Correlation of Fluorine-19 Chemical Shielding and Chemical Shift Nonequivalence

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Abstract: The nonequivalence of the chemical shift of nuclei in equivalent bonding environments but inequivalent intermolecular environments can arise in different ways, and electrostatic perturbation is one of the most direct mechanisms. We have carried out large basis set ab initio calculations for a collection of fluorine-substituted hydrocarbons experiencing the electrostatic influence of an external ideal electric dipole. As a function of the separation from the dipole, the chemical shielding at the fluorine nucleus has been evaluated. We find that the change in shielding from the dipole perturbation serves as a secondary signature of the chemical bonding environment since it correlates with the shielding. The biggest effect of an external dipole on the isotopic shielding of a fluorine nucleus comes about when the fluorine is bonded to a doubly-bonded or aromatic carbon. A lesser effect develops from attachment to a triply-bonded carbon, and the least from attachment to a singly-bonded carbon. For the series of molecules, there is a striking, near-linear correlation of the dipole induced shift and the paramagnetic shielding, making the nonequivalence of shifts an indirect measure of the paramagnetic component of the shielding. The size of the nonequivalence effects associated with a nearby dipole can be on the order of 20 ppm for the typical charge fields of small molecules (e.g., water) at van der Waals separations from fluorine.

Introduction

It is well-known that NMR chemical shifts observed in native proteins differ from those of the denatured protein. For example, individual C^α resonances of the γ-carbons of the six tryptophan residues in hen egg-white lysozyme have been observed to cover a range of 3.8 ppm (81.4–85.2 ppm),[1] whereas in the denatured state, a single, unresolvable resonance at 83.8 ppm was observed. These changes in the chemical shift due to the protein's folded structure[1,2] have been termed chemical shift nonequivalences. These nonequivalencies are even more striking for ^{19}F-labeled tryptophan residues with the range in shifts being up to about 10 ppm.[3–5] A similar range of effects has been observed for ^{17}O in heme proteins.[6]

Since the covalent bonding of a protein is unchanged in the native (folded) state compared to the denatured state, nonequivalences must be due to interresidue interactions and/or changes in the solvent–protein interactions. A number of our studies of small clusters[7–9] have provided a strong indication that electrical polarization has the primary role in the changes in molecular properties upon weak interaction with a partner molecule or fragment. Ab initio calculations of NMR chemical shieldings and the effects of intermolecular electrostatic effects on shieldings have already provided certain useful correlations and predictions. For instance, we have found that the correlation of the CO vibrational frequency, the ^{13}C chemical shift, the ^{17}O chemical shift, and the oxygen nuclear quadrupole coupling in a series of carbonmonoxyheme proteins corresponds to varying fields of the distal ligands.[10] We have argued that the ranges of chemical shifts in proteins vary with the type of nuclei and with the electrostatic environment[11] via intrinsic shielding polarizabilities. The shielding polarizabilities are simply the changes in the shielding with respect to an external field, analogous to the dipole polarizability being the change in the molecular dipole with respect to an external field. Buckingham introduced power series expansions of the chemical shielding in terms of external fields and field gradients[12] and defined these properties. They have been calculated by semiempirical[13] and finite difference methods[14–17] and by our analytical derivative Hartree–Fock (DHF) approach.[18]

An essential aspect of our calculational investigations is the nature of inter- and intramolecular interaction in relation to chemical shielding. Consistent with the notion that the primary electronic structure change upon weak interaction is polarization of the charge distribution of a molecule,[7–9] electrostatic interaction between molecules should be manifested in a change in the chemical shielding brought about because of the polarization that occurs. We have previously calculated the first derivative of the shielding with respect to a uniform electric field (i.e., the shielding polarizability) and with respect to a field gradient for magnetic nuclei (H, ^{13}C, ^{17}O, ^{14}N, ^{19}F) in a number of small molecules. Comparison with a large body of chemical shift data for proteins shows that a greater range of nonequivalencies occurs for nuclei with the bigger shielding polarizabilities.[11] In itself, this is further evidence of the role of electrical perturbation, because such a correlation would be unlikely were there other strongly competing effects. This leads to a more detailed inquiry of the manner in which the nonequivalencies depend on the extended chemical environment, and not simply on the atomic

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number. Ab initio calculations are used to address that question for ^{19}F chemical shifts in this report, and we show that the response in shielding is essentially proportional to the paramagnetic contribution to the shielding.

Calculational Approach

A charge field perturbation approach[19] was used to explore the effects of electrostatic influence on chemical shielding of ^{19}F in different chemical environments. This means that a conventional ab initio calculation was carried out to obtain the absolute shielding, but included in the molecular Hamiltonian was a particular electrostatic perturbation. Since dipoles are the longest range contributor to the electrostatic potential of a neighboring neutral molecule or molecule fragment, our charge field perturbation calculations were carried out with an ideal dipole in a chosen position in the vicinity of the molecule. The evaluation of the chemical shielding of magnetic nuclei of the perturbed species was performed with the derivative Hartree–Fock method.[18] Comparison with the calculated value in the absence of a dipole provides the relative chemical shielding, a shift, due to the dipole. We used a dipole of 1.0 au (2.54 D) as representative of the size of the dipole of small molecules such as water and of the local bond dipoles that may exist in small organic molecules. The dipoles were placed at a number of distances from the fluorine atom of the molecule being studied and were aligned with the axis of fluorine's chemical bond.

The molecules that were studied are a sampling of different bonding environments for fluorine in hydrocarbons. Of course, since fluorine forms only single bonds, the differences in the environments are secondary, at the connected center. ^{19}F chemical shifts were calculated for CH_3F, C_2H_5F, C_2H_3F, HC_2F, C_2F_2, HC_4F, and fluorobenzene. The molecular geometries were structures determined spectroscopically (C_2H_3F,[20] HC_2F,[21] and C_2F_2[22]) or by ab initio calculations (C_2H_5F[23] and fluorobenzene[14]). The HC_4F structure was that obtained by repeating the $-C{\equiv}C-$ unit of the HC_2F structure and taking the central C–C bond distance to be 1.387 Å.[25] The structural parameters used for CH_3F are $R_{CF} = 1.3889$ Å, $R_{CH} = 1.0839$ Å, and $\angle FCH = 108.78°$.

The SCF-level DHF calculations for all molecules except fluorobenzene used large basis sets that were modifications of basis sets designated ELP.[26] These sets consist of Dunning's triple-ζ contraction[27] of Huzinaga's (10s6p) primitive sets of Gaussian functions,[28] augmented with diffuse valence functions and three sets of polarization functions. In the modified basis sets we employed and which are designated here as ELP^+, the valence p functions were less contracted, (6p/5p) instead of (6p/3p) since this additional flexibility in the valence set is important for describing NMR chemical shieldings.[10,18,29] For fluorobenzene calculations, the basis was that previously used.[11] This basis is also based on the Dunning triple-ζ valence set, but the contraction is (6p/4p) instead of (6p/3p) and the augmentation was with a single set of polarization functions (exponents: $p_H = 0.7$, $d_C = 0.75$, and $d_F = 0.9$).

Tests were carried out on the HF molecule to evaluate the sensitivity of the shielding to the location of the gauge origin for the ELP^+ basis. Our choice of these bases follows from prior work on carbon monoxide where we showed that gauge invariance is distinct from basis completeness[29] but that as basis completeness is approached, gauge sensitivity becomes minimal. Since the charge field perturbation calculations implicitly involve the shielding polarization response of each molecule, the basis requirements are actually more stringent than achieving gauge invariance. The basis must be sufficient to describe the polarization response, and this is why the chosen ELP^+ bases are triply polarized. For fluorobenzene, the basis requirements to describe accurately the polarization response are not as stringent because the response is more a valence, interatomic charge rearrangement. With the ELP^+ bases, the gauge sensitivity is relatively small,[29] and this is illustrated for ^{19}F shielding by results for HF shown in Figure 1. Over the length of the molecule, sensitivity to the location of the gauge origin, relative to the usual choice of the gauge origin at the fluorine nucleus, is well within the error limits of the reported experimental value of 410 ± 6 ppm.[30] With a consistent choice of one gauge center, the atomic nucleus, the relative gauge effect between the molecules that were studied is not significant.

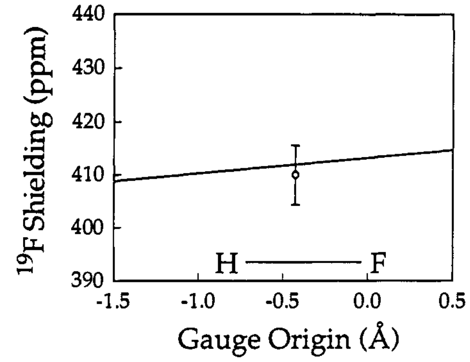

Figure 1. Dependence of the isotropic ^{19}F chemical shielding on the choice of the gauge center location along the molecular axis. The location of the hydrogen and fluorine atoms is indicated, and the shielding (in ppm) is given relative to the gauge origin at the fluorine nucleus. The experimental value and errors bars are shown.[30]

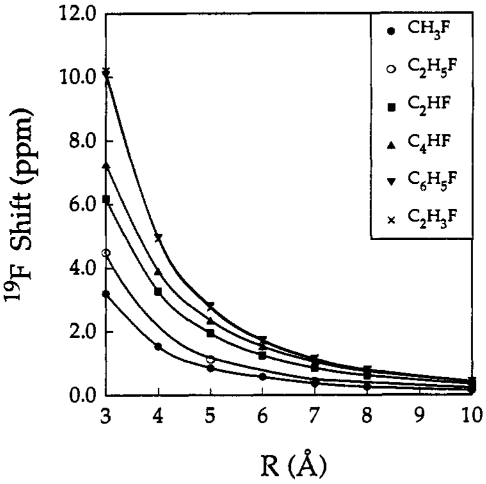

Figure 2. Relative changes in the ^{19}F chemical shielding (in ppm) for a number of molecules as an ideal point dipole of −2.54 D approaches at a distance from the fluorine given by the coordinate of the horizontal axis.

Results and Discussion

The calculated relative isotropic ^{19}F shieldings (in ppm) for several fluorohydrocarbons as a function of the separation distance from the fluorine nucleus and the perturbing ideal dipole (2.54 D) are shown in Figure 2. An interesting feature is the near grouping of curves that matches the chemical environment of the fluorine according to the following categories, from least to greatest effect: (i) fluorine bonded to a center that has no multiple bonds (CH_3F, C_2H_5F); (ii) fluorine bonded to a triply-bonded carbon (FCCH, FC_4H); (iii) fluorine bonded to a center that is doubly bonded or aromatic (FC_6H_5, H_2C_2HF). The role of the secondary chemical environment, or the bonding of the carbon to which the fluorine is attached, would seem to mostly diminish or augment fluorine shielding through interatomic polarization. In that sense, we might expect the ordering to be from triply-bonded, to doubly-bonded, and to singly-bonded carbons because the dipole polarizability goes in the order $C_2H_6 > C_2H_4 > C_2H_2$;[31] however, that is not found. In fact, the dipole polarizability,

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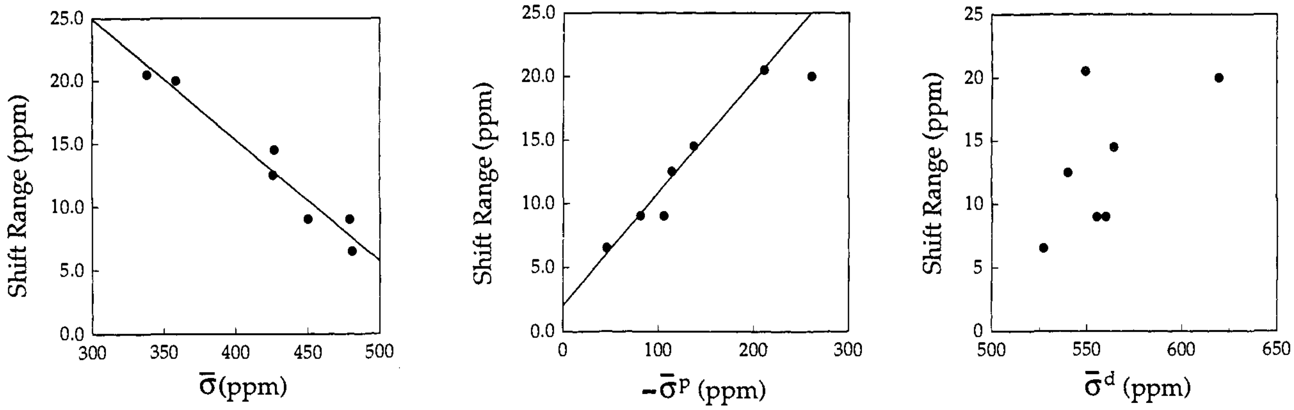

Figure 3. Calculated absolute isotropic (a, left) total shielding, (b, middle) paramagnetic shielding, and (c, right) diamagnetic shielding (horizontal axis) of ^{19}F for several C, H, F molecules plotted against the range of the chemical shift due to an external dipole approaching the fluorine center up to a distance of 3.0 Å. In parts a and b, the solid lines represent a least-squares fit of the data to a linear function, with the fluorobenzene data excluded from the fitting of part b. A linear least-squares fit for the points in part c yields a poor correlation: $R^2 = 0.39$ versus 0.93 for the data in part b, where R^2 is the ratio of the square of the deviation of the function from the mean to the square of the deviation of the data points from the mean.

Table I. Calculated Isotropic Shielding[a] of ^{19}F and the Effect of a Dipolar Electrostatic Potential

molecule	$\bar{\sigma}^{d}$ (ppm)	$\bar{\sigma}^{p}$ (ppm)	$\bar{\sigma}$ (ppm)	$\Delta\bar{\sigma}$ (ppm)
CH_3F	526.9	−45.5	481.4	3.2
FCCF	559.7	−80.8	478.9	4.5
CH_3CH_2F	555.0	−105.0	450.0	4.5
HCCF	539.9	−114.2	425.7	6.2
HC_4F	564.3	−137.2	427.1	7.3
CH_2CHF	549.3	−211.4	337.9	10.2
C_6H_5F	619.6	−261.4	358.2	10.1

[a] $\bar{\sigma}^{d}$ is the diamagnetic component of the isotropic shielding, and $\bar{\sigma}^{p}$ is the paramagnetic component. $\bar{\sigma}$ (the total shielding) = $\bar{\sigma}^{d} + \bar{\sigma}^{p}$. $\Delta\bar{\sigma}$ = $\bar{\sigma}$ (in the presence of the dipole at 3.0 Å from the ^{19}F along the C–F bond axis) − $\bar{\sigma}$.

a usual measure of polarization response, does not correlate with the effects of the ideal dipole on the shielding. Notice that HCCF and HC_4F fluorine's have nearly coincident curves in Figure 2, as would be expected on the basis of their similar chemical environments. On the other hand, our calculation of the dipole polarizability shows the longer molecule to be about *twice* as polarizable as HCCF. Therefore, polarizability values simply do not account for the shifts arising from electrostatic interaction.

A more detailed analysis of the origin of the shifts due to electrostatic interaction comes about from comparing the molecules with the perturbing dipole at one specific separation. So, Table I lists the calculated isotropic ^{19}F chemical shieldings for the molecules studied along with the shifts due to the presence of the ideal dipole at a distance of 3 Å from the fluorine nucleus. The shielding values are partitioned into the diamagnetic and paramagnetic contributions. We find from selected test calculations that reversing the orientation of the dipole in the charge field perturbation calculations yields a shift of nearly the same size (to within 5%) but of opposite sign. Thus, the range of the effect of the dipole, going from one orientation to the other, is roughly twice the calculated shift value given in Table I. Now, for an ideal dipole at 3 Å from a fluorine center, plots of the range of the effect (i.e., twice the value of the shift in Table I) against the total chemical shielding, against the paramagnetic shielding, and against the diamagnetic shielding are displayed in Figure 3. The plot of shift range versus the absolute shielding (Figure 3a) shows a good correlation, and a linear function can be fitted to the data rather well. The plot of the shift range versus the paramagnetic shielding (Figure 3b) reveals a linear relation for all the molecules studied with the ELP$^+$ bases, whereas the plot of the shift ranges versus diamagnetic shieldings (Figure 3c) shows no correlation. From these results, it is clear that the greater the paramagnetic shielding, the proportionately greater is the response to the external dipole. Since the paramagnetic shielding diminishes the overall shielding ($\sigma = \sigma^{\text{diag}} + \sigma^{\text{para}}$; $\sigma^{\text{para}} < 0$), then there is an anticorrelation between the total shielding and the shift range to the extent to which the diagmagnetic contribution is either unchanging or changing in parallel. As shown in Table I, there are certain sizable differences in the diagmagnetic shielding among the molecules studied, and an absence of correlation (Figure 3c) with the shift ranges. So, the only certain correlation is between the shift ranges and the paramagnetic contributions.

The response of the shielding at a nucleus to an external electrostatic potential necessarily reflects the net local polarization or the distortion in the electron cloud in the vicinity of the magnetic nucleus. According to our previous study of ranges in shift nonequivalencies,[12] there is an ordering in ranges that goes according to atomic number, *Z*, which from smallest to largest ranges is proton, carbon-13, oxygen-17, and fluorine-19. While hydrogen centers are likely to have a much less polarizable local charge distribution than carbon, oxygen, and fluorine centers, the ordering by atomic number among carbon, oxygen, and fluorine is not entirely expected: The ordering of the isotropic dipole polarizabilities of the hydrides CH_4 (16.0 au), H_2O (12.8 au), and HF (4.8 au) is clearly opposite.[31] Again, the response of the shielding cannot be explained as simply a shift of charge, such as that leading to an induced dipole. Rather, it must be a manifestation of more detailed polarization changes, particularly intraatomic changes.

Standard low-order perturbative analysis of diamagnetic and paramagnetic chemical shielding[21] of an atom shows that for linear orbital mixing of the type $l \leftrightarrow l+1$ (e.g., $s \rightarrow s + \epsilon p$) there will be at least a first- and second-order dependence of the paramagnetic contribution on the mixing parameter, ϵ. An electric field, and the electrostatic potential of an ideal dipole, will bring about that type of mixing with the parameter ϵ then being the field (dipole) strength. Thus, there is formally a first- and second-order dependence of the paramagnetic shielding on the field or dipole. There will also be a dependence of the diagmagnetic shielding, but we consider that later. The fundamental question now becomes should the dependence on the electrostatic potential vary with the size of the paramagnetic shielding?

Fluorine is a particularly good example nucleus for considering the fundamental link between the shielding and the shift range. Its atomic electron occupancy is one away from that of a closed-shell rare gas, neon. In neon, perturbative orbital mixing involves a change in principal quantum number (i.e. 2s → 3p or 2p → 3s). In contrast, elements to the left of neon in the periodic table tend to have more sizable polarizabilities because s → p mixing can be done within an orbital shell, and from a perturbative standpoint, that means a smaller, more favorable energy denominator. So, we may expect that greater electronic population of a fluorine center in a molecule diminishes the ease for local $l \leftrightarrow l + 1$ atomic orbital change. That is, completion of the fluorine valence shell should diminish the paramagnetic shielding's response to an electrostatic perturbation. That accounts for the observed correlation and the trends mentioned above provided that the diagmagnetic shielding is not significantly participating in the response to the ideal dipole.

To check the role of the diamagnetic shielding, we carried out a calculation on the neon atom, because relative to fluorine, it offers a limiting closed-shell situation, and of course, the paramagnetic contribution is identically zero.[21] In this case, the effect of the ideal dipole at 3.0 Å was, in fact, very small and less than 0.01 ppm. Interestingly, if the line in Figure 3a were continued till it intersects the ordinate, which is the point of a zero shift range, the chemical shielding is very nearly equal to that which we calculated for neon, 552 ppm. Thus, the calculational results fit the formal analysis in showing that the effect of an electrostatic interaction on the chemical shielding is mostly via the paramagnetic contribution.

It is clear that the shielding response to an electrostatic perturbation, such as that of weak inter- and intramolecular interaction, refers to something different than does an induced dipole, or other induced electrical moment. The response is a consequence of intraatomic hybridization more so than a gross shift in electron density. The demonstrated linear relation of the shift due to an ideal dipole and the paramagnetic contribution to the shielding offers a fundamental basis for understanding chemical shift nonequivalencies[11] and for modeling them in simulations of complicated systems. It also suggests that shift nonequivalences may serve as a more intricate experimental probe of electronic structure features such as the paramagnetic shielding contribution.

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