CHAPTER 1

GENERAL INTRODUCTION

1.1. WHY FLUORINATED COMPOUNDS ARE INTERESTING?

The reason that organic chemists are interested in compounds that contain fluorine is simple. Because of fluorine's steric and polar characteristics, even a *single* fluorine substituent, placed at a propitious position within a molecule, can have a remarkable effect upon the physical and chemical properties of that molecule. Discussions of the impact of fluorine on physical and chemical properties of compounds have appeared in numerous reviews and monographs.[1–13] There are also a number of recent reviews on the subject of fluorine in medicinal, agrochemical, and materials chemistry.[14–23]

1.1.1. Steric Size

In terms of its steric impact, fluorine is the smallest substituent that can replace a hydrogen in a molecule, other than an isotope of hydrogen. Table 1.1 provides insight into the comparative steric impact of various fluorinated substituents on the equilibrium between axial and equatorial substitution in cyclohexane.[24]

Guide to Fluorine NMR for Organic Chemists, Second Edition. William R. Dolbier, Jr.

TABLE 1.1. Values of *A* for Some Common Substituents

$-\Delta G^0$ (kcal/mol) = ***A***

X	***A*** value	X	***A*** value
H	[0]	F	0.2
OH	0.5	OCF_3	0.8
OCH_3	0.6	SCF_3	1.2
CH_3	1.7	CH_2F	1.6
C_2H_5	1.8	CHF_2	1.9
i-C_3H_7	2.2	CF_3	2.4
Ph	2.8	C_2F_5	2.7

TABLE 1.2. Substituent Effects: σ_p-Values and *F*-Values

Substituent	σ_p	*F*	Substituent	σ_p	*F*
H	[0]	[0]	CH_2F	0.11	0.15
F	0.06	0.45	CHF_2	0.32	0.29
Cl	0.23	0.42	CF_3	0.54	0.38
OH	−0.37	0.33	C_2F_5	0.52	0.44
NH_2	−0.66	0.08	OCF_3	0.35	0.39
NO_2	0.78	0.65	SCF_3	0.50	0.36
CH_3	−0.17	0.01	SF_5	0.68	0.56
			CH_2CF_3	0.09	0.15

1.1.2. Polar Effects

Fluorine is, of course, the most electronegative atom on the periodic table. σ_p-Values and *F*-values (the "pure" field inductive effect) provide indications of the electron-withdrawing influence of substituents, and it can be seen that fluorine itself has the largest *F* value of an atomic substituent. The values for σ_P and *F* for various other fluorinated (and nonfluorinated) substituents provide insight into the relative electron-withdrawing power of fluorinated substituents (Table 1.2).[25]

1.1.3. Effect of Fluorine Substituents on Acidity and Basicity of Compounds

The strong electronegativity of the fluorinated substituents is reflected in the effect that this group has upon the acidity of alcohols, carboxylic acids, and sulfonic acids, as well as the effect it has on the basicity of amines (Tables 1.3–1.6).[1, 26]

TABLE 1.3. Carboxylic Acid Acidity

XCH_2CO_2H	pK_a
X = H	4.8
X = F	2.59
X = NO_2	1.32
X = CF_3	2.9
X = CF_3CH_2	4.2
CF_3CO_2H	0.2

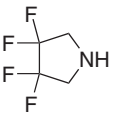
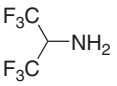
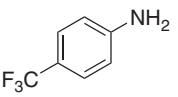
TABLE 1.4. Sulfonic Acids

	pK_a
CH_3SO_3H	−2.6
CF_3SO_3H	−12

TABLE 1.5. Alcohol Acidity

	pK_a
CH_3CH_2OH	15.9
CF_3CH_2OH	12.4
$(CF_3)_2CH–OH$	9.3
$(CF_3)_3C–OH$	5.4

TABLE 1.6. Amine Basicity

XCH_2NH_2	pK_b			
X = CH_3	3.3			
X = CH_2CF_3	5.1			
X = CF_3	8.3			
		10.0	12.8	27.0 (DMSO)

(*all in H_2O, unless otherwise indicated)*

1.1.4. Effect of Fluorinated Substituents on Lipophilicity of Molecules

Lipophilicity is an important consideration in the design of biologically active compounds because it often controls absorption, transport, or receptor binding; that is, it is a property that can enhance the

bioavailability of a compound. The presence of fluorine in a substituent gives rise to enhanced lipophilicity.

For substituents on benzene, lipophilicities are given by values of π_X, as measured by the equation in Scheme 1.1, where P values are the octanol/water partition coefficients.

Scheme 1.1

$$\pi_X = \log P_{C6H5X} - \log P_{C6H6}$$

$$SO_2CH_3 < OH < NO_2 < OCH_3 < H < F < Cl < SO_2CF_3 < CH_3 < SCH_3 < CF_3 < OCF_3$$

$$< SF_5 < SCF_3 < C_2F_5$$

Representative π values: CH_3 (0.56), CF_3 (0.88), OCF_3 (1.04), SF_5 (1.23), SCF_3 (1.44)

As a measure of the impact of fluorine on a molecule's lipophilicity, the π-value of a CF_3 group is 0.88, as compared to 0.56 for a CH_3 group.

1.1.5. Other Effects

There is also evidence that single, carbon-bound fluorine substituents, particularly when on an aromatic ring, can exhibit specific polarity influences, including H-bonding, that can strongly influence binding to enzymes.[16, 27]

These and other insights regarding structure–activity relationships for fluorinated organic compounds allow researchers interested in exploiting the effects of fluorine substitution on bioactivity to more effectively design fluorine-containing bioactive compounds. In the process of the synthesis of such compounds, it is necessary to characterize the fluorine-containing synthetic intermediates and ultimate target compounds. Knowledge of ^{19}F NMR is essential for such characterization.

1.1.6. Analytical Applications in Biomedicinal Chemistry

Over the last decade or so, NMR spectroscopy has emerged as a screening tool to facilitate the drug discovery process, and nowhere has this been more the case than with ^{19}F NMR spectroscopy (more about this in Chapter 2).

1.2. INTRODUCTION TO FLUORINE NMR[28]

Aside from carbon and hydrogen, fluorine-19 is probably the most studied nucleus in NMR. The reasons for this include both the properties of the fluorine nucleus and the importance of molecules containing fluorine. The nucleus ^{19}F has the advantage of 100% natural abundance and a high magnetogyric ratio, about 0.94 times that of ^{1}H. The chemical shift range is very large compared to that of hydrogen, encompassing a range of >350 ppm for organofluorine compounds. Thus, resonances of different fluorine nuclei in a multifluorine-containing compound are usually well separated and the spectra are usually of first order. The nuclear spin quantum number for fluorine is $1/2$ and thus fluorine couples to proximate protons and carbons in a manner similar to hydrogen, and relaxation times are sufficiently long for spin–spin splittings to be resolved. Moreover, long-range spin–spin coupling constants to fluorine can have substantial magnitude, which can be particularly useful in providing extensive connectivity information, especially in ^{13}C NMR spectra.

Although it is of less general importance because of the limited number of phosphorous-containing fluoroorganics, ^{31}P also has a nuclear spin quantum number of $1/2$, its natural abundance is 100%, and it couples strongly to neighboring fluorine. When present, it can therefore have a significant influence on fluorine NMR spectra. ^{15}N also has a nuclear spin quantum number of $1/2$. However, its couplings to fluorine are almost never measured directly because of the very low natural abundance of ^{15}N (0.366%), combined with its small gyromagnetic ratio (−4.314 MHz/T), which is about 1/10th that of ^{1}H. Thus, indirect methods are almost always used to determine both the chemical shifts and any F–N coupling constants.

As hopefully demonstrated by the many examples in this book, a judicious use of fluorine NMR in combination with proton, carbon, phosphorous, and nitrogen NMR can provide unique advantages in the art of structure characterization. This is particularly true when one brings to the task a knowledge of the impact of fluorine substituents on the chemical shifts of and coupling constants to neighboring H, C, P, and N atoms.

1.2.1. Chemical Shifts

Fluorotrichloromethane ($CFCl_3$) has become the accepted, preferred internal reference for the measurement of ^{19}F NMR spectra, and, as

such it is assigned a shift of zero. Signals upfield of the $CFCl_3$ peak are assigned negative chemical shift values, whereas those downfield of $CFCl_3$ are assigned positive values for their chemical shifts. When reporting fluorine chemical shifts, it is advised to report them relative to $CFCl_3$.

Other compounds that are commonly encountered as internal standards, particularly in the earlier literature are as follows:

CF_3CO_2H: −76.2 ppm
Hexafluorobenzene: −162.2 ppm
Trifluoromethylbenzene: −63.2 ppm
Ethyl trifluoroacetate: −75.8 ppm.

However, $CFCl_3$ has the advantage that its presence will not have any influence upon a compound's chemical shifts, plus its observed signal lies substantially downfield of most signals deriving from carbon-bound fluorine. Therefore, most fluorine chemical shifts (δ) are negative in value.

Nevertheless, one must be aware that some significant fluorine-containing functional groups, such as acylfluorides ($\delta \sim +20$ ppm), sulfonylfluorides (~+60 ppm), and pentafluorosulfanyl (SF_5) substituents (up to +85 ppm), have signals in the region *downfield* from $CFCl_3$. Signals deriving from aliphatic CH_2F groups lie at the high field end of the range, with *n*-alkyl fluorides absorbing at about −218 ppm. Methyl fluoride has one the highest field chemical shifts of an organofluorine compound at −268 ppm, tetrakis(fluoromethyl)silane having perhaps the highest (−277 ppm). Chapter 2 provides an overview of fluorine chemical shifts, with subsequent chapters providing details for each type of fluorinated substituent.

All chemical shift data presented in this book come either from the primary literature or from spectra obtained in the author's laboratory. All spectra actually depicted in the book, unless otherwise noted, derive from spectra obtained by the author at the University of Florida. All data from the literature were obtained via searches using Reaxys or SciFinder. Persons interested in accessing such primary literature can do so readily via these databases by simply searching for the specific compound mentioned in the text.

It should be noted that there are variations in reported chemical shifts for particular compounds in the literature, as would be expected. *Usually these variations are less than ±2 ppm,* and they can usually be attributed to concentration and solvent effects (as well as simple experimental error!). When given a choice, data reported using $CDCl_3$

as solvent have been preferred, with chemical shifts being reported to the nearest ppm (except occasionally when comparisons within a series from a common study are reported). When multiple values have been reported in the literature, the author has used his judgment regarding choice of the value to use in the book.

Increasingly effective efforts have been made to calculate fluorine chemical shifts. Some leading references to such theoretical work are provided.[29–32]

1.2.2. Coupling Constants

Fluorine spin–spin coupling constants to other fluorine nuclei, to neighboring hydrogen nuclei and to carbons, phosphorous, or nitrogen in the vicinity of the fluorine substituents are highly variable in magnitude but are also highly characteristic of their environment. The magnitude of such characteristic coupling constants is discussed in each of the subsequent chapters that describe the different structural situations of fluorine substitution.

Spin–spin coupling constants are reported throughout this book as absolute values of $|J|$ in hertz (Hz), and they have all been obtained either from the primary literature or from spectra obtained in the author's laboratory.

REFERENCES

Regarding the multitude of NMR chemical shifts of specific compounds that are provided within the text, references for chemical shifts of individual compounds will for the most part not be cited. It is assumed that if such references are required, the reader can find them by a quick search using either Reaxys or SciFinder. The author found Reaxys much the superior database for locating specific NMR data.

1. Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell Publishing: Oxford, **2004**.
2. Chambers, R. D. *Fluorine in Organic Chemistry*; John Wiley and Sons: New York, **1973**.
3. Uneyama, K. *Organofluorine Chemistry*; Blackwell Publishing: Oxford, **2006**.
4. Hiyama, T. *Organofluorine Compounds. Chemistry and Applications*; Springer: Berlin, **2000**.
5. Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, **1991**.

6. Begue, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, NJ, **2008**.
7. Smart, B. E. In *Organofluorine Chemistry – Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, **1994**, p 57.
8. O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
9. Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, **2004**.
10. Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hullinger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496.
11. Bissantz, C.; Kuhn, B.; Stahl, M. *J. Med. Chem.* **2010**, *53*, 5061.
12. Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, UK, **2009**.
13. Huchet, Q. A.; Kuhn, B.; Wagner, B.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Mueller, K. *J. Fluorine Chem.* **2013**, *152*, 119.
14. Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637.
15. Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
16. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
17. Kirk, K. L. *Org. Proc. Res. Dev.* **2008**, *12*, 305.
18. Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303.
19. Begue, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992.
20. Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013.
21. Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16.
22. Ampt, K. A. M.; Aspers, R. L. E. G.; Jaeger, M.; Geutjes, P. E. T. J.; Honing, M.; Wijmenga, S. S. *Magn. Res. Chem.* **2011**, *49*, 221.
23. Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.
24. Carcenac, Y.; Tordeux, M.; Wakselman, C.; Diter, P. *New J. Chem.* **2006**, *30*, 447.
25. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
26. Roberts, R. D.; Ferran, H. E., Jr.; Gula, M. J.; Spencer, T. A. *J. Am. Chem. Soc.* **1980**, *102*, 7054.
27. Champagne, P. A.; Desroches, J.; Paquin, J.-F. *Synthesis* **2015**, *47*, 306.
28. Hesse, M.; Meier, H.; Zeeh, B. *Spectroscopic Methods in Organic Chemistry*; Georg Thieme Verlag: Stuttgart, **1997**.
29. Wiberg, K. B.; Zilm, K. W. *J. Org. Chem.* **2001**, *66*, 2809.
30. Fukaya, H.; Ono, T. *J. Comput. Chem.* **2004**, *25*, 51.
31. Saielli, G.; Bini, R.; Bagno, A. *Theor. Chem. Acc.* **2012**, *131*, 1140.
32. Raimer, B.; Jones, P. G.; Lindel, T. *J. Fluorine Chem.* **2014**, *166*, 8.