Ab Initio and Density Functional Calculations of ^{19}F NMR Chemical Shifts for Models of Carbonic Anhydrase Inhibitors

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Ab initio (HF) and density functional theory (DFT) calculations of ^{19}F NMR chemical shifts were performed for models of fluoroaromatic inhibitors of carbonic anhydrase II (CA). DFT gave slightly better agreement with the experimentally measured chemical shifts of the actual inhibitors, suggesting that *intramolecular* dispersion does contribute significantly to the chemical shifts in these molecules. HF and DFT calculations for the stacked complex of hexafluorobenzene with benzene gave excellent agreement with experimental ^{19}F chemical shifts in this system. The fact that both approaches to this calculation were successful suggests that *intermolecular* dispersion is not an important contributor to ^{19}F chemical shifts in this system. Electron transfer and electrostatics must, therefore, be responsible for the changes in the ^{19}F NMR spectra observed on complexation. Finally, an unsuccessful attempt was made to apply HF and DFT methods to the calculation of the ^{19}F chemical shift of a pentafluorobenzyl-derived CA inhibitor bound to the protein in close proximity to a phenylalanine residue. A model of the inhibitor's aromatic ring interacting with the protein's aromatic residue gave a calculated chemical shift change that was much greater than that observed experimentally. Effects on the chemical shift from the field due to atoms omitted from the calculation, as well as from extensive rovibrational freedom, cannot easily be addressed in calculations of these large systems and are the likely reasons for the failure of these calculations.

Introduction

Ab initio and density functional calculations have become an increasingly common method of accurately predicting chemical shifts for a number of magnetic nuclei. These calculations augment the utility of NMR spectroscopy by providing magnetic shielding data for highly unstable species,[1] aiding in the interpretation of experimental spectra, and probing the dependence of chemical shifts on the orientation of flexible groups.[2−10] Although computational approaches have proved very successful for a wide variety of systems, relatively little is known about the efficacy of these methods in determining the chemical shifts of aromatic fluorines. To our knowledge, the early work of de Dios and Oldfield,[11] using self-consistent field methods, the calculations of Alkorta and Elguoro on hexafluorobenzene,[12] and the study of 1,2-disubstituted benzenes presented by Smith[13] are currently the only works available on this topic.

Although ab initio calculations of NMR parameters have been successfully applied for less than a decade, the general expression for nuclear magnetic shielding was developed in the early 1950s by Ramsey in terms of perturbation theory.[14] Recent advances in computer technology and the development of special methods for the calculation of NMR properties have greatly enhanced the accuracy and speed of such calculations. The GIAO (gauge-including atomic orbital) method[15] first applied by Ditchfield,[16] as well as the IGLO (individual gauge for localized orbitals)[8] and LORG (local orbitals−local origins) algorithms,[17] have all yielded satisfactory results. The GIAO method used in this study has been particularly successful in yielding reliable data with smaller basis sets.[18]

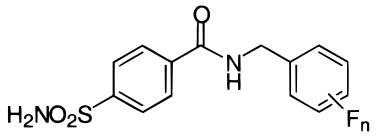

Figure 1. General structure of fluorinated inhibitors of carbonic anhydrase II.

Prior studies suggested that accurate magnetic shielding calculations require fairly large basis sets.[18,19] Furthermore, some consideration of electron correlation may be beneficial, particularly for aromatic systems and atoms possessing lone pairs.[20] To meet these conditions while keeping the calculations tractable, we employed density functional theory (DFT). DFT is an approximate post-SCF method of treating electron correlation, which has yielded results comparable to second-order Moller−Plesset theory (MP2) for many applications, at substantially reduced computational cost.[3]

In this paper, we present results from calculations of magnetic shieldings of fluorines in a small library of fluoroaromatic inhibitors of carbonic anhydrase II (CA)[21] (Figure 1) and in models of these inhibitors interacting with aromatic species. Through a comparison of these calculations, we hope to understand the effects that are responsible for ^{19}F chemical shift in fluoroaromatics and to assess the efficacy of several computational approaches.

The inhibitors that we have studied were developed on the basis of the known affinity of aromatic sulfonamides for CA.[22] The addition of fluorobenzyl groups to the primary binding site

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of these inhibitors leads to tighter binding for two reasons: (1) the increase in hydrophobicity of the inhibitors and (2) a specific interaction between this ring and Phe 131 of CA.[23] Weak, noncovalent forces due to hydrophobicity, electrostatics, dispersion, and specific F−H contacts all appear to play a role in this secondary interaction. The details of such interactions are still not fully understood and remain controversial.[23−26] The effects of these forces on ^{19}F chemical shift are also not known. It was our hope that, by elucidating the interactions that are responsible for changes in chemical shifts on complexation, we might be able to infer the forces that are responsible for enhanced binding. We modeled our inhibitors using fluorotoluenes as surrogates for the complete inhibitor structures. This model is reasonable given that much of the error in shielding calculations is systematic in nature,[27] suggesting that errors resulting from our approximation of the inhibitors can be corrected by linear scaling.

The magnetic shielding parameters of a molecule can serve as sensitive probes of intermolecular interactions and solvent effects. Unfortunately, little is known about the reliability of shielding calculations that include intermolecular effects. Much of the work on intermolecular forces has been limited to the SCF level,[28] which we believed would be inappropriate for our system for several reasons, specifically, aromatics groups and lone pairs are present and dispersion forces may be involved in the interactions. In this context, we also attempted supermolecular DFT calculations of the chemical shifts of a number of fluoroaromatic−aromatic systems in the hope of learning more about the effect of weak, noncovalent interactions on chemical shift.

Chemical shifts were calculated for a stacked benzene−hexafluorobenzene (HFB) complex at a number of intermolecular distances and were then correlated with solution-state experimental data. This comparison permitted an estimation of the equilibrium distance, which was then compared to the actual crystal structure. ^{19}F shifts were also calculated for a conformation found in the crystal structure of the bound pentafluorobenzylamide-linked CA inhibitor[29] and were compared to experimental, solution-state measurements. Furthermore, we attempted to apply counterpoise corrections (CP) as well as charge field approximations to these intermolecular calculations in order to assess the applicability of these methods.

Methods

Free Fluorotoluenes. Fluorotoluene structures were optimized at the DFT level using the Becke-style hybrid functionals, which take advantage of the gradient-corrected correlation functional of Lee, Yang, and Parr.[30] B3LYP calculations of this type have yielded slightly better correlation than other hybrid functionals, such as B3P86 and B3PW91.[23] Optimizations were performed using the 6-311G(d) basis set. In past studies, the use of larger basis sets for molecular geometry optimizations has had almost no effect on the accuracy of predicted magnetic properties.[3,18] To simplify the calculations, the aromatic rings were forced to be precisely planar, and any symmetry (as in the case of the 2,6- or 4-substituted molecules) was maintained. The methyl group was also restricted to one common C−H bond length and to dihedral angles that maintained a mirror plane through the group and perpendicular to the ring, as symmetrical fluorine atoms were observed to have equivalent solution-state shifts.

After the geometries were optimized, magnetic shieldings were calculated for these structures using the GIAO algorithm at the B3LYP/6-311++G(d,p) level, as recommended by Rablen.[18] This larger basis set includes a set of d-type orbitals on the heavy atoms and a set of p-type orbitals on the hydrogens, as well as diffuse functions on all atoms. For comparison, the same calculations were performed using the Hartree−Fock level of theory. Chemical shifts were determined by subtracting the calculated shieldings for the fluorine nuclei of interest from that of the fluorine in fluorobenzene.[31] These calculated fluorotoluene ^{19}F chemical shifts were then correlated with experimental solution-state chemical shifts for the free inhibitors obtained in acetone-d_6 on a Bruker Avance DRX 400.[21]

Benzene−Hexafluorobenzene Dimer. The structure of the benzene−HFB dimer was restricted such that both molecules were planar, the two planes were parallel, and the benzene hydrogens eclipsed the HFB fluorines.[24] Chemical shifts were calculated at the B3LYP/6-311++G(d,p) level. These calculations were repeated over the relevant intermolecular distances between 3 and 10 Å (3.0, 3.2, 3.4, 3.6, 4.0, 4.5, 5.0, 6.5, and 10 Å). The change in shielding, $\Delta\sigma$, was calculated by taking the difference between the fluorine shieldings for the bound and free hexafluorobenzene molecule.

Charge field approximation-based calculations[32] were performed on the complex using point charges located at the benzene nuclei. Charges were derived from the electrostatic potential of the isolated molecule via the ChelpG scheme of Breneman and Wiberg.[33] The benzene electron densities for the calculation were obtained at the MP2/6-311G(d,p) level of theory using the MP2 density matrix (density = current).

Counterpoise (CP) corrections to $\Delta\sigma$ were also calculated. The CP method, first proposed by Boys and Bernardi,[34] was performed by obtaining the chemical shift of the HFB monomer in the presence of the basis functions of benzene (without its electrons or nuclei). The differences between these shifts and those for the complete dimer are the CP-corrected $\Delta\sigma$ values.

The above calculations were also performed on a fragment of the crystal structure of the bound pentafluorobenzylamide-linked CA inhibitor,[29] with pentafluorotoluene and toluene as models for the inhibitor and the interacting Phe131 residue, respectively. The results of calculations on this model were compared with the experimental solution-state ^{19}F shifts of the bound complex.

Computational Details. All calculations were performed using the Gaussian 98[35] software package, installed on a Pentium III 500-MHz workstation or a 380-MHz AMD K6-2 processor.

Results and Discussion

Comparison of Calculated Chemical Shifts with Experimental Results. In Table 1, we present the calculated GIAO results for all fluorotoluenes at both the HF and B3LYP levels. Also included are the experimental solution-state ^{19}F shifts of these inhibitors in acetone. At the bottom of the table are the average deviations and the root-mean-square (RMS) deviation between calculated and experimental shifts. The chemical shifts span a range of 55 ppm, effectively the entire range for common aromatic fluorines. Chemical shifts in this range can be grouped into three sub-ranges, depending on the number of adjacent fluorines. Each ortho fluorine tends to have a shielding effect of about 20 ppm.

The experimental shifts for all available inhibitors are plotted in Figure 2 as a function of the calculated GIAO/HF and GIAO/B3LYP ^{19}F chemical shifts from Table 1 for the corresponding fluorotoluene. The starting materials required for the synthesis of 2,3,5- and 2,3,4,6-fluorinated inhibitors were unavailable, so no experimental data for these species have been obtained. Immediately apparent is the excellent linear correlation of the

TABLE 1: Calculated and Experimental ^{19}F Chemical Shifts for Fluorotoluenes/Fluorinated Carbonic Anhydrase Inhibitors[a]

fluorine substitution pattern	position of fluorine	δ (ppm[b]) B3LYP/ 6-311++G(d,p)	δ (ppm[c]) HF/ 6-311++G(d,p)	δ (ppm) experimental
2	2	−118.6	−118.6	−119.3
3	3	−115.4	−113.3	−113.9
4	4	−119.8	−119.1	−116.4
23	2	−142.0	−139.8	−144.9
	3	−139.0	−134.3	−140.1
24	2	−113.5	−112.6	−112.3
	4	−114.5	−113.2	−114.8
25	2	−125.0	−125.2	−125.0
	5	−121.2	−119.3	−119.3
26	26	−115.0	−113.6	−114.9
34	4	−142.9	−139.7	−141.7
	3	−138.1	−133.9	−139.2
35	35	−111.5	−108.3	−110.5
234	3	−161.2	−153.9	−161.5
	4	−137.6	−134.2	−138.9
	3	−137.6	−133.9	−136.4
245	5	−144.5	−140.0	−143.9
	4	−137.4	−133.5	−136.6
	2	−120.5	−119.3	−120.1
236	3	−143.5	−139.7	−143.6
	2	−136.7	−133.7	−138.2
	6	−120.7	−120.0	−119.6
246	4	−112.4	−109.4	−111.5
	26	−111.8	−108.6	−109.3
345	4	−165.6	−159.9	−164.5
	35	−135.0	−129.1	−135.8
235	2	−148.1	−145.8	
	3	−133.8	−128.3	
	5	−117.4	−114.4	
2345	5	−159.5	−153.2	−157.2
	3	−155.3	−148.0	−155.8
	2	−143.3	−140.3	−142.6
	5	−141.3	−135.2	−139.0
2356	26	−144.0	−140.6	−142.1
	35	−140.6	−135.0	−139.0
2346	3	−166.9	−159.9	
	4	−136.0	−129.9	
	2	−134.8	−129.7	
	6	−119.3	−115.8	
23456	26	−143.7	−137.6	−143.0
	35	−164.0	−155.5	−164.2
	4	−158.4	−150.2	−157.2

[a] Average and RMS deviations of experimental and calculated chemical shifts are 1.1 and 1.4 ppm (B3LYP) and 3.4 and 4.1 ppm (HF), respectively. [b] Referenced to fluorobenzene, which has a calculated shift using B3LYP/6-311++G(d,p) of 287.5 ppm and an experimental shift of 113.1 ppm. [c] Referenced to fluorobenzene, which has a calculated shift using HF/6-311++G(d,p) of 341.5 ppm and an experimental shift of 113.1 ppm.

calculated shifts from both methods with the experimental values. Linear regression analyses of the two data sets yield the following results:

$$\delta_{exp} = 14.586 + 1.135\delta_{calc}(\mathrm{HF}) \quad (1)$$

$$\delta_{exp} = 2.262 + 1.013\delta_{calc}(\mathrm{B3LYP}) \quad (2)$$

The R^2 values for the HF and B3LYP fits are 0.988 and 0.994, respectively, and the RMS deviations between experimental chemical shifts and shifts predicted by these fits were 1.82 and 1.27 ppm, respectively. These deviations are comparable to typical line widths for experimental peaks. The DFT calculations are particularly impressive as not only are they superior to the HF results, but they also agree with solution-state results. Such agreement is rather astounding given that no solvent effects are included in the calculations and a large portion of each inhibitor (the benzenesulfonamide group) was neglected. The success of the calculation suggests that the long-range intramolecular shielding caused by the rest of the inhibitor is negligible. In addition, the slight offset in the fit is likely a consequence of neglecting the solvent, which, according to Lau and Gerig,[36] should shield the nuclei by a few ppm.

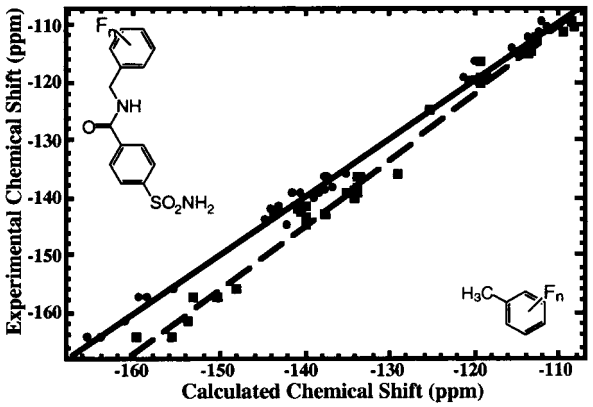

Figure 2. Correlation between experimental ^{19}F NMR chemical shifts of carbonic anhydrase II inhibitors in acetone and GIAO calculations relative to fluorobenzene at both the B3LYP/6-311++G(d,p) (filled circles and solid line) and the HF/6-311++G(d,p) levels (open squares and dashed line).

Our prior ab initio calculations of the energetics of fluoroaromatic−aromatic systems, taken together with binding affinities for the library of fluorinated inhibitors, have suggested the possibility of an intramolecular F−H contact between the fluorines at the ortho positions and the benzylamide hydrogens.[23] We postulated that the electron densities and chemical shifts near these ortho fluorines might be affected by this interaction. In general, hydrogen-bond-like interactions in which a proton is shared between two electronegative elements lead to an increased separation of charge.[37] In our system, however, if an F−H contact has altered the distribution of charge, it apparently has not affected chemical shift. Predicted shifts for the ortho fluorines based on eq 2 show equal distributions of chemical shifts both greater than and less than their experimental counterparts. The RMS error for these fluorine chemical shifts is 1.35 ppm, approximately the same as the average for the entire library, suggesting that the electron distribution is not significantly affected by these weak F−H contacts.[38]

One of our goals in this work was to assess the role of so-called van der Waals dispersion effects on ^{19}F chemical shifts in fluoroaromatics. The issue remains somewhat unresolved, as previous work has suggested either that dispersion has a fairly strong impact on chemical shift[39] or that the dominant effects are the results of electrostatic interactions.[24] Because the HF level of theory neglects electron correlation whereas the DFT approach at least approximates these effects, a comparison of the two approaches may yield insight into the question of dispersion. The most telling trends in the results are that, as the number of adjacent fluorines, as well as the total number of fluorines, increases, the HF results diverge from those obtained by DFT. The average differences in chemical shift are 1.74, 4.28, and 7.17 ppm for fluorines with 0, 1, and 2 ortho fluorines, respectively. These results suggest that electron correlation effects increase with the number of ring fluorines. As the number of neighboring fluorines increases, the augmented electron density around fluorine, particularly as a result of the additional fluorine lone pairs, would naturally lead to greater electron correlation in the system. Furthermore, relative to those of the

HF calculations, the electron correlation effects implicit in the DFT method reduce the differences in shifts between adjacent fluorines on the same molecule, bringing them into better agreement with experimental results.

Benzene−HFB Dimer. A number of groups have performed supermolecular calculations of NMR properties in which some neighboring molecules are explicitly added to the calculation.[28] These studies of smaller molecules have been fairly successful and generally have been restricted to the HF level, often with locally dense basis sets. We wished to consider the intermolecular NMR effects in a complex of benzene with HFB. Because dispersion and other weak, noncovalent interactions have been implicated in the binding of this dimer, we used the relatively large 6-311++G(d,p) basis set.

Crystal structures[40] and solution-state proton−proton dipolar couplings[41] have indicated that benzene and HFB form a stacked complex. The molecular planes of the species are parallel and are separated by 3.5 Å. This distance is in agreement with ab initio studies of the complex.[24,42] In the liquid state, this geometry has also been supported by thermodynamic data.[43] To establish the efficacy of the GIAO/DFT approach for studies of fluoroaromatic interactions, we calculated the ^{19}F shielding effects for this well-studied heterodimer. Changes in shielding were calculated between 3 and 10 Å, because there is no evidence that the molecules come any nearer than 3 Å and the intermolecular NMR effects should be insignificant at a distance of 10 Å.

For each data point, DFT and HF calculations were performed. As Helgaker et al. have indicated,[10] basis-set superposition errors (BSSE) may be significant in supermolecular calculations. Consequently, we calculated CP-corrected shifts using the standard ghost orbital approach.[34] A charge field approximation was also attempted.[32] These calculations were performed so that we could better understand the relative importance to chemical shift of the four particular effects that we propose: ring current, dispersion interactions, $\pi-\pi$ charge transfer, and long-range electrostatic interactions.

The classical ring current effect of the benzene π cloud was modeled by calculating the magnetic field due to the equivalent dipole, μ, of the system,[37] given by

$$\Delta\delta(\text{ppm}) = \mu(1 - 3\cos^2\theta)/r^3 \qquad (3)$$

where r is the distance from the benzene centroid in angstroms, θ is the angle from the perpendicular through the centroid, and μ can be approximated by the value 27.0. The dispersion interaction can be discerned qualitatively via the difference between the DFT and HF results, because DFT at least partially accounts for eletron correlation whereas HF does not. The $\pi-\pi$ charge transfer[44] is incorporated into the HF calculations. Long-range electrostatics can be isolated using the charge field approximation, which does not explicitly include the orbitals required for the calculation of other effects. These electrostatic interactions of charge distributions, particularly the quadrupole moments of the molecules, have been implicated as the primary contributor to binding.[24]

Figure 3 is a plot of the change in shielding upon complexation, $\Delta\sigma$, as calculated using each of the above methods, as a function of centroid distance. Each data set was fit to a series of weighted inverse exponentials. In an equimolar solution, the experimental value of $\Delta\sigma$ is −1.48 ppm. According to the uncorrected B3LYP results, this change in chemical shift corresponds to an intermolecular distance of 3.46 Å, in excellent agreement with the solid-state result of 3.5 Å.

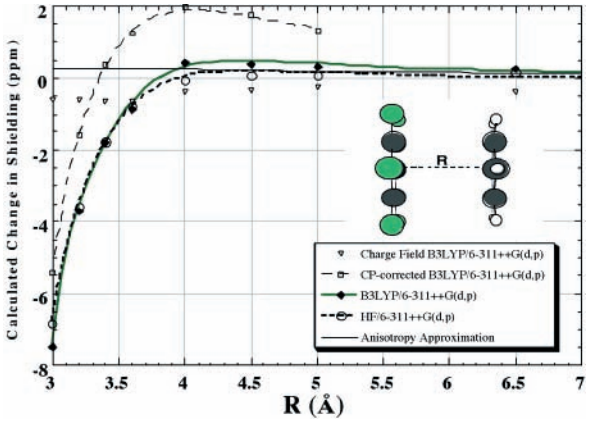

Figure 3. Calculated change in ^{19}F chemical shielding for hexafluorobenzene complexed with benzene in an eclipsed and stacked geometry at different centroid distances. Closed diamonds represent B3LYP/6-311++G(d,p) calculations, closed circles represent HF/6-311++G(d,p) calculations, open squares represent counterpoise-corrected B3LYP/6-311++G(d,p) calculations, open triangles represent charge-field approximated results at B3LYP/6-311++G(d,p), and the line without symbols represents the approximate ring current effects due to benzene.

The CP-corrected data set in Figure 3 also suggests that such corrections are inappropriate for this type of system. In the relevant range of 3−4 Å, neither the magnitude nor the direction of the shielding effects after CP correction agree with the experimental results. This approach to BSSE correction in studies of the energetics of complexes has received some criticism,[45] and although a few groups have successfully employed the technique for NMR calculations on simple systems,[32] work on this subject is still preliminary. Our results imply that there may be no simple method of correcting for and determining the extent of BSSE in this system, but given that the uncorrected results show good agreement with experimental work and that a large basis set was used, we expect that the BSSE is minimal.

Finally, a comparison of the data sets in Figure 3 suggests the following in the relevant range of about 3.5 Å: The long-range electrostatic effects represented by the charge field calculation, and the ring current effects estimated by the equivalent dipole eq 3, contribute to the total shielding but have small contributions that are of opposite signs. Any difference between the DFT and HF calculations should then be an indicator of significant dispersion interactions as opposed to electron transfer. We believe that dispersion plays a relatively small role in the stacked interaction between benzene and HFB, as both the HF and B3LYP calculations are in excellent agreement below 3.7 Å. This result supports Dougherty's assertion that such stacking interactions are not controlled by dispersion.[24] Some combination of electron transfer and electrostatics (quadrupolar interactions), therefore, appears to be responsible for the change in shielding observed for the complex. Although our approach to assessing the relative contributions to shielding is qualitative, our data suggest that these two phenomena play a role in the binding of benzene to HFB and that dispersion effects are minimal in the stacked geometry.

CA−Inhibitor Crystal Structure. The computational methods described above were then applied to the interaction between Phe131 of CA and our pentafluorobenzylamide-linked CA inhibitor. The system was modeled with toluene and pentafluorotoluene aligned in the conformation indicated by crystallographic studies of the enzyme−inhibitor complex (Figure 4).[29] Unfortunately, as shown in Table 2, our approach was unsuccessful and yielded inconclusive results. The success of our

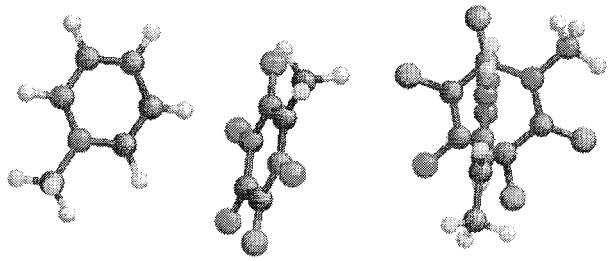

Figure 4. Two perspectives of the toluene/pentafluorotoluene geometry modeled on the interaction of Phe131 with the pentafluorobenzylamide-linked CA inhibitor in the crystal structure of the CA complex. Fluorine atoms are depicted in dark gray.

TABLE 2: Experimental and Calculated Changes in ^{19}F Shielding for Pentafluorotoluene/Toluene Model and Crystal Structure[a]

position of fluorine[b]	$\Delta\sigma$ (ppm) B3LYP/6-311++G(d,p)	$\Delta\sigma$ (ppm) experimental
2	+0.01	0.0
3	−1.62	−0.5
4	−1.30	−0.5
5	+0.65	−0.5
6	−1.27	0.0

[a] Kim, C.-Y.; Doyon, J. B.; Baird, T. A.; Fierke, C. A.; Jain, A.; Christianson, D. W., manuscript in preparation. [b] Ordered starting from the fluorines closest to the methyl group of the toluene.

calculation depends on the contribution of the rest of the protein to the field around the inhibitor being ideally minimal or at least homogeneous. We hoped this would be the case, as no other residues of CA are within 5 Å of the pentafluorobenzyl ring in the crystal structure. The poor agreement between calculation and experiment shown in Table 2 suggests otherwise. Finally, rovibrational freedom in the system could be the source of the discrepancy. In solution, the ^{19}F spectrum of the bound complex yields only three peaks, which suggests that the inhibitor has enough freedom to move away from Phe131 and rotate.

Conclusions

Our results show that, in calculating the NMR properties of a fluoroaromatic compound, DFT approaches with large basis sets yield excellent agreement with experimental results. Such calculations come at little or no additional computational cost relative to the HF approach and yield results that correlate slightly more closely with experiment. Our results also suggest that intramolecular dispersion does contribute significantly to the chemical shifts in these species. Finally, the calculations on free fluorotoluenes suggest that F−H contacts in our system do not significantly affect the chemical shift of interacting fluorines.

Chemical shift calculations for the benzene−HFB complex using both the DFT and the HF methods correspond to an equilibrium intermolecular distance comparable to experimental solid-state results. Although these two calculations proved successful, CP corrections and charge-field approximations alone could not account for the observed change in shielding on complex formation. This leads us to believe that, although intramolecular dispersion forces exist, there are minimal intermolecular dispersion effects on chemical shifts involved in the stacked aromatic interaction between benzene and HFB. In this system, electron transfer and electrostatics appear to be responsible for the observed chemical shift changes on complexation.

Finally, the application of these methods to the crystal structure of the CA−inhibitor complex reveals the limitations in such supermolecular calculations. Any field resulting from atoms excluded from the calculation may result in discrepancies between calculated and experimental results. Furthermore, extensive rovibrational freedom cannot be addressed rigorously in calculations on such large systems.

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