

Evaluating ^{19}F Chemical Shielding in Fluorobenzenes: Implications for Chemical Shifts in Proteins

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The topic of fluorine-19 chemical shifts or shielding in fluorobenzenes has been of great interest for over 40 years,¹ but there has been surprisingly little work done using *ab initio* methods to evaluate these shifts. For the fluorobenzenes themselves, there is a ~ 63 ppm range in isotropic chemical shifts² and about a 237 ppm range in the shielding tensor elements,³ and over the years a variety of methods have been tried in order to explain the large shift values seen experimentally.^{3,4} More recently, many investigators have incorporated fluoroaromatic amino acids into proteins and have used the ^{19}F chemical shifts observed as structure probes,⁵⁻⁷ and again the nature of the origins of ^{19}F chemical shifts has become of interest.⁸⁻¹⁰ In one approach to predicting shifts, it has been suggested that the major contributions to shielding nonequivalencies due to folding arise from the charge field of the protein, and a charge field perturbation gauge including atomic orbital as well as multipole shielding polarizability models^{11,12} has been used to predict shielding.^{8,13} In a second approach, shielding nonequivalencies have been attributed to dispersion, the so-called van der Waals (vdW) interactions.^{5,9,10} Here, we investigate some of the assumptions inherent in the latter method, an approach which has its origins in early investigations of ^{19}F shielding in fluorobenzenes.⁴ Our results provide a remarkably good account of ^{19}F isotropic chemical shifts as well as solid-state ^{19}F shielding tensors without invoking vdW dispersion interactions.

In early work, Stephen¹⁴ and Buckingham¹¹ described electrical contributions to shielding as

$$\delta^E = AE_z + BE^2 \quad (1)$$

where A is a shielding polarizability ($\partial\sigma/\partial E$), B is a shielding hyperpolarizability ($\partial^2\sigma/\partial E^2$), and E_z is the z -component of the

uniform field, E , acting along, in this case, a CF bond. This approach was then extended to consideration of van der Waals dispersion interactions, where non-zero time-average fields, $\langle E^2 \rangle$, may affect shielding, and a new expression,

$$\delta^E = AE_z + B(E^2 + \langle E^2 \rangle) \quad (2)$$

was used by several groups.^{2,4,9,10} The AE_z term has been assumed in many cases to be negligible for ^{19}F , and the total electrical contributions to shielding have often been expressed by equating $\langle E^2 \rangle$ with the van der Waals/London dispersion formula for $\langle E^2 \rangle$ as^{4,9,10,15-17}

$$\delta^{\text{vdW}} = B \sum \frac{3P_i I_i}{2r_{ij}^6} \quad (3)$$

where P_i is the polarizability of interacting atom i , I_i is the first ionization potential of atom i , and r_{ij} is the distance between atom i and atom j , containing the ^{19}F nucleus of interest. B is a coefficient of proportionality, taken to be $67.7 \times 10^6 \text{ \AA}^3/\text{eV}$ by Chambers et al.¹⁰ from the early work of Boden, Emsley, Feeney, and Sutcliffe.⁴

The above discussion suggests that there are at least three points to be considered when using the van der Waals approach to shielding. *First*, are there *any* proven examples of vdW dispersion effects dominating shielding? *Second*, what is the basis for the evaluation of B . *Third*, what is the convergence behavior of the multipole shielding polarizability expression if long-range interactions are to be considered?

The systems most likely to have their shielding dominated by van der Waals interactions might be expected to be rare gases such as Xe, since they are polarizable but have no permanent moments. The dominance of vdW dispersion effects on shielding was presumed to be the case for many years, but in very recent work using LOG¹⁸ and SOLO,¹⁹ it has been shown that while second-order effects contribute to the intermolecular interaction energies, they do not affect the shielding functions perceptibly,²⁰ and indeed the pressure dependence of rare gas shielding²⁰ as well as that of the shielding of Xe clusters in zeolites²¹ has been well described using shielding functions calculated at the SCF level. Furthermore, it has been shown that the *ab initio* values of B calculated from the quadratic shielding response to a uniform electric field²² is at least an order of magnitude too small to account for the observed gas-phase shifts of xenon in the form of a $B\langle E^2 \rangle$ term. These results bring into question the dominance of second-order or vdW ($B\langle E^2 \rangle$) effects on shielding in other molecules.

We have therefore reconsidered in detail the case of ^{19}F shielding in the fluorobenzenes, where Boden et al.⁴ deduced a range of B values, centering around $\approx 67.7 \times 10^6 \text{ \AA}^3/\text{eV}$. Their work involved both analyzing the chemical shifts of fluorobenzenes and fluorobiphenyl^{4,23} and using an average energy approximation to evaluate the electronic contribution to shielding and the assumption that the A term is negligible.⁴ Moderate accord with experiment was achieved with assumptions about ΔE , P , I , r , A , E , and B ,^{4,23} although not all experimental results could be fitted, e.g., in the case of pentafluorobenzene.⁴

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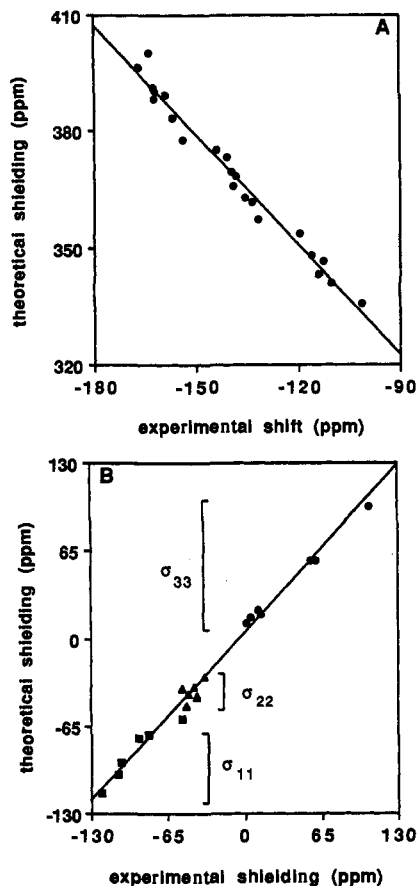


Figure 1. Experimental versus theoretical ^{19}F chemical shift/shielding results for fluorobenzenes. (A) Liquid-state isotropic chemical shifts (in ppm from external CFCl_3) plotted versus computed shielding values; slope = -0.94 , $R^2 = 0.975$. Molecules studied: $\text{C}_6\text{H}_5\text{F}$; 1,2- $\text{C}_6\text{H}_4\text{F}_2$; 1,3- $\text{C}_6\text{H}_4\text{F}_2$; 1,4- $\text{C}_6\text{H}_4\text{F}_2$; 1,2,3- $\text{C}_6\text{H}_3\text{F}_3$; 1,2,4- $\text{C}_6\text{H}_3\text{F}_3$; 1,3,5- $\text{C}_6\text{H}_3\text{F}_3$; 1,2,3,4- $\text{C}_6\text{H}_2\text{F}_4$; 1,2,3,5- $\text{C}_6\text{H}_2\text{F}_4$; 1,2,4,5- $\text{C}_6\text{H}_2\text{F}_4$; C_6HF_5 ; C_6F_6 ; and $\text{C}_6\text{F}_5\text{Cl}$. (B) Solid-state shielding tensor components (in ppm from C_6F_6 ; ref 3) plotted versus computed shielding tensor elements; slope = 0.954 , $R^2 = 0.989$. Molecules studied: $\text{C}_6\text{H}_5\text{F}$; 1,2- $\text{C}_6\text{H}_4\text{F}_2$; 1,3- $\text{C}_6\text{H}_4\text{F}_2$; 1,4- $\text{C}_6\text{H}_4\text{F}_2$; 1,3,5- $\text{C}_6\text{H}_3\text{F}_3$; 1,2,4,5- $\text{C}_6\text{H}_2\text{F}_4$; and C_6F_6 . The "ortho-effect", the shielding of σ_{22} by ~ 50 ppm on each *o*-F substitution, is clearly seen in B, as is the invariance of σ_{33} with substitution (ref 3). Chemical shielding calculations were carried out on geometry-optimized structures using the Texas 90 program on a cluster of IBM/RISC-6000 computers (1 Gflop peak, 40 Gbytes storage).

With numerous theoretical developments over the past 30 years^{24–26} and greatly improved computer hardware, it is now of course possible to carry out much more accurate evaluations of chemical shielding than possible in 1964, so we have reinvestigated ^{19}F shielding in fluorobenzenes in order to assess the likelihood that additional second-order or vdW dispersion contributions to shielding might be significant. At the SCF level, dispersion or $B\langle E^2 \rangle$ terms are neglected, enabling the hypothesis that they do not affect shielding to be tested. The isotropic chemical shift range for 13 fluorobenzenes investigated was 63 ppm, and the shielding tensor elements (derived from solid-state NMR measurements, ref 3) cover over a 237 ppm range—a fairly stringent test for theory. We carried out geometry optimization at the

SCF level (with a uniform 6–31G** basis) and used a locally-dense basis GIAO approach for shielding computations^{24–26} (with a 6–311G basis, two sets of d functions and a set of diffuse functions for F, a set of d functions on C, and a set of p functions on H), and our results are shown in Figure 1. Figure 1A shows the experimental isotropic shifts for 13 fluorobenzenes versus their computed shieldings, while Figure 1B shows 21 experimentally determined ^{19}F (relative) shielding tensor elements, again plotted as a function of computing shielding. For the isotropic (liquid state) chemical shifts, the slope is -0.94 , $R^2 = 0.975$, and the root mean square deviation (rmsd) is 3.1 ppm over the 63 ppm shift range. For the solid-state shielding tensor elements, the slope is 0.954 , $R^2 = 0.989$, and the rmsd is 6.5 ppm over a 237 ppm chemical shielding range (about the experimental uncertainty). The correlations seen in Figure 1 explain the long-standing "ortho" effect,³ previously posed as a challenge for theory,³ as well as the previously refractory pentafluorobenzene problem.⁴ Since there are no assumptions about ΔE , P , I , r , A , E , or B in these calculations, which reproduce the experimental liquid and solid-state results exceptionally well, no basis seems to exist for assuming the dominance of the $B\langle E^2 \rangle$ van der Waals dispersion terms in determining chemical shifts or shielding in these systems, since these effects are absent at the SCF/HF level of theory used. Any works relying on such B terms to explain observed fluorine shifts are therefore suspect.

The final point we consider is the convergence behavior of the long-range electrical contributions to shielding given by eq 1. Equation 1 considers only the uniform field contributions to shielding, and it has been pointed out elsewhere that nonuniform components, due to the field gradient and the field hypergradient, are also important.^{27–29} For fluorobenzenes, the field, field gradient, and field hypergradient terms are typically $\sim 10^2$ times larger than the BE^2 hyperpolarizability term, with the AE_z uniform field component being largest.²⁹ Theoretical calculations of A_z in fluorobenzene, *p*-difluorobenzene, and *p*-lithiofluorobenzene center around ~ 2000 ppm/au,¹² about 10^2 larger than the value estimated previously.⁹

The results we have discussed above show a remarkably good correlation between isotropic chemical shifts and computed shielding in a range of fluorobenzenes as well as an excellent correlation between solid-state NMR-derived ^{19}F shielding tensor elements in fluorobenzenes and predicted shielding. Based on these results, as well as rare-gas shielding calculations,^{20–22} there seems to be no reason to assume that ^{19}F shielding nonequivalencies in fluorobenzenes or in proteins due to folding are significantly influenced by $B(E^2 + \langle E^2 \rangle)$ or van der Waals dispersion interactions.^{9,10} Longer-range inter-residue shielding interactions in proteins are best viewed as being dominated by electrostatic polarization and can be explicitly evaluated either by using charge field perturbation-GIAO/SCF methods^{13,30} or by using the multipole shielding polarizability-local reaction field approach.^{8,29} The assumption of a major van der Waals $B\langle E^2 \rangle$ or dispersion contribution to shielding does not appear to have any basis, either for rare gases,^{20–22} where it was originally thought to dominate, or for any of the fluorobenzenes used to establish $B^{4,9,10,23}$ (Figure 1), or, implicitly, in proteins.

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