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Prediction of ^{19}F NMR Chemical Shifts for Fluorinated Aromatic Compounds

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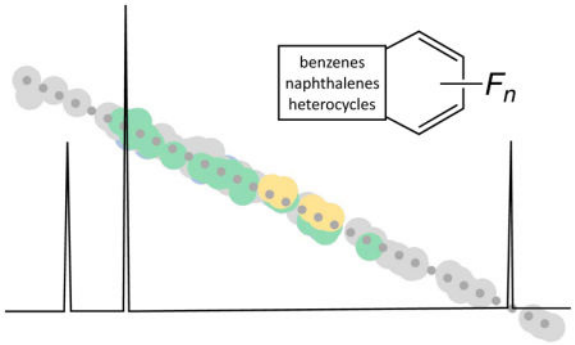
Abstract

Scaling factors are reported for use in predicting ^{19}F NMR chemical shifts for fluorinated (hetero)aromatic compounds with relatively low levels of theory. Our recommended scaling factors were developed using a curated data set of >50 compounds, with 100 individual ^{19}F shifts spanning a range of >150 ppm. With a maximum deviation of 6.5 ppm between experimental and computed shifts, or 4% of the range tested, these scaling factors allow for the assignment of chemical shifts to specific fluorines in multifluorinated aromatics. The utility of this approach is highlighted by several structural reassignments.

Graphical Abstract



Introduction

The incorporation of fluorine atoms in organic molecules (e.g., materials,[1] agrochemicals,[2–3] pharmaceuticals[4]) is becoming increasingly common, as a result of the unique electronic and steric properties of fluorine atoms.[5–12] Consequently, ^{19}F NMR is applied ever more frequently in structural assignments. Fortunately for chemists working with fluorine, there

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Energies for all computed structures, table with shifts and experimental solvents for all compounds used (PDF)

Coordinates for all computed structures (mol2)

are many appeals of using ^{19}F NMR, e.g., the NMR active isotope is 100% naturally abundant, has a gyromagnetic ratio of about 0.94 times ^{1}H, and is spin ½.[13] Nonetheless, ^{19}F spectra can be difficult to interpret, especially when multiple fluorine atoms are present in a molecule. Some of us have been involved in developing methods for regioselective defluorination of polyfluorinated aromatics, methods that produce exactly the sort of compounds subject to assignment difficulties.[5–9, 14] Useful resources are available to assist organic chemists in the interpretation of ^{19}F NMR, but it remains challenging to reliably assign all ^{19}F shifts within a multifluorinated molecule.[13] Here we endeavor to provide a readily accessible method for reliably predicting ^{19}F shifts of fluorinated aromatic compounds.

Predicting ^{1}H and ^{13}C NMR chemical shifts with quantum chemical methods (especially density functional theory [DFT]) is now commonplace.[15–18] Often, linear scaling methods are used with such approaches to remove systematic errors in computations.[19–20] In doing so, absolute isotropic shieldings are computed for a “training set” of molecules and compared to experimental chemical shifts. When tight linear correlations between computed and experimental data are found, simple scaling factors (slope and y-intercept for the correlation line, particular to the specific theoretical method used) fall out, and can then be used for predicting chemical shifts for molecules not included in the training set. This approach has been explored previously for ^{19}F chemical shifts, including fluorinated aromatic compounds,[21–27,28] but we provide scaling factors here that work with relatively low level theoretical methods accessible to non-experts. We also demonstrate the applicability of these scaling factors for heterocycles (common in bioactive compounds) and highlight their use in assigning structures of multifluorinated compounds.

Our training set consisted of approximately 50 compounds, with 100 individual ^{19}F shifts spanning a range of >150 ppm (Chart 1). This set contains fluorinated aromatics, many with multiple fluorine atoms in the same molecule, and mono- and bicyclic heteroaromatics. A variety of issues made compiling this data set difficult, including variations in reported shifts across the literature and the use of different reference compounds.[27] The compounds in Chart 1 were chosen not just for the variety of environments in which their fluorine atoms reside, but because their ^{19}F shifts were supported by multiple published reports or a single report with sufficient experimental details to make us confident in their validity.[27, 29–42]

Methods

Geometry optimizations were run using B3LYP/6-31+G(d,p) in the gas phase using *Gaussian09*, and resulting structures were confirmed as minima using frequency calculations.[43–47,26] These structures were subjected to NMR (GIAO)[48–54] calculations at B3LYP/6-31+G(d,p), B3LYP/6-311+G(2d,p) and B3LYP/6-31G levels in the gas phase. B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p) calculations were repeated using the SMD implicit solvent model for experimental solvents in NMR calculations.[55] Experimental shifts were plotted against calculated isotropic shielding values, and scaling factors were derived according to equation (1):

$$\sigma_{Experimental} = slope * \theta_{Isotropic} + intercept \quad (1)$$

These scaling factors were applied to all each test compound using equation (2):

$$\frac{\theta_{Isotropic} - intercept}{slope} = \sigma_{Scaled} \quad (2)$$

While the compounds in Chart 1 were chosen, in part, for their lack of conformational flexibility, some compounds to which the developed scaling factors were applied were conformationally flexible. For such compounds, conformational searches were run with *Spartan10*, and then optimized in *Gaussian09* with B3LYP/6-31+G(d,p) in the gas phase.[26,56–57] Conformers within 3 kcal/mol of the lowest energy conformer were included in the NMR calculations, with their contributions weighted with a Boltzmann distribution based on their relative free energies.

Results and Discussion

Using B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p), the maximum error on any one ^{19}F shift was 6.5 ppm, with a mean absolute deviation (MAD) of 2.1 ppm over a range of 153 ppm (Figure 1, middle). Performance was similar when NMR calculations were repeated with a larger basis set (B3LYP//6-311+G(2d,p))//B3LYP/6-31+G(d,p)): maximum error of 6.6 ppm and MAD of 1.7 ppm (Figure 1, right). Use of a smaller basis set (B3LYP/6-31G//B3LYP/6-31+G(d,p)) resulted in a much higher maximum deviation (28 ppm) and a much higher MAD of 4.0 ppm (Figure 1, left). On the basis of these results, we recommend the B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p) for rapid predictions of ^{19}F chemical shifts.

Although the ^{19}F spectra for compounds used in the training set were taken in a variety of solvents, the majority were taken in either $CDCl_3$ or CCl_4 (a full list of the solvents is available in the Supporting Information). To test the effect of solvent on our predictions, the gas phase optimized structures were subjected to NMR calculations in continuum solvent (SMD) and new scaling factors were determined (Figure 2). For the 45 ^{19}F shifts from our test set that were measured in chloroform, gas phase NMR calculations had a maximum error of 8.2 ppm, while continuum chloroform calculations had a maximum error of 7.2 ppm. The MAD also decreased slightly, from 2.9 to 2.6 ppm. For the 27 shifts determined in carbon tetrachloride, the maximum error decreased from 5.1 to 4.6 ppm, while the MAD remained the same at 1.5 ppm. Although including solvent in the calculations did provide small improvements in prediction accuracy, gas phase calculations appear to be sufficient.

To put our scaling factors to the test, we applied them to several multifluorinated compounds synthesized in one of our labs (Chart 2). The original assignment of one structure was found to be in error on the basis of our predicted ^{19}F shifts. The shifts for the corrected structure (Chart 2) are completely consistent with the experimental spectrum.

After discovering this misassignment, a group of 13 substituted benzene and pyridine compounds with various substitution patterns (Chart 3) were examined to confirm, or correct, the published structures.[7, 9, 12] Although many of the spectra match experiment, two of the structures had large errors (Chart 3, red). Based on the correction described above, revised structures were tested and these match the experimental values within the error expected for our scaling factors. These straightforward applications of computational ^{19}F shift prediction highlight its utility in avoiding mistakes in assignments for highly fluorinated compounds.

Conclusion

We have developed scaling factors aimed at fast and accurate prediction of ^{19}F shifts for fluoroaromatics. In particular, the methods described here allow for the assignment of challenging structures bearing multiple fluorine atoms. The application of these scaling factors does not require advanced computations and, as a result, we hope that it will be applied broadly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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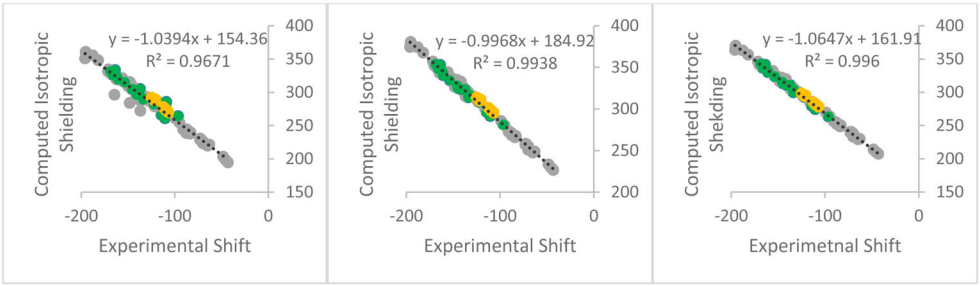

Figure 1.

Correlation data for two NMR computational methods (all using B3LYP/6-31+G(d,p) geometries): Left: B3LYP/6-31G Middle: B3LYP/6-31+G(d,p); Right: B3LYP/6-311+G(2d,p). Mono-cyclic aromatic compounds (group **A**, Chart 1) are shown in green, non-heterocyclic compounds (group **B**) are shown in grey, and bicyclic-heterocyclic compounds (group **C**) are shown in yellow.

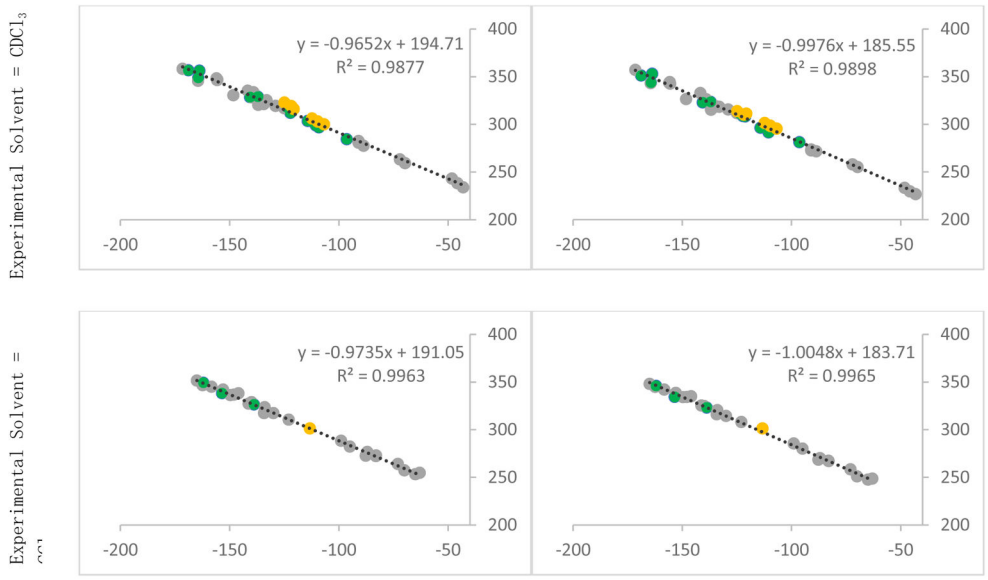

Figure 2.

Experimental and computed shifts for the training set used for optomization and NMR calculation at B3LYP/6-31+G(d,p) – structures taken in chloroform (top) and calculated in gas (left) and chloroform (right), structures taken in carbon tetrachloride (bottom). Mono-cyclic aromatic compounds (group A) are shown in green, non-heterocyclic compounds (group B) are shown in grey, and bicyclic-heterocyclic compounds (group C) are shown in yellow.

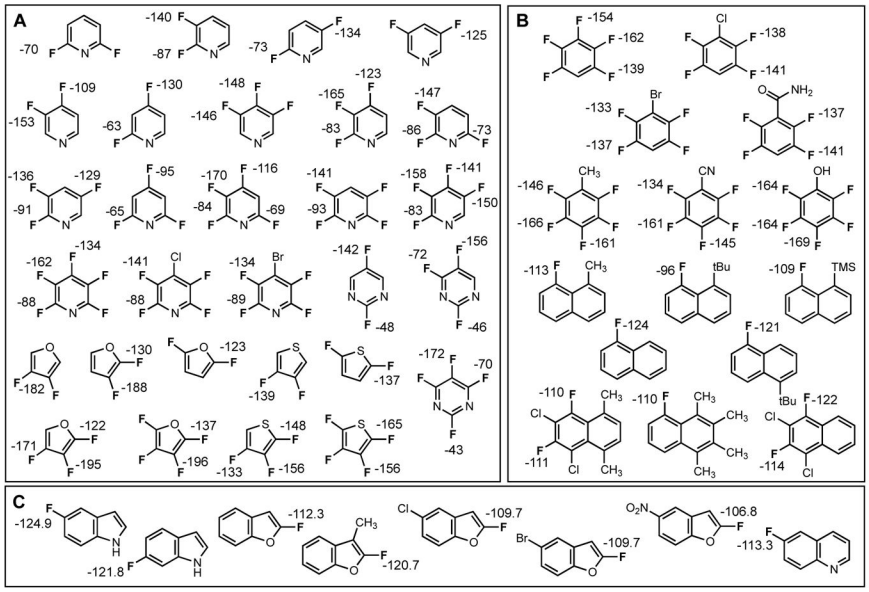

Chart 1.

Experimental shifts of compounds used as training set to develop scaling factors: **A:** substituted mono-cyclic heterocylces, **B:** substituted non-heterocyclic aromatics, **C:** substituted bicyclic heterocycles.

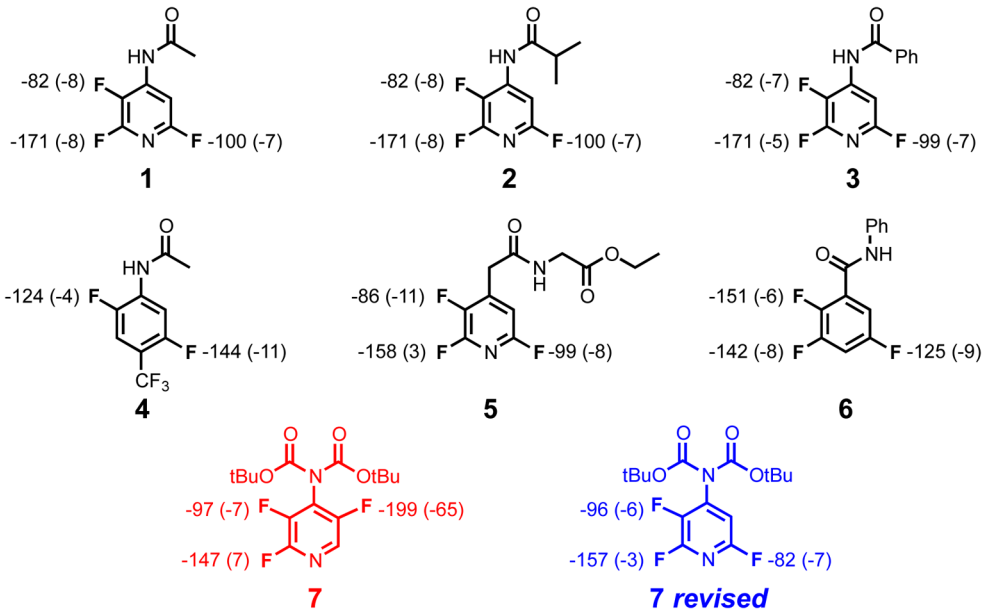

Chart 2.

Initial compounds explored, including a structure that was corrected by computations (highlighted in red). Computed shifts and error from experiment are shown for each aromatic fluorine.

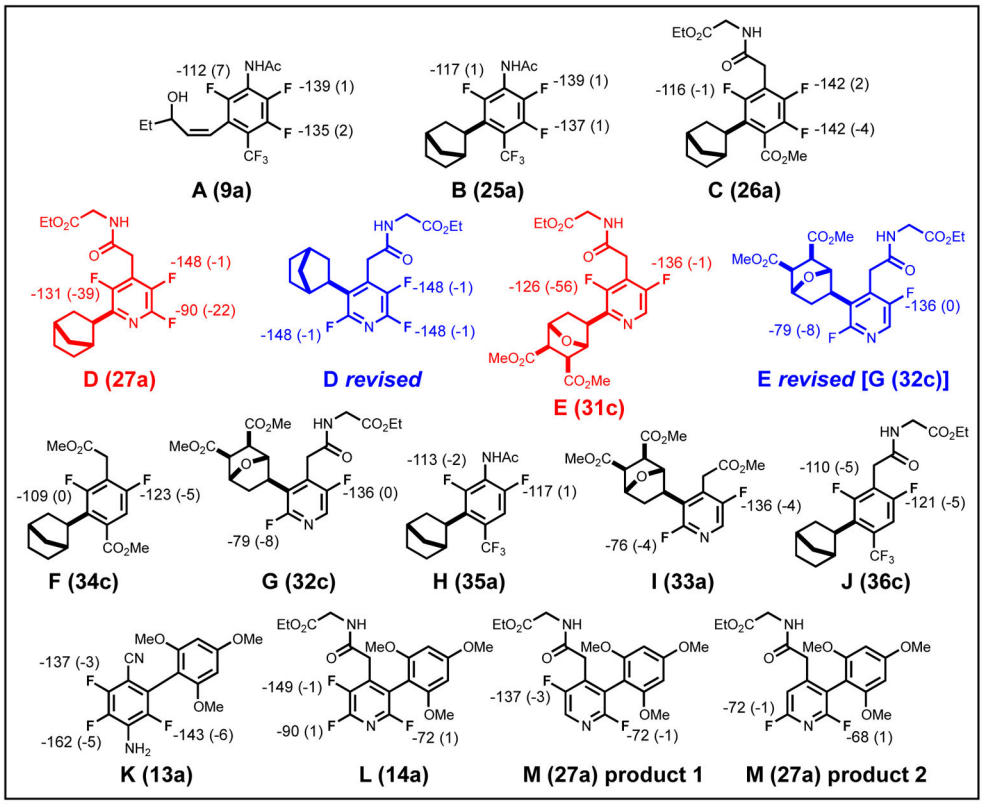

Chart 3.

Fluorinated aromatic compounds for which assignments were not certain. Numbers in parenthases are numbering from the original paper. The calculated shifts and error from experimental shift are shown for each aromatic fluorine.