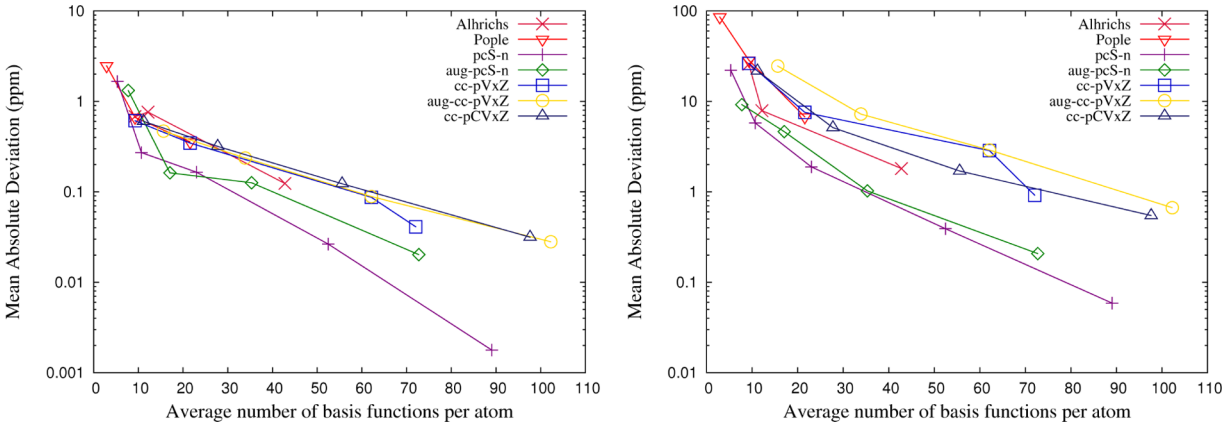


**Figure 1.** Mean absolute deviation from aug-pcS-4 shieldings as a function of the average number of basis functions per atom. (a) hydrogens and (b) non-hydrogens.

and $^{18}$O vary over an even larger scale. For the purpose of this study, absolute deviations of 0.1 ppm for $^{1}$H and 1 ppm for all other nuclei are deemed satisfactory, as this represents approximately 1% (or less) of the total shielding scale.

The results at MP2 for the various basis sets studied are displayed in Figure 1 as a function of the average number of basis functions per atom, taken to be the total number of basis functions for all molecules divided by the total number of atoms for all molecules. Comparing Jensen's results[30] with those of Figure 1b reveals that for the pcS-*n* basis set series, the reduction in MADs with increasing *n* is slower for MP2 than for DFT methods. Nonetheless, convergence of shielding constants toward the basis set limit at MP2 is more rapid for pcS-*n* than for the other basis sets studied, indicating that these bases represent a sensible choice for shielding calculations at the MP2 level. We note in passing that the corresponding MADs for HF/pcS-*n* shielding constant calculations demonstrate more rapid convergence to the basis set limit than observed for the MP2 calculations of Figure 1.

The similarity in convergence for the pcS-*n* and aug-pcS-*n* basis sets also indicates that the addition of diffuse functions only improves shielding predictions to the extent that they add basis functions. This has been observed previously by Jensen.[30]

The results of uniform basis set calculations at the HF, B3LYP, and KT3 levels for the 28 molecules used in the LDBS study are displayed in Figure 2 for hydrogens. From this figure, it is evident that convergence is essentially achieved by the time pcS-3 is reached. These results also confirm the assertion made by Jensen that rates of convergence at DFT and HF are similar.[30]

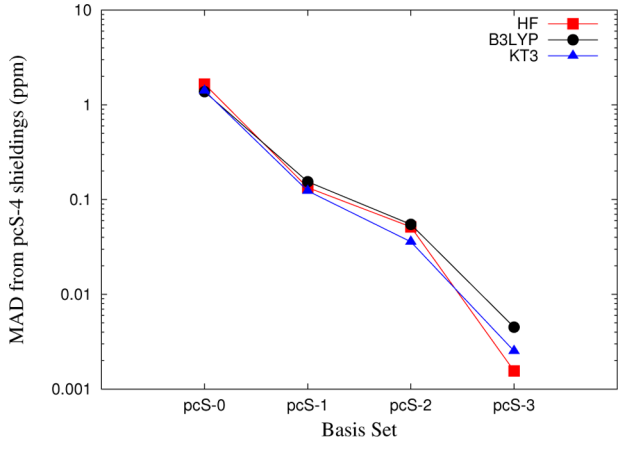


**Figure 2.** Mean absolute deviations from pcS-4 shieldings for hydrogens with the pcS-*n* basis set.

As a final note, one practical consequence of the difference in rates of convergence between MP2 and HF or DFT[55] is that a partitioning scheme deemed satisfactory in the following section may be less so at the MP2 level.

**3.2. Locally Dense Basis Set Partitionings.** An initial indication of the effect of locally dense basis sets on the shielding of the focus atom was obtained by placing a pcS-4 basis set on the focus atom alone, and varying the basis set in the remainder of the molecule. The MADs for calculations on the set of 28 molecules are presented in Figure 3. For hydrogens, it can be seen that satisfactory results are achieved with the pcS4/pcS2/pcS2 partitioning, while for non-hydrogens the desired accuracy is achieved at pcS4/pcS1/pcS1. This indicates that a large basis set is only required on the focus atom, with a moderate basis set sufficing in all other parts of the molecule. Group based calculations mirrored these results, exhibiting a slightly more rapid convergence toward the basis set limit. A summary of the deviations at these paritionings (and all others considered in this work) can be found in Tables S40−42 of the Supporting Information.

To investigate the possibility of using smaller basis sets in the distal regions of the molecule, calculations were performed with the pcS4/pcS*n*/pcS0 and pcS4/pcS*n*/pcS0$^{G}$ partitionings. MADs and maximal deviations with the group based partitioning are displayed for hydrogens in Figure 4. While it can be seen that average deviations slowly converge toward the basis set limit, the same behavior is not observed for the maximal deviations, which remain well above the desired level of accuracy. Since, for this set of molecules, the pcS4/pcS4/pcS0$^{G}$ partitioning generally assigns the pcS-0 basis set to only one or two groups, this implies that pcS-1 or higher is required in all portions of the molecule, at least in systems of the size studied in this work.

Results for non-hydrogens are similar, the only notable difference being the relative convergence behavior of the levels of theory studied. This is evident from the MADs presented in Figure 5. Maximal deviations (not shown) again indicate that at least a pcS-1 basis set is required in all portions of the molecule. This being the case, it can be concluded that the previously explored pcS4/pcS1/pcS1 partitioning (see Figure 3a) represents an appropriate choice for non-hydrogen shieldings.


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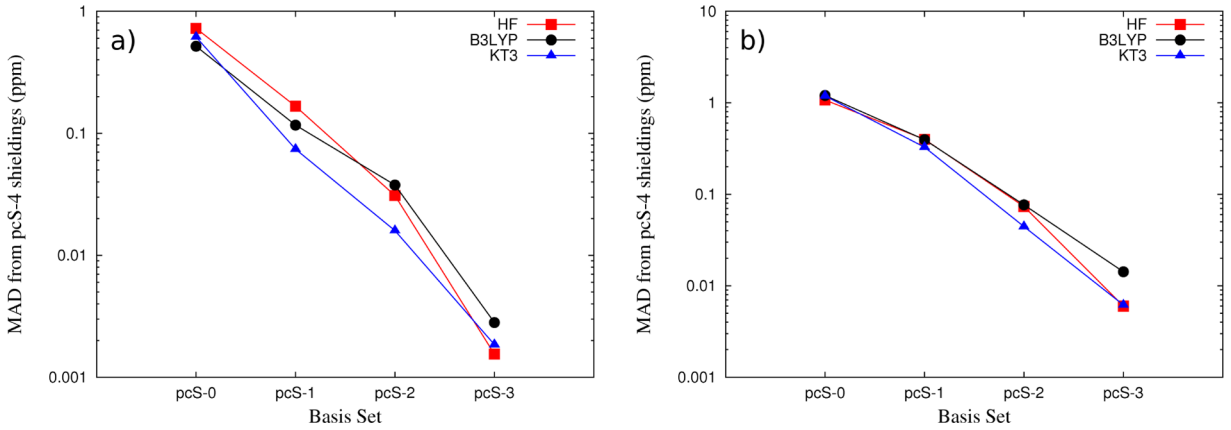


**Figure 3.** Mean absolute deviations from pcS-4 shieldings with a pcS-4 basis set on the focus atom and pcS-*n* on the remainder of the molecule. (a) hydrogens; (b) non-hydrogens.

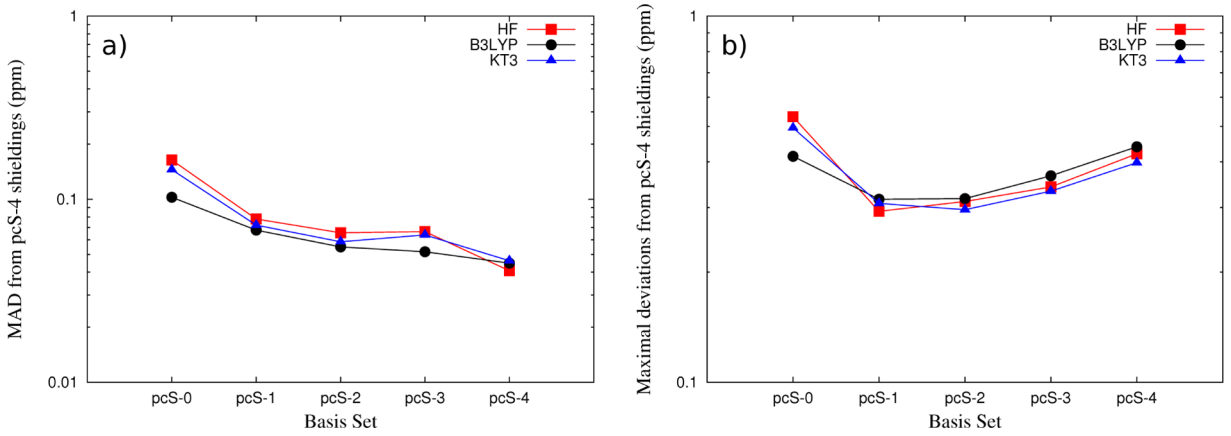


**Figure 4.** (a) Mean absolute and (b) maximal deviations from pcS-4 shieldings for hydrogens with the pcS4/pcS*n*/pcS0 partitioning.

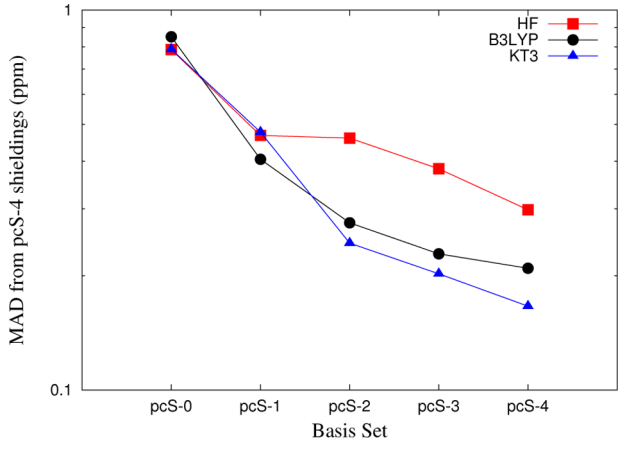


**Figure 5.** Mean absolute deviations from pcS-4 shieldings for non-hydrogens with the pcS4/pcS*n*/pcS0$^{G}$ partitioning.

Further calculations will thus focus on determining appropriate partitioning schemes for hydrogens.

As a final note on non-hydrogen results, the difference in errors between the pcS4/pcS0/pcS0, pcS4/pcS0/pcS0$^{G}$, and pcS4/pcS4/pcS0 partitionings provide an indication of the relative importance of hydrogens and heavy atoms directly bonded to those species. For any given non-hydrogen, the first and second schemes differ only in having pcS-0 and pcS-4 basis sets on attached hydrogens (if they exist), while the second and third schemes differ only in having pcS-0 and pcS-4 basis sets on adjacent heavy atoms. MADs for non-hydrogens at these levels were 1.07, 0.787, and 0.407 respectively. While this is far from rigorous, it provides some support for the conclusion that adjacent heavy atoms influence shieldings more strongly than adjacent hydrogens, a conclusion that has been previously made by others.[56]

With a view toward decreasing the computational cost associated with obtaining hydrogen shieldings, calculations were performed with the pcS4/pcS*n*/pcS1 atom and group based partitionings. Group based MADs and maximal deviations are displayed in Figure 6. While improvement is consistent between the levels studied in going from $n = 1$ to $n = 2$, the benefit of increasing $n$ to 3 is more variable. Since both average and maximal deviations are satifactory with $n = 2$ and CPU time was a factor of 3 greater with $n = 3$, the pcS4/pcS2/pcS1$^{G}$ partitioning is recommended.

Results with atom based partitionings were similar, though convergence toward the basis set limit was less rapid. The predominant cause of this is that hydrogens bonded to the same parent atom as the focus atom are given a pcS-1 basis set under this scheme. For this reason, group based partitionings are to be preferred for practical hydrogen shielding calculations. Adopting this scheme also presents the advantage of yielding accurate non-hydrogen shieldings, should they be desired.

As it was noted previously that deviations between pcS-3 and pcS-4 in unpartitioned calculations were small, the possibility of using pcS-3 in place of pcS-4 on the focus group was evaluated.


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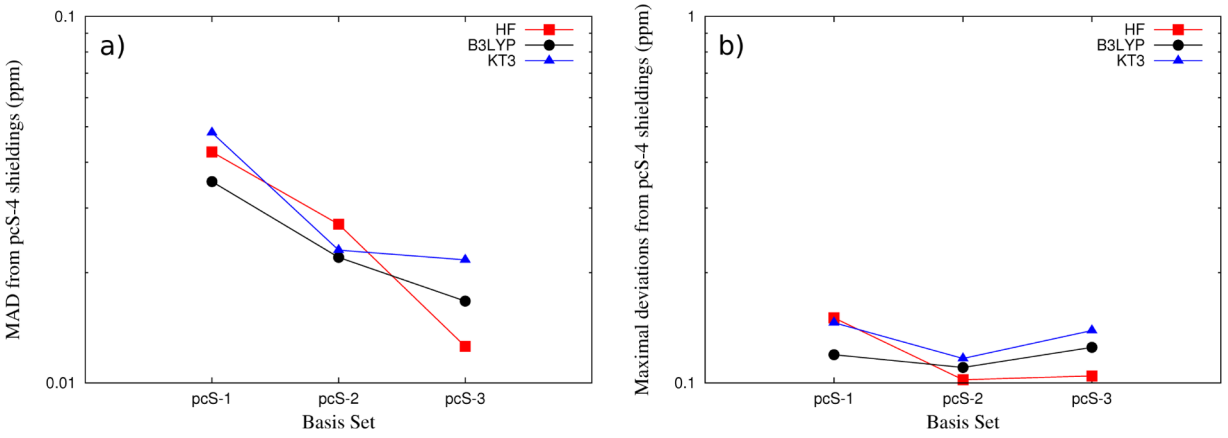


**Figure 6.** (a) Mean absolute and (b) maximal deviations from pcS-4 shieldings for hydrogens with the pcS4/pcS*n*/pcS1$^G$ partitioning.

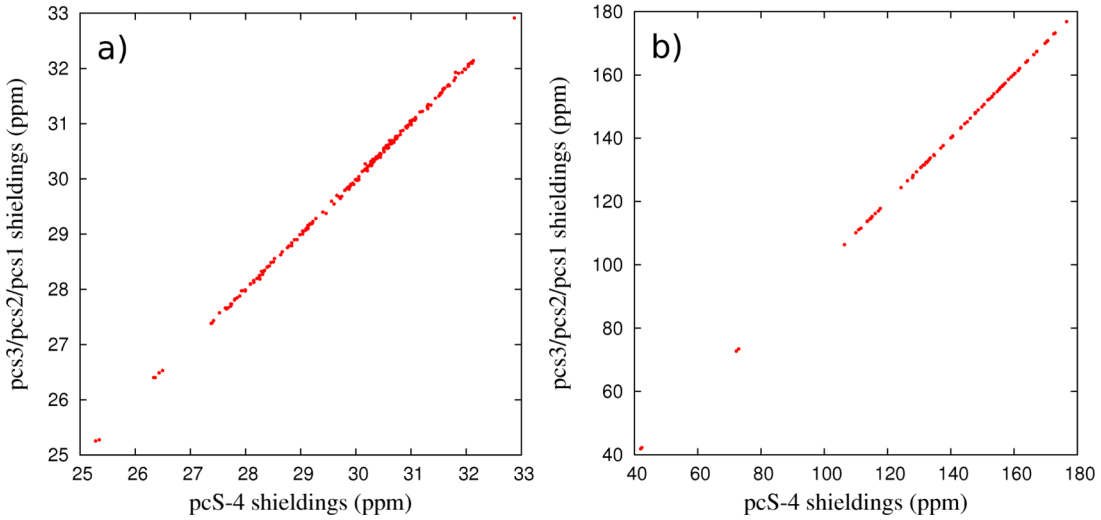


**Figure 7.** Comparison of the shieldings obtained using the pcS3/pcS2/pcS1$^G$ partitioning and pcS-4 on all atoms for (a) hydrogens and (b) carbons.

MADs for the pcS4/pcS2/pcS1$^G$ and pcS3/pcS2/pcS1$^G$ partitioning are virtually identical for hydrogens, though for non-hydrogens they are 0.170 and 0.328, respectively. The majority of this difference is due to the oxygen and nitrogen atoms within the test set, which, if examined separately, have MADs of 0.421 and 0.720 for the two schemes. Shieldings with the pcS3/pcS2/pcS1$^G$ partitioning are compared to those obtained through full molecule pcS-4 calculations in Figure 7 for hydrogens and carbons. While the correlation is evidently better for carbons, it is fair to conclude that it is satisfactory for both types of atoms, and this method thus represents a good balance of computational cost and accuracy for these nuclei.

In addition, the possibility of reducing the basis set size further by replacing pcS-n with pc-n in the distal and adjacent regions was investigated: the localized basis set pcS3/pcS2/pcS1$^G$ was replaced by pcS3/pcS2/pc1$^G$ and pcS3/pc2/pc1$^G$. While this slightly reduced the total number of basis functions, the mean absolute and maximal errors were found to increase significantly (see Supporting Information Tables S40−42). Hence, this approach was not further pursued.

An indication of the relative computaional cost of the various schemes is given in Table 1. It is evident from these results that the recommended partitionings represent a significant reduction in computation time, even though separate calculations are required for each atom or group. Furthermore, the relative computational saving is expected to become more pronounced as the system size is increased.

**Table 1. Number of CPU Hours Required to Obtain NMR Shieldings at KT3 for All Nuclei in a Molecule, Averaged over the 28 Molecules in the Test Set**

| basis set | avg. CPU time (h) |
|---|---|
| pcS-4 | 256.67 |
| pcS-3 | 31.51 |
| pcS4/pcS2/pcS1$^G$ | 20.19 |
| pcS4/pcS1/pcS1 | 12.25 |
| pcS3/pcS2/pcS1$^G$ | 5.69 |

## 4. SUMMARY

It has been successfully demonstrated that for nuclear magnetic shieldings the pcS-*n* basis sets converge more rapidly at MP2 than all other tested basis sets. While the difference in convergence behavior is not as pronounced at this level as for DFT, this still indicates that the pcS-*n* basis sets are the most suitable for shielding calculations at post-SCF levels.

The examination of partitioning schemes has revealed that at least pcS-1 is required everywhere in a molecule, though it is not necessary to go beyond pcS-2 except on the focus atom. The pcS3/pcS2/pcS1$^G$ partitioning was found to yield


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satisfactory results for both hydrogens and carbons, while other heavy nuclei benefited from pcS-4 on the focus group. If only non-hydrogen shielding constants are required, the pcS4/pcS1/pcS1 partitioning provides an economical alternative.

The limits of this study should, however, be noted. The test set does not include carbonyls, aromatics, formally charged groups, or species possessing intramolecular hydrogen bonds. In summary, many systems that would be expected to exhibit long-range interactions have not been considered, and it is possible that modified partitioning schemes will be required for these.

Also, as previously mentioned, convergence at MP2 is slower than at the other levels of theory. Hence it is possible that the partitioning schemes presented as satisfactory in this study will be less so at post-SCF levels. This potential problem is difficult to quantify, as calculations at MP2 with a pcS-4 basis set are impractical for any molecules for which the partitioning schemes examined are meaningful.

It is also important to recognize that while the recommended local basis sets can provide reliable estimates of the shielding constants, they are unlikely to yield accurate or reliable estimates of molecular electronic energy. If the electronic energy is required, for example to obtain a thermal average of the shielding constants, then separate calculations should be performed using other well-established methods and basis sets.

Finally, it should be noted that the LDBS approximation in isolation only allows for the extension of quantitative calculations to moderate sized molecules. However, if used in conjunction with other approximations, such as systematic fragmentation, accurate nuclear magnetic shielding calculations on biologically relevant systems may be feasible.

## ■ ASSOCIATED CONTENT

### Supporting Information

Cartesian coordinates (in Ångstrom) for all the molecules in this work; mean deviations, standard deviations, and maximal deviations from full molecule pcS-4 shieldings for each basis set partitioning and at each of the levels of theory employed in this work. This material is available free of charge via the Internet at http://pubs.acs.org/.

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### Notes

The authors declare no competing financial interest.

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