Solvent Effects on Fluorine Shielding in Fluorobenzene

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Abstract: Computer simulations of fluorobenzene dissolved in ten organic liquids and water have been used to explore the origins of solvent-induced changes in the fluorine chemical shielding parameter when this molecule is transferred from the gas phase to a solvent. Relying on recent theoretical calculations, it is demonstrated that short-range (van der Waals) interactions between the fluorine nucleus and solvent molecules are the predominant source of shielding parameter changes. Electric fields created by the solvent also have a detectable effect on shielding. The approaches used to estimate the van der Waals and electrostatic contributions inherently contain adjustable parameters and, if these are optimized, excellent agreement between calculated shielding effects and those found experimentally is obtained. The treatment used leads to reliable estimates of solvent-induced changes for solvents as diverse as water, hexane, and methylene iodide.

Introduction

The fluorine chemical shielding parameter for fluorobenzene is reduced 5−12 ppm when the molecule is transferred from the gas phase to a solution. Suntioinen and Laatikainen have summarized much of the theoretical and experimental work that has been aimed at understanding the origins of this effect.[1] A starting point for all studies has been the assumption (eq 1) that the shielding change δ_{obs} (= $\sigma_{\text{solvent}} - \sigma_{\text{gas}}$) can be considered to result from a collection of additive terms representing shielding changes arising from the bulk magnetic susceptibility of the solvent (δ_{b}), the magnetic anisotropy of the solvent molecules (δ_{a}), van der Waals interactions between solvent molecules and the dissolved fluorobenzene (δ_{vdW}), electric fields produced at the fluorine nucleus by the solvent (δ_{E}), and specific interactions with solvent molecules such as the formation of hydrogen bonds (δ_{H}).[2]

$$\delta_{\text{obs}} = \delta_{\text{b}} + \delta_{\text{a}} + \delta_{\text{vdW}} + \delta_{\text{E}} + \delta_{\text{H}} \qquad (1)$$

Corrections for bulk susceptibility are readily made,[3] and the magnetic anisotropy of the solvent molecules can at most contribute a few tenths of a ppm to the gas-to-solvent shifts observed.[4] Thus, the gas-to-solution fluorine shielding change in fluorobenzene is largely determined by the last three terms of eq 1.

Hydrogen-bonding effects on fluorine shielding in fluorobenzene have been considered from a molecular orbital perspective.[5] At the level of approximation used (INDO-3/SOS) an increase in the fluorine shielding parameter of 5−10 ppm was predicted but the sensitivity of the direction and magnitude of the predicted effects to the computational methods used in that work suggest that some caution in accepting this conclusion is advisable. Experimental studies of fluorine shielding in neutral fluorinated molecules in hydroxylic solvents imply that, if there is an effect of hydrogen bonding on fluorine shielding in these solvents, it is small.[1,6] The formation of hydrogen bonds to aromatic fluorine and their influence on fluorine shielding are subjects which could bear further theoretical and experimental investigation.

The shielding influences of van der Waals interactions (δ_{vdW}) and electric fields within the solution (δ_{E}) must be the principal determinants of the gas-to-solution shielding effect in non-hydroxylic solvents. The generally accepted conclusion[1,7] that the change of a fluorine shielding parameter upon transfer from the gas phase to solution is primarily the result of van der Waals interactions between solvent and solute has recently been brought into question by suggestions that the large range of fluorine shielding effects often observed in proteins containing fluorinated amino acids[8] is primarily the result of electric fields within proteins.[9,10] A protein structure is highly compact, and the polypeptide components and solvent that surround a particular fluorinated amino acid define a fluctuating chemical and electrical environment that presumably influences chemical shielding in the same ways that a collection of solvent molecules encompassing a small solute molecule influences shielding. The purpose of the present work was to examine more closely the relative importance of van der Waals interactions and electric fields in determining gas-to-solution fluorine shift effects and, thus, provide a basis for consideration of the relative contributions of these effects to fluorine shielding in proteins.

Methodology

When a molecule is transferred from the gas phase to solution a collection of electrical solute−solvent interactions develop that ultimately produce the shielding effects represented by δ_{vdW}, δ_{E}, and δ_{H}. These interactions continually change as a result of molecular motions and it will be their average effects that are observed experimentally. We have used molecular dynamics simulations of fluorobenzene dissolved in 11 different solvents to estimate the averaging of those quantities needed to apply

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theoretical treatments of the van der Waals and electric field shielding effects to these systems. The solvents were chosen to provide a range of polarities, dielectric constants, atomic polarizabilities, and hydrogen-bonding capabilities.

Dynamics Simulations. A sphere of solvent 1.9−2.0 nm in radius was constructed around a molecule of fluorobenzene using the modeling program QUANTA (Molecular Simulations, Inc., Burlington, MA). The solvation sphere typically contained about 250 molecules of solvent; the model corresponds to a molar concentration of fluorobenzene of approximately 0.05 M. The entire system was minimized with respect to potential energy by a combination of steepest descents and adopted basis Newton−Raphson methods using CHARMM (Versions 21.3 and 22.0, kindly supplied by Prof. Martin Karplus, Harvard University).[11] Parameters for the bond stretching, bond angle deformation, internal rotational barriers, and nonbonded (van der Waals) interaction terms in the empirical force field were those given in the QUANTA 3.0 parameter file. Electrostatic interactions between atoms in the system were taken into account through Coulomb's law by assigning partial point charges to each atom. The partial atomic charges for the solvent molecules were primarily taken from previous simulations done by others that led to results in agreement with experiment, as discussed in ref 12.[12] Charges for propane were obtained from the residue topology file (RTF) provided with CHARMM 22.0, while the charges for methylene iodide were calculated using the Gasteiger method[13] as implemented in QUANTA 3.3. The TIP3P model for water of Jorgensen *et al.* was used.[14] Charges for fluorobenzene were obtained from an *ab initio* calculation.[15] The charges for dimethyl sulfoxide were the same as those of Rao and Singh[16] except that an all-atom representation of the molecule was used, with a partial charge of 0.09 au placed on each hydrogen. (This charge for methyl hydrogen is consistent with the charge given in the RTF for this molecule in CHARMM 22.0.) The charges for methanol were those given in the RTF provided in QUANTA 4.0. A dielectric constant of 1 was used in all simulations. A switching function between 10 and 11 Å was used on all Lennard-Jones terms[11] and a shifting function was used with the Coulombic terms at 12 Å.[17,18]

Once energy minimizations were completed the systems were heated to 300 K over 5 ps and allowed to equilibrate at this temperature for 10 (halomethanes) or 30 ps (all other solvents). Production dynamics were usually performed for 100 ps using the Verlet algorithm with a time step of 1 fs.[12] The SHAKE procedure[19,20] was used to constrain bonds to hydrogen to their equilibrium lengths. A harmonic potential (250 kcal mol^{-1} $\mathrm{Å}^{-2}$) was placed on the carbon bonded to fluorine to prevent significant excursions of the fluorobenzene molecule from the center of the solvent sphere. A spherical boundary potential was applied to all solvent molecules to prevent "evaporation" from the surface of the solvent sphere.[21]

Coordinate sets were output from the dynamics simulations each picosecond and were used to compute the averaged interaction terms indicated below. Replicate dynamics runs made with different values for the random number generator "seed" (differently assigned starting velocities for atoms) generally produced results within 10% of the average.

van der Waals Shielding Contribution. Recent work from this laboratory has shown that the effects of solvents on the neon shielding parameter can be quantitatively accounted for in terms of van der Waals interactions between the rare gas atom and the atoms of the solvent molecules.[12] Because of the spherical symmetry of the solute neon atom, electric field effects on shielding are negligible in these systems. Molecular dynamics simulations were used in that work to average solvent−solute interaction geometries over about 100 ps. It was found, in consonance with previous theoretical results of Jameson and de Dios,[12,22] that the contributions of pairwise interactions between the solute atom and atoms of the solvent molecules to the van der Waals shielding term were reliably given by eq 2.

$$\delta_{\mathrm{vdW}} = \frac{-3}{2} B_1 \frac{U_{\mathrm{Ne}} U_{\mathrm{S}} \quad \alpha_{\mathrm{S}}}{(U_{\mathrm{Ne}} + U_{\mathrm{S}}) r^6_{\mathrm{Ne-S}}} \tag{2}$$

Here U_{Ne} and U_{S} are the first ionization potentials of the neon and solvent atom, respectively, α_{S} is the static polarizability of the solvent atom, $r_{\mathrm{Ne-S}}$ is the distance between the two atoms, and B_1 is a parameter which incorporates the polarizability of neon. A value for B_1 of 74 ppm $\mathrm{Å}^3$ eV^{-1} was determined by comparison to experimental results,[12] and is in good agreement with expectations of theory.[22,23] It was found in the previous work that when the interacting solvent atom is a hydrogen, the distance dependence in eq 2 is better given as $r^{6.5}_{\mathrm{Ne-H}}$.

Covalent fluorine has a local electronic structure ($1s^2 2s^2 2p^6$) that is identical to that of the neon atom. The polarizabilities of fluorine and neon are similar (0.38[24] *vs* 0.396[25] $\mathrm{Å}^3$), as are their first ionization potentials (18.2 *vs* 21.6 eV[26]). We started with the assumption that the van der Waals contribution to fluorine shielding of fluorobenzene in solution can be reasonably estimated within the framework of our previous molecular modeling procedures by application of an equation analogous to eq 2, with the value for B_1 the same as that found for neon.

Electric Field Shielding Contribution. Studies of the influences of an electric field on NMR shielding have long history.[27] In a homogenous electric field the change in the shielding tensor element $\Delta\sigma_{\mathrm{ab}}$ due to a field F is assumed to be expressible by a series expansion:

$$\Delta\sigma_{\mathrm{ab}} = \sigma'_{\mathrm{ab},\gamma} F_\gamma + \sigma''_{\mathrm{ab},\gamma,\delta} F_\gamma F_\delta + ... \tag{3}$$

where the repeated subscripts imply summation over the Cartesian coordinates *x*, *y*, and *z*. The first term describes the effect of a linear electric field with components $F\gamma$ where $\sigma'_{\mathrm{ab},\gamma}$ is the dipole shielding polarizability tensor, while the next term includes the dipolar shielding hyperpolarizability tensor $\sigma''_{\mathrm{ab},\gamma,\delta}$.[28,29] With fluorobenzene it appears that the first term in this series

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is the dominant one.[30] In fluorobenzene−solvent systems the field experienced by the fluorine nucleus arises from the charges or dipoles of the surrounding solvent molecules and will be highly inhomogeneous. As discussed by Buckingham and Lawley[31] and, more recently, by Augspurger *et al.*[32] and Pearson *et al.*,[10] the field F_γ can be expanded, affording

$$\Delta\sigma_{\mathrm{ab}} = \sigma'_{\mathrm{ab},\gamma}F_\gamma + \sigma'_{\mathrm{ab},\gamma\delta}F_{\gamma\delta} + \sigma'_{\mathrm{ab},\gamma\delta\epsilon}F_{\gamma\delta\epsilon} + ... \qquad (4)$$

if only the first term of eq 3 is retained. The second term in eq 4 depends on the field gradient tensor $F_{\gamma\delta}$.

There has been significant progress in the use of theoretical methods to compute the elements of the chemical shielding tensor σ_{ab} and components of the various tensors shown in eqs 3 and 4.[33,34] The fluorine shielding tensor of fluorobenzene computed by derivative Hartree−Fock methods is in good agreement with experiment.[32] Also, the convergence behavior of the expansions shown has been examined and it has been confirmed that only the linear term in eq 3 is important.[30] The first three terms of eq 4 account for at least 85% of field effects on fluorine shielding when the distance between a dipole or point charge and the center of the carbon−fluorine bond in fluorobenzene is greater than 0.3 nm.[35]

The theoretical efforts described above provide a starting point for the application of eq 4 to quantitative estimation of the electric field contribution to the gas-to-solvent chemical shift effects of fluorobenzene. Molecular motions will average over time the electric field and field gradients experienced by the fluorine. Assuming that the fluorobenzene moves isotropically relative to the magnetic field, the change produced in the observed (isotropic) shielding parameter $\Delta\sigma \equiv \delta_{\mathrm{E}}$ produced by the time-varying electric field will be given by

$$\delta_{\mathrm{E}} = \bar{A}_x\langle V_x\rangle + \bar{A}_{xx}\langle V_{xx}\rangle + \bar{A}_{yy}\langle V_{yy}\rangle + \bar{A}_{zz}\langle V_{zz}\rangle + ... \qquad (5)$$

where the broken brackets indicate the average of an electric field component (V_{n}) and field gradient components (V_{nm}). The coefficients $\bar{\mathrm{A}}$ given by Pearson *et al.* for fluorobenzene (for an expansion centered on the fluorine nucleus) were used to estimate the electric field effect on fluorine shielding in our fluorobenzene−solvent models.[10,35]

Application of eq 5 requires an explicit means of representing the electric field. Despite the clear importance of electrostatics in solvent−solute interactions there appears to be no computationally rapid way to include with rigor electrostatic contributions to the potential energy of a large collection of atoms such as our model for dissolved fluorobenzene.[36] Electrostatics, of course, play a significant part in defining the forces on atoms that are important in molecular dynamics as well as producing a shift effect.[36] We have taken the simplest and most common approach[37] to estimating the electric field terms needed for eq 5, namely we have assumed that the electric field at fluorine is due to the partial charges of the surrounding solvent atoms and can be written

$$\vec{F} = \frac{C}{\epsilon}\sum_j\left(\frac{q_j}{r^2_j}\right)\frac{\vec{\mathbf{r}}}{r_j} \qquad (6)$$

where ϵ is the dielectric constant, q_j is a point charge centered on atom j, $\vec{\mathbf{r}}$ is the vector of length r_j from the fluorine nucleus to solvent atom j, and C is a constant that depends on the units for the other quantities in the equation.[38] Field gradients were calculated from derivatives of eq 6.

The atom charges used for application of eq 6 in the present work were those present in the force fields used in the molecular dynamics simulations and the dielectric constant was initially set equal to 1. However, we note that adjustment of the dielectric constant or making the dielectric constant some function of r has been used to compensate for electric polarization and screening effects in molecular dynamics simulations.[38,39]

The collection of molecules within the solvent sphere of our model will polarize the surrounding bulk medium to produce a reaction field $\vec{R}$ which will also be experienced by the fluorine. This field was calculated by the standard formulation[37,40]

$$\vec{R} = \frac{8\pi(\epsilon - 1)}{3V(2\epsilon + 1)}\sum_j q_j\vec{\mathbf{r}}_j \qquad (7)$$

where V is the volume of the simulation sphere, ϵ is the bulk dielectric constant, and the summation represents the collective dipole moment of the atoms within the sphere. In all cases examined here the contribution of the reaction field to the total electric field experienced by the fluorine atom was minor.

Results

Structure and Dynamics of the Fluorobenzene−Solvent Models. To have any hope that the calculations carried out for this work will provide reliable indications of the origins of medium-induced changes in the fluorine shielding parameter of fluorobenzene it is necessary that the computational models give reasonable predictions of the properties of dissolved fluorobenzene. In particular, local arrangements of solvent atoms around the fluorine nucleus peculiar to a specific solvent and the time-dependence of solvent atom−fluorine interactions must be correctly represented.

We calculated radial distribution functions (RDFs) to provide a quantitative indication of the bulk structure of the solvent molecules in our models. The RDF $g_{ij}(R)$ has the form

$$g_{ij}(R) = \frac{\langle N_{ij}\rangle}{4\pi\langle\varrho_{ij}\rangle R^2\,\mathrm{d}R} \qquad (8)$$

where $\langle N_{ij}\rangle$ is the number of atoms of type j at a distance between R and $R + \mathrm{d}R$ from atom i, and $\langle\rho_{ij}\rangle$ is the density of the solution. The distances at the first maximum and first minimum in the RDFs computed for each fluorobenzene−solvent simulation are given in Table 1 and compared there to experimental determinations or the results of other computer simulations. In general, we find that the RDFs are in good agreement with previous simulations by others and with experimental data for the pure solvents. The RDFs are also

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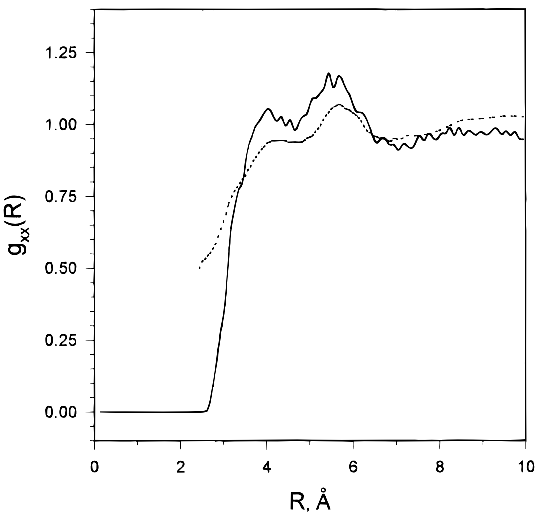

Figure 1. Heavy atom−heavy atom radial distribution function computed from a simulation of fluorobenzene in dimethyl sulfoxide (this work, solid line) compared to the experimental RDF obtained for neat dimethyl sulfoxide by neutron diffraction as reported in ref 41.

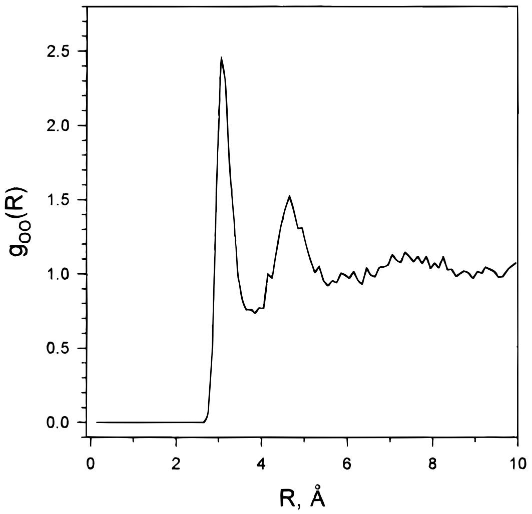

Figure 2. O−O RDF for methanol in our fluorobenzene−methanol simulation.

very similar to those obtained previously in simulations of neon dissolved in many of these solvents;[12] the discussion of the agreement between experiment and simulations for those systems in ref 12 is appropriate for the fluorobenzene systems reported here.

Various heavy atom RDFs for fluorobenzene in dimethyl sulfoxide obtained from our simulations generally compare well to simulations of the neat liquid.[41] Only a single composite RDF for the heavy atoms has been obtained experimentally for neat dimethyl sulfoxide. The calculated heavy atom−heavy atom RDF for fluorobenzene−dimethyl sulfoxide, prepared using the weighting factors given by Lazar, Soper, and Chandler,[41] is in reasonably good agreement with the corresponding experimental RDF for the neat liquid (Figure 1).

Figure 2 shows the oxygen−oxygen RDF calculated for fluorobenzene in methanol in the present work. It is in agreement as regards magnitude with that obtained from a simulation of pure methanol by Jorgensen.[42] There is a disagreement with regard to the position of the first maximum in this function. However, first maxima for the $g_{CO}(r)$ and $g_{CC}(r)$ RDFs for fluorobenzene−methanol were in better agreement with the results of Jorgensen. We have been unable to find experimental RDFs which can be compared to either of these simulations.

The temporal properties of the molecules in the fluorobenzene−solvent simulations were examined by computing the correlation time (τ_c) for rotational reorientation. Integration of the autocorrelation function $C_2(t)$ defines τ_c:

$$\tau_c = \int_0^\infty C_2(t)\,dt = \int_0^\infty \langle P_2[\vec{\mu}(0)\cdot\vec{\mu}(t)]\rangle\,dt \qquad (9)$$

where $\vec{\mu}$ is the vector along a chemical bond of interest and P_2 is the second-order Legendre polynomial. Correlation times were calculated from the dynamics trajectories as detailed by Steinhauser and Neumann.[43] Correlation times for solvent molecules in the simulations carried out are shown in Table 1 and compared there to experimental data or the results of other simulations. For most systems the values for τ_c do not differ significantly from the results obtained earlier in the neon simulations, although there is a tendency for solvents with heavier atoms such as Cl or I to have longer correlation times in the fluorobenzene system than in the corresponding neon system. A major discrepancy is carbon tetrachloride where τ_c for the C−Cl bond is more than twice the value found either in the neon−CCl_4 simulations or by experiment with the neat liquid. The reasons for this disagreement are not clear.

The solvents methanol and dimethyl sulfoxide were not part of the neon study done previously. For methanol the computed correlation time for the O−H bond (1.2 ps) is significantly shorter than the experimental value (3.7 ps) obtained by oxygen-17 NMR spectroscopy.[44] The correlation time for the S−O bond in dimethyl sulfoxide is computed to be 3.3 ps in the fluorobenzene mixture. A recent simulation of the pure liquid gave a value of 3.9 ps[45] while the experimental value obtained by sulfur-33 NMR is 5.2 ps.[46] Both methanol and dimethyl sulfoxide either are appreciably associated or have an unusually high viscosity at ambient temperatures. It is unknown at this time what the effects of dissolved fluorobenzene will be on these properties or that the simulations done can reliably reproduce these effects.

Overall, we believe that the radial distribution functions and correlation times obtained from our fluorobenzene−solvent simulations indicate that the structural and temporal properties of these theoretical systems correspond moderately well to those of the actual systems. The simulations thus should provide a reasonable means for estimating the averaging of intermolecular interactions that lead to the gas-to-solvent fluorine shielding effect.

van der Waals Contribution. Table 2 gives the computed van der Waals contribution to fluorine shielding in the solvents considered, reckoned using eq 2 and the value for B_1 found in the previous studies of neon gas-to-solvent shifts (74 ppm $Å^3$ eV^{-1}). As shown in the table, these estimated contributions to solvent shielding are close to the experimental gas-to-solvent fluorine shifts in fluorobenzene.

Electric Field Contribution. Equation 5 and the mean field and field gradients computed from the models were used to estimate the effect of electric fields generated by the solvent molecules and the reaction field. Table 2 gives the electrostatic

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Table 1. Properties of Simulations of Fluorobenzene-Solvent Systems

	RDF, Å		correlation time (τ_c), ps	
solvent	calc max, min	exp max, min[a]	calc	exp[a]
CH_3OH	C−O: 3.85, 5.75	3.6, 4.1[42] (simulation)	O−H: 1.2	3.7[44]
	O−O:3.05, 3.85			
CH_3CN	C_N−C_N: 4.65, 6.65	4.7[63] (simulation)	C−N: 1.4	1.2[44]
$(CH_3)_2CO$	O−O: 5.25, 7.15	∼5.4,[b] ∼7.0[64] (simulation)	C−O: 1.6	1.1[44]
CH_2Cl_2	Cl−Cl: 3.95, 4.96	3.6, 4.5[67] (simulation)	C−Cl, 1.2	1.2[66]
			C−H, 0.78	0.7[68]
	C−Cl: 3.95, 4.65			
H_2O	O−H: 1.85, 2.35	1.85, 2.35[69] (exp)	O−H, 1.3	2.0[70]
	O−O: 2.75, 4.55			
$CH_3CH_2CH_3$	C−C: 4.15, 4.45	4.4, 4.8[71] (exp)	C−H, 0.5	0.95−1.3[72]
$CHCl_3$	Cl−Cl: 3.75, 4.75	3.8, 4.4[73]	C−Cl, 2.3	2.0[66]
			C−H, 2.1	1.6[68]
$(CH_3)_2SO$	C−C: 4.05, 4.75	(see text)	O−S, 3.3	5.2[46]
	C−O: 3.25, 4.65			
	O−O: 5.15, 7.45			
	O−S: 4.65, 5.55			
CH_3I	I−I: 4.25, 4.95	4.42, 6.52[74]	C−H, 0.5	1.4[75]
CCl_4	Cl−Cl: 3.75, 4.95	3.8, 4.8[76]	C−Cl, 3.8	1.7[66]
CH_2I_2	I−I: 4.15, 5.15	4.2, 5.6[77]	C−H, 5.0	3.3[78]

[a] Experimental data are for pure solvents. [b] A maximum of ∼3.1 is observed experimentally.[65]

Table 2. Gas-to-Solvent Fluorine Chemical Shifts for Fluorobenzene

solvent	van der Waals shift, ppm (eq 2)	electric field shift, ppm (eq 4)	total shift, ppm (adjusted)[a]	experimental shift, ppm[b]
CH_3OH	−5.75	7.20	−4.54	−4.67
CH_3CN	−5.80	5.58	−4.96	−5.28
$(CH_3)_2CO$	−5.97	4.82	−5.31	−5.33
CH_2Cl_2	−6.27	3.82	−5.86	−6.29
H_2O	−7.94	8.19	−6.66	−6.58
$CH_3(CH_2)_4CH_3$	−5.36	0.	−5.75	−6.96[c]
$CHCl_3$	−7.77	5.49	−7.09	−7.13
$(CH_3)_2SO$	−8.51	5.44	−7.90	−7.28
CH_3I	−8.35	3.28	−8.22	−8.16
CCl_4	−8.09	0.	−8.68	−8.38
CH_2I_2	−11.25	1.53	−11.72	−11.42

[a] Gas-to-solvent shift computed using eq 10 and the weighting coefficients described in the text. [b] A negative number corresponds to a downfield shift relative to the fluorine signal from fluorobenzene vapor. [c] Experimental value was for hexane while the simulations were done with propane.

contribution to shielding estimated in this way. Those solvents which are highly nonpolar (propane, carbon tetrachloride) exhibit a negligible electrostatic contribution to fluorine shielding, while electric fields in the more polar solvents, in particular water, are predicted to have a large, upfield effect on the fluorine shielding parameter. Solvents containing large, polarizable atoms such as methylene iodide have relatively small partial charges on these atoms and are thus predicted to have only a small shielding contribution from the electric fields produced by the solvent. However, these solvents produce some of the largest gas-to-solvent shifts observed.

Refinement. The expressions used to estimate both the van der Waals contribution to shielding and the effect of electric fields have adjustable parameters. In the case of eq 2 the value of B_1 used was based on the notion that the response of the electronic structure of neon to interactions with solvent molecules should be reasonably similar to the response of covalent fluorine. However, this is an approximation and, while the form of eq 2 should be valid for considering fluorine interactions with solvent atoms,[47] there may be a more appropriate value for B_1 than the one chosen. A better treatment of electrostatic interactions in our model systems would consider the polarizabilities of the atoms and recognize that the charge distribution in a molecule is more diffuse than would be implied by a collection of point charges. Molecular dynamics force fields usually do not explicitly include polarization effects. Rather these effects are taken into account by using exaggerated point charges for the atoms[48] and, therefore, electric fields calculated by means of eq 6 would be overestimated. Correction for polarization effects could be made (roughly) by increasing the dielectric constant ϵ in eq 6.[39] (The reaction field effects are small and adjustment of ϵ in eq 7 would not make a significant difference.) Alternatively, atom polarizabilities could be included explicitly and the atomic charges appropriately reduced.[49]

As a means of refining the estimates of δ_{vdW} and δ_{E} we sought values for the weighting coefficients P_{vdW} and P_{E} in the linear combination of shielding contributions indicated in eq 10.

$$\delta_{\mathrm{calc}} = P_{\mathrm{vdW}}\delta_{\mathrm{vdW}} + P_{\mathrm{E}}\delta_{\mathrm{E}} \qquad (10)$$

The van der Waals and electric field shielding contributions, δ_{vdW} and δ_{E}, respectively, are those calculated as described above. Adjustment of P_{vdW} and P_{E} by the least-squares criterion to optimize the agreement between δ_{calc} and the experimental gas-to-solution shifts led to values of 1.07 and 0.226, respectively, for these weighting coefficients. Using calculated van der Waals and electrostatic contributions weighted in this way produced calculated shielding effects in good agreement with experiment, as shown in Figure 3, with a mean deviation between the observed and calculated shifts of 0.29 ppm. The deviations are insignificant in light of the errors in the experimental determination of the solvent shift, the variations in calculated shifts in replicate dynamics simulations, and the neglected contributions of solvent magnetic anisotropies.

The coefficient P_{vdW} found by this analysis implies that B_1 for fluorine in fluorobenzene is 79 ppm $Å^3$ eV^{-1}. The suggestion that B_1 is well-approximated by the value found for neon is thus strongly supported. The electrostatic contribution to shielding in each solvent, while not negligible, appears to be over-estimated by eq 5. Use of eq 5 with an effective dielectric constant of about 4.4 ($=1/P_{\mathrm{E}}$) would produce results of the correct magnitude.

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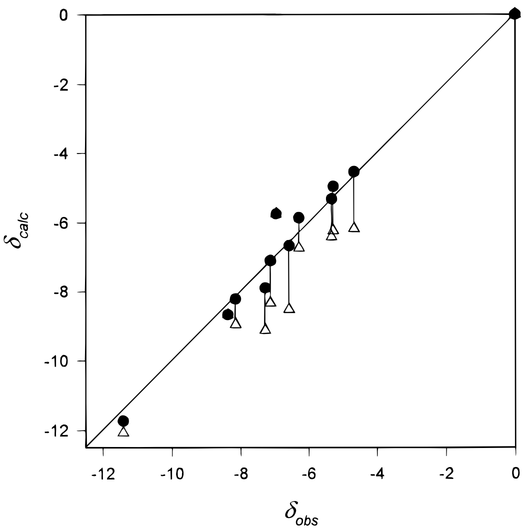

Figure 3. Comparison of observed and calculated gas-to-solution fluorine chemical shift effects for fluorobenzene in 11 solvents. The solid symbols are the shifts calculated using eq 10 with optimum values for P_{vdW} and P_E as described in the text. For each solvent, the open symbol indicates the value of the van der Waals contribution; the distance from an open symbol to the corresponding solid symbol indicates the contribution of the electrostatic term. The 45° line drawn corresponds to a perfect correlation of experimental and calculated shifts. The point (0, 0) corresponds to the gas phase shift.

Discussion

There have been many attempts to correlate fluorine gas-to-solvent shift effects with bulk properties of the solvent such as dielectric constant or molar polarizability. Commonly such attempts produce separate correlations for each group of chemically similar solvents. Our approach is noteworthy not only for the good predictions of shielding effects that it leads to, but also for the wide range of chemical types, dielectric constants, and polarizabilities that are represented by the solvent systems studied.

The treatment is least successful with *n*-hexane, although leaving the hexane data out does not significantly change the values of P_{vdW} and P_E or the conclusions drawn from them. Hexane was investigated because of a desire to include a solvent that is nonpolar and aliphatic. An all-atom dynamics simulation of liquid hexane has not been described in the literature. Because of the number of internal degrees of freedom for the hexane molecule, producing and validating a simulation of either the pure solvent or fluorobenzene dissolved in hexane appeared to be a significant project in itself and was one that we preferred not to undertake at this time. Propane can be considered half of the hexane molecule and the number and type of intermolecular interactions present between propane molecules and between propane and the solute should be similar to those present in the fluorobenzene−hexane system. The molecular dynamics simulations were therefore done with propane as the solvent molecule. (It is not possible to obtain the gas-to-solution shift for fluorobenzene in propane at the same temperature and pressure that were used for the other solvent systems considered.) Interestingly, the gas-to-solvent shift for ^{129}Xe in aliphatic hydrocarbons, where the shielding effect is completely due to van der Waals interactions, is quite sensitive to the structure of the solvent molecule.[50] Thus, our assumption that propane is a good model for hexane may be too crude.

The apparent overestimation of the electrostatic shielding contribution by eq 5 is of concern. The empirical force field used for the molecular dynamics simulations considers electrostatic effects through Coulombic two-body potentials. The parameter set for the force field includes point charges for each atom in the system. Selection of values for these point charges can be done in several ways but their values must be such that calculations using the force field produce good agreement with experimental properties. This method for inclusion of electrostatic effects is only approximate and the empirical parameters equated to atomic point charges so-developed may not reliably indicate the actual electronic distribution. For example, inclusion of electron polarizability explicitly in the treatment of electrostatic interactions leads to a reduction of the values for point charges.[48] Thus, the average electric field and derivatives needed for eq 6 computed using the point charges of the force field may be overestimated because the point charges used are too large for this purpose.

The first theoretical treatment of the electric field contribution to shielding was by Buckingham.[28] His work suggested that the first term in eq 6 should be the dominant term, at least for the shielding of the hydrogen nucleus. There have been many attempts subsequently to provide an experimental value for the coefficient $\bar{A}_x$ for fluorine by examination of shifts in conformationally rigid fluorinated molecules. For systems in which the fluorine is attached to an sp^2 carbon atom (usually in an aromatic ring) these efforts have produced values for $\bar{A}_x$ in the range 142 to 583 ppm/au field with most near 550 ppm/au field.[51−54] A semiempirical calculation of $\bar{A}_x$ at the INDO level suggested a value of 790 ppm/au field.[55] The value from the theoretical work of Augspurger *et al.*[10,32] mentioned earlier (the one used in the calculations of δ_E in our work) is 1885 ppm/au field. A reduction in the value of $\bar{A}_x$ to 428 ppm/au field (=1885 P_E), along with corresponding reductions in the values of other coefficients in eq 10, while retaining a dielectric constant of 1, would give calculated values of δ_E in agreement with the magnitudes of δ_E suggested by our analysis of the gas-to-solvent chemical shifts for fluorobenzene. This reduced value of $\bar{A}_x$ is more in line with previous experimental estimates.

It is rather firmly established that fluorine shifts in aryl fluorides depend on the detailed structure of the π-electronic manifold of these systems.[56] Our methods for estimating the van der Waals and electric field contributions to fluorine shielding in fluorobenzene do not take into consideration possible influences of the intermolecular interactions on the π-electronic structure of the fluorobenzene. Collisions of solvent molecules with the aromatic ring must have a significant if transient effect on these electrons. Further, given the relatively high polarizability of π-electrons, it could be anticipated that electric fields produced by more distant solvent molecules could also produce a shielding effect. We are unaware of theoretical or experimental studies that address the magnitude or direction of these possible mechanisms for altering the fluorine shielding parameter in solution, but if they are significantly deshielding, then the large value for $\bar{A}_x$ indicated by the calculations of Augspurger *et al.* could well be correct.

There are no indications from the present study that the presence of hydrogen bond donors in the medium has any

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unusual effect on shielding. As shown in Table 2, the gas-to-solvent shifts for both water and methanol are well-accounted for by the van der Waals and electric field contributions we consider. We detected no particular tendency in the molecular dynamics simulations for the formation of configurations that would suggest hydrogen bond formation to fluorine. Any special shielding effect that would have to be assigned to the formation of such hydrogen bonds (δ_H) appears to be less than 0.1 ppm. This conclusion is consonant with the results of Muller which indicated the lack of any sizable contribution to fluorine shielding in solutions of 1,1,1,10,10,10-hexafluorodecane in various solvent alcohols.[6]

A number of improvements could be made to the procedures we used in this computational approach to examination of fluorine shielding effects in solvents. Equation 2 for prediction of the van der Waals contribution could incorporate more completely the shape of the shielding parameter−internuclear distance function[22] and recognize that the atomic polarizability and, probably, the ionization potential of aromatic fluorine are anisotropic.[57] The most appropriate ways to include electrostatic effects in simulations of molecular dynamics of polar systems is an area of active research.[17,36,58−61] If the reduction in the calculated electrostatic term that we find necessary is accepted, our procedures for estimating fluorine gas-to-solvent shifts appear to give adequate results and incorporation of additional considerations such as those mentioned would appear to offer little prospect for enhancement of accuracy of the predictions. However, such extensions of these procedures may be of benefit in studies of macromolecular systems such as proteins.

Experimental Section

Fluorobenzene (Aldrich) and the various organic solvents used were the best grade obtainable commercially and were used without further purification. The vapor phase sample of fluorobenzene was prepared by placing a single drop of the compound in a 10-mm NMR tube which was then evacuated and sealed. The solution samples were 0.04−0.05 M in fluorobenzene, except for water where the concentration of solute was that at saturation. Fluorine spectra were recorded at 470 MHz using a General Electric GN500 instrument running unlocked, with the Larmor frequency of the fluorine signal in each sample being recorded to an accuracy of 1 Hz. The sample temperature was 20 °C. The gas-to-solution shifts reported are corrected for volume magnetic susceptibility, assumed to be the susceptibility of the pure solvent, using the equation

$$\delta_{\mathrm{obs}} = \left(\frac{\nu_{\mathrm{solvent}} - \nu_{\mathrm{gas}}}{\nu_{\mathrm{gas}}}\right) + \frac{4\pi}{3}\chi_{\mathrm{v}} \qquad (11)$$

where ν_{gas} and ν_{solvent} are the observed resonance frequencies for the corresponding samples, and χ_{v} is the volume magnetic susceptibility.[3] The susceptibilities (generally at 20 °C) were taken from the compilation given by Emsley, Feeney, and Sutcliffe,[27] except for dimethyl sulfoxide, for which the value of Abraham and Wileman was used.[62−78] The magnitude of the susceptibility corrections ranged from 1.9 to 4.8 ppm. Considering possible errors in volume susceptibilities and the determination of the fluorine resonance condition in our experiments it is believed that the gas-to-solvent shifts are accurate to at least 0.1 ppm. Where comparisons are possible our results agree well with previous determinations.[1]

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