Computing nuclear magnetic resonance chemical shielding in large systems via multipole shielding polarizabilities

Joseph D. Augspurger [a], Angel C. deDios [b], Eric Oldfield [b] and Clifford E. Dykstra [a]

[a] *Department of Chemistry, Indiana University – Purdue University at Indianapolis, 402 North Blackford Street, Indianapolis, IN 46202, USA*

[b] *Department of Chemistry, University of Illinois at Urbana – Champaign, 505 South Mathews Avenue, Urbana, IL 61801, USA*

Received 29 June 1993; in final form 10 August 1993

Whereas ab initio methods are feasible for computational evaluation of chemical shielding parameters in small molecules or molecular fragments, a simpler method is demonstrated for the evaluation of the relative effects of shielding due to electrostatic interactions, such as those which may arise from both inter- and intra-residue interactions in proteins and other biomolecules. The shielding of a small molecule or molecular fragment is expanded in a multipole power series, and the terms of the series may be evaluated by contemporary ab initio methods. The convergence behavior of this expansion using fluorobenzene is shown as a prototypical molecule, and we conclude that the first three multipole polarizability terms are important, but that hyperpolarizability shielding corrections are negligible.

1. Introduction

The NMR chemical shift observed in the laboratory usually pertains to a molecule that (1) undergoes intramolecular motions and (2) interacts with other molecules. So, while the observable chemical shift is unavoidably an average over the different conformations and various interactions during the time period of the NMR measurement, a theoretically computed chemical shift usually refers to an isolated molecule at a fixed geometry. More complete methods of theoretical calculation of chemical shielding are needed, particularly methods for dynamically averaging effects.

Molecular dynamics (MD) simulations afford one means of following the time-evolution of large molecular systems, e.g. proteins. These simulations can be used to time-average NMR parameters, as recently reported, for example, by deDios, Pearson and Oldfield [1]. A crucial element of such simulations, however, is the evaluation of the shielding at each successive structure processed in the MD simulation. Ab initio calculations may be used to map a shielding surface analogous to a potential energy surface, and this has been done at least for small molecules such as water [2]. A fit of the points on a surface will enable the rapid evaluation of shielding tensors in the course of an MD simulation for an isolated molecule. The medium, however, presents a further complication.

In certain cases, it is practicable to obtain medium effects directly from ab initio calculations. For example, the density coefficients for ^{129}Xe shielding, and their temperature dependence in xenon gas, or in the presence of other buffer gases, have been satisfactorily reproduced by a sequence of ab initio calculations [3]. First, the shielding was computed for an argon atom in the presence of another argon atom, at various internuclear separations, Then, the density coefficient for xenon was derived by scaling the intermolecular shielding function of argon to that of xenon followed by averaging over the intermolecular potential. Unfortunately, this detailed approach is specific to this type of problem.

There is a need to analyze medium effects on shielding in complex systems, such as proteins and nucleic acids, especially since large bodies of data have become available through the advent of multidimensional NMR spectroscopy [4,5]. In proteins, it is the folding of the polypeptide chain into its na-

tive conformation which causes the large range of chemical shift non-equivalence that permits multidimensional NMR studies to be carried out. These shift ranges, $\approx$10 ppm for ^{13}C [6], $\approx$20–30 ppm for ^{15}N [7], $\approx$15 ppm for ^{17}O [8], and $\approx$20 ppm for ^{19}F [9], may often contain significant contributions from medium effects, as well as intramolecular effects. These all involve weak interactions that are usually referred to as van der Waals attractions, hydrogen bonding, and so on, and the effects of the medium may be partitioned [10,11] similar to partitioning of weak interaction energetics. In the end, the understanding and modelling of these effects are distinct from that involving changes in chemical bonding.

Consistent with the notion that the electronic structure change due to weak interaction is largely electrical polarization of the charge distribution [12–14], a direct incorporation of the polarization effects on chemical shielding may be sufficiently accurate for incorporating medium effects in MD simulations. We have already used this notion of electrical polarization in accounting for the correlation of the ^{13}C chemical shift, ^{17}O chemical shift, and the C–O vibrational frequency in a series of carbonmonoxyheme proteins [15]. We have also used it in an analysis of conformational stabilities in proteins [16], as a basis for the range in shift nonequivalencies as they depend on atomic number [17] and on chemical environment [18], and for a generalized view of Sternheimer shielding in nuclear quadrupole coupling [19]. Other recent work [20] has shown good agreement between ^{19}F shieldings in fluorobenzene in a number of C_6H_5F–$(HF)_n$ clusters computed from full ab initio calculations or from a sum of pair (dimer) calculations. In this Letter, we take a critical look at the issue that underlies a polarization approach to the calculation of chemical shieldings: the convergence of the polarization expansion. We show that the effects are first order (i.e. involving first derivative terms), and that field, field gradient, and hypergradient (the gradient of the field gradient) are the primary sources of shielding polarization.

2. Theoretical approach

If we consider a molecule to be perturbed by an external electrostatic potential (e.g. the presence of a field, a field gradient, and so on), then it is appropriate to consider the general chemical shielding tensor to be a power series expansion in terms of the elements of the field, of the field gradient and so on. Buckingham introduced this expansion of the shielding [21,22], and we may refer to the first derivatives of the shielding as the shielding polarizabilities. This is analogous to the dipole polarizability being the first derivative of the dipole with respect to the strength of an external electric field. Second derivatives of the shielding are hyperpolarizabilities, and so on. Our interest in this Letter is to examine the convergence of this expansion.

The chemical shielding tensor for a magnetic nucleus in a molecule is formally a second derivative of the molecular energy. Thus, a shielding polarizability is found from an electronic structure calculation as a third derivative. Hyperpolarizabilities are fourth and higher-order derivatives. Shielding polarizabilities have been calculated by semi-empirical [23] and finite difference methods [24–27]. They have also been obtained by an analytical ab initio approach, derivative Hartree–Fock (DHF) theory [28]. Because DHF is open-ended with respect to the order of differentiation, it may also be employed for obtaining the shielding hyperpolarizabilities.

The first calculations were DHF evaluations of the multipole shielding polarizabilities of ^{19}F in fluorobenzene, which we use as representative of fluoro-aromatic amino acids in proteins. C_6H_5F is small enough to be tractable for ab initio calculations, and yet it is sizeable enough for significant polarization along the molecular backbone. The geometry of fluorobenzene was set to the experimentally derived values [29]. The basis set consisted of the Dunning triple zeta contraction [30] of the Huzinaga [31] atomic bases augmented by a single set of polarization functions (with exponents of 0.7 for the hydrogen p functions, 0.75 for carbon d functions, and 0.9 for fluorine d functions). The p functions on carbon and fluorine were contracted into four functions via a 3111 contraction. This flexibility in the p-valence set has been found to be important for calculating magnetic properties [32]. The calculations on fluorobenzene with this basis used 191 contracted functions.

The gauge origin of the external magnetic field was

chosen to be the fluorine nucleus. Tests of the sensitivity of the ^{19}F chemical shielding revealed that the isotropic shielding varied by only a few percent as the gauge origin was moved along the C–F bond axis over a range of 2 Å.

The next set of calculations was a type of ab initio calculation referred to as charge field perturbation [33] calculations. A one-electron operator is added to the molecular electronic Hamiltonian to correspond to the presence of an external ideal multipole. In this study, the multipole was a dipole (1 au = 2.54 D) or simply a point charge (−1 au). These ab initio calculations are the benchmarks to test convergence of the polarization expansion. The last step was to compute the field, field gradient, and so on from an external dipole or point charge, combine these values with associated shielding derivatives for a truncated expansion of the shielding, and compare the results with the benchmarks.

In a multipole polarization expansion, the properties which describe the response are necessarily referenced to a specific point in space, the multipole expansion center. If the expansion center is changed, certain of the property values are changed, and in this way, the expansion implies a point where an external electrostatic potential acts. The first non-zero electrical moment is a property that is invariant to the choice of the expansion center, and so are all related higher-order derivatives. For a neutral molecule, the dipole moment is invariant. The dipole is the first derivative of the energy with respect to the components of a uniform field, and higher-order derivatives with respect to the field are likewise invariant. Similarly, the derivative of the chemical shielding with respect to a field (and higher derivatives) is invariant to the choice of the multipole expansion center for a neutral molecule. However, the derivative with respect to a field gradient is not. Thus, there arises a practical consideration of what choice of expansion center leads to an accurate representation of the molecule's response to an electrical perturbation.

We have examined the effect of the choice of expansion center on the calculated ^{19}F chemical shielding of fluorobenzene for an external ideal dipole at various distances from the ^{19}F nucleus. The center was moved along an axis coincident with the C–F bond axis, from a position beyond the ^{19}F nucleus, across the benzene ring, and nearly to the opposite H nucleus. At each point, the multipole shielding polarization (MSP) expansion was used to find the change in the shielding due to the dipole. The expansion was truncated after including the first derivative with respect to the field, to the field gradient, and to the hypergradient, as well as the second derivative with respect to the field. The curves resulting from dividing these MSP values by corresponding ab initio values are given in fig. 1. When the dipole is far away, as shown by the curve where the dipole is 10 Å from the ^{19}F nucleus, the choice of origin over the range examined is unimportant. This is nearly so at a separation as close as 7 Å. However, at 3 and 5 Å, the choice of origin influences the results: As the expansion center gets closer to the dipole (e.g. within about 4 Å), then the expansion is less convergent. The practical result is that an origin at the center of mass leads to a convergent electrical representation for the dipole locations tested, and as well, there is the least sensitivity to small changes in

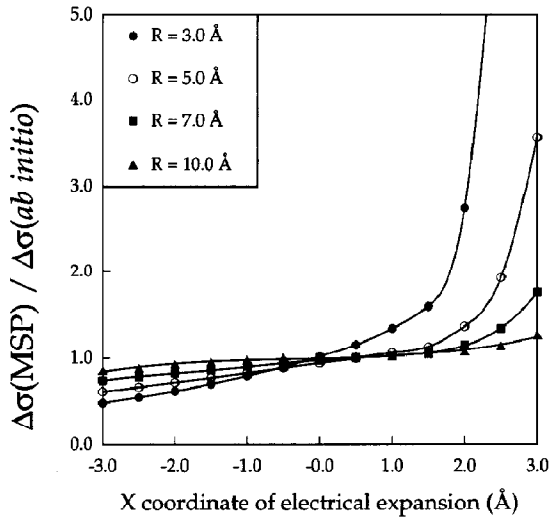

Fig. 1. The calculated change in the ^{19}F chemical shift from the multipole shielding polarization expansion (MSP) relative to ab initio results for fluorobenzene experiencing an ideal dipole. Lines are drawn for the dipole placed at a position of either 3.0, 5.0, 7.0, or 10.0 Å from the ^{19}F nucleus along the C–F axis (x coordinate) and as a function of the expansion center of the external electrical potential. For each line, the MSP values were divided by the corresponding ab initio value, which is not dependent on an expansion center's position. $x=0.0$ is the mass center of fluorobenzene, and the curves show that an expansion center in the vicinity of $x=0.0$ avoids the breakdown seen when the expansion center is very close to the perturbing dipole.

the location of the expansion center if it is in the vicinity of the mass center. On this basis we have chosen the perturbation of the fluorobenzene mass center as the multipole expansion center.

3. Results and discussion

Results of full ab initio calculations on the effect of an approaching dipole or point charge on the ^{19}F chemical shielding are given in table 1. In addition, the low-order contributions to the multipole shielding polarization expansion are presented. The first-order or linear effect of a uniform field is the most significant. Next is the effect of the field gradient, and still more diminished is the effect of the hypergradient (gradient of the gradient) of the field. This is illustrated by the curves in fig. 2. So, the linear expansion converges well over the distances considered, with the quadratic dependence of the shielding on field components turning out to be essentially zero. The same is true for the nonlinear terms of the gradient components, according to selected test calculations. The calculated linear shielding polarizabilities are listed in table 2.

The comparison of the MSP expansion truncated at the point of linear field, field gradient and hypergradient terms with the benchmark ab initio results shows good agreement, both for a dipole and a point-charge perturbation, although the error increases with decreasing separation as expected. For example, at a 3 Å separation, the error of the MSP approach for an approaching dipole is 1.3 ppm and the error for a point charge is 6.4 ppm. In both cases the error is within 20% of the net effect. An isolated point charge of -1 au at 3 Å is not a particularly plausible representation of a protein environment, but the agreement in this extreme case serves to validate the approach. On this basis, we conclude that a low-order MSP expansion provides an efficient and accurate means for evaluating the effects on shielding due to an electrical charge field. This is expected at long range, but it is significant that low-order truncation is accurate closer-in at distances of a few ang-

Table 1
^{19}F NMR isotropic chemical shielding of fluorobenzene in the presence of a unit dipole moment or point charge

R (Å) [a]	$\delta\sigma=\sigma-\sigma(C_6H_5F)$ contributions (ppm) [b]				Total $\delta\sigma$ (ppm) [c]	
	field	field gradient	field hyper-gradient	(field)^2	MSP	ab initio
1.0 au dipole						
3.00	3.965	2.522	2.321	−0.068	8.74	10.07
4.00	2.340	1.248	0.964	−0.024	4.53	4.95
5.00	1.494	0.687	0.456	−0.010	2.63	2.79
6.00	1.012	0.408	0.238	−0.004	1.65	1.72
8.00	0.526	0.171	0.080	−0.001	0.78	0.79
10.00	0.307	0.083	0.033	0.000	0.42	0.42
−1.0 au point charge						
3.00	−19.490	−8.266	−5.704	−1.645	−35.11	−41.49
4.00	−10.170	−3.115	−1.553	−0.448	−15.29	−12.89

[a] The distances, R, are from the F atom to the dipole or point charge and along the C–F bond. The field, field gradient, and hypergradient due to the dipole or point charge were calculated at the center of mass of fluorobenzene.

[b] $\delta\sigma$ is the incremental effect on the shielding due to the presence of the ideal dipole or point charge. Positive values correspond to high-field, low-frequency, diamagnetic or shielded values (σ scale). The contributions are from terms in the multipole shielding polarization (MSP) expansion that enter proportional to the field, or to the square of the field, or to the field gradient, and so on.

[c] The MSP total shielding is the sum of the contributions in the columns to the left, and should be compared with the values obtained from ab initio calculations.

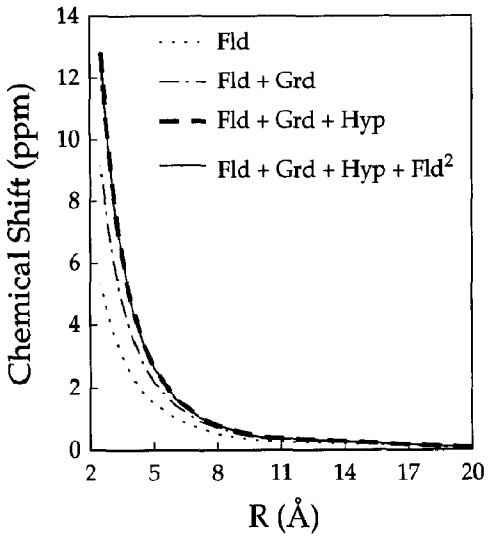

Fig. 2. Plot of the incremental chemical shielding due to the presence of an external ideal dipole (1.0 au) at a distance, R(Å), from the ^{19}F nucleus. The curves are drawn for different truncations in the multipole shielding polarization expansion. The most significant linear effect is that arising from the field of the dipole's electrostatic potential. The field gradient gives the next biggest contribution. The quadratic dependence on the field strength is negligible.

strom, the typical distances of weakly interacting species. Day and Buckingham [25] investigated the linear and quadratic effects of only the uniform field arising from a point charge approaching an HF molecule, and this led them to conclude that the non-uniform nature of the field was likely to be important.

The negligible role of shielding hyperpolarizabilities (i.e. the field-squared dependence) provides further enlightenment about the recent results of deDios and Oldfield [20]. They found through ab initio calculations that the effects of an interacting HF molecule placed along the C–F axis on the ^{19}F shielding in fluorobenzene were of similar magnitude but opposite sign, depending on the orientation of the HF molecule. This fits our conclusion that the shielding effect arises via the first derivatives in the MSP expansion, and also that the field term is the most significant [34]. Also, for multiple weakly interacting partner molecules, the field is a vector sum of the fields arising from each partner. With an MSP expansion, this sum is multiplied by the shielding polarizability to yield the incremental effect on shielding. That is, the sum is used linearly, and so, the effects of the partner molecules are additive.

Table 2
Calculated multipole shielding polarizability tensor elements for the ^{19}F nucleus in fluorobenzene with respect to a uniform field, field gradient, and field hypergradient

Tensor elements and values (ppm/au) [a]			
$P_{xx,x}$	1483	$P_{yy,x,x}$	−52907
$P_{yy,x}$	3577	$P_{yy,y,y}$	−3165
$P_{zz,x}$	593.6	$P_{yy,z,z}$	−6019
$P_{xx,xx}$	2224	$P_{zz,x,x}$	−16356
$P_{xx,yy}$	−716.6	$P_{zz,y,y}$	−6483
$P_{xx,zz}$	−488.4	$P_{zz,z,z}$	−2244
$P_{yy,xx}$	6175	$P_{xx,xxx}$	7259
$P_{yy,yy}$	−2717	$P_{xx,xyy}$	−141.9
$P_{yy,zz}$	−652.9	$P_{xx,xzz}$	422.5
$P_{zz,xx}$	1319	$P_{yy,xxx}$	17087
$P_{zz,yy}$	−796.6	$P_{yy,xyy}$	−1428
$P_{zz,zz}$	−283.8	$P_{yy,xzz}$	1449
$P_{xx,x,x}$	−23025	$P_{zz,xxx}$	3325
$P_{xx,y,y}$	1105	$P_{zz,xyy}$	−694.5
$P_{xx,z,z}$	−2917	$P_{zz,xzz}$	−21.1

[a] The tensor elements, P, are subscripted with the shielding tensor element (e.g., xx) followed after a comma by the field, field gradient, or field hypergradient element. Thus, $P_{yy,xyy}$ is the first derivative of the σ_{yy} tensor element with respect to a field hypergradient component in the xyy direction. The second derivatives with respect to field components have two commas to separate the shielding tensor element, the first field component and the second field component. The convention used is that a positive field vector points toward the carbon along the C–F bond. Only tensor elements that relate to the diagonal shielding tensor elements have been given because these are the only ones needed for evaluating an electrical effect on the isotropic shielding. We have used a traced (Cartesian) moment convention for the gradient and hypergradient shielding polarizabilities. The values are converted to traceless form by following the definition of traceless moments. Thus, $P^{\text{traceless}}_{xx,xx} = P_{xx,xx} - \frac{1}{3}(P_{xx,xx} + P_{xx,yy} + P_{xx,zz}) = 2033$ ppm/au.

Acknowledgement

This work was supported, in part, by a grant from the US National Institutes of Health (Grant No. HL-19481).

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