GUIDE TO FLUORINE NMR FOR ORGANIC CHEMISTS

WILLIAM R. DOLBIER, JR.

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PREFACE

Fluorine's unique polar and steric properties as a substituent, and the influence that fluorinated substituents can have upon the physical and chemical properties of molecules, have induced increasing numbers of synthetic organic chemists to incorporate fluorine into target compounds of synthetic interest. In preparing compounds that contain fluorine, one first faces the daunting task of learning the intricacies of fluorine's often unique synthetic methodologies.

Then, once the desired fluorine-containing compounds have been synthesized, the real fun begins as the world of fluorine NMR is entered. However, one's first encounter with fluorine NMR can also present a problem because although most synthetic organic chemists are thoroughly familiar with the use of proton and carbon NMR for compound characterization, few have much experience with the use of fluorine NMR for that purpose. Moreover, there is presently no single place where a person can turn to obtain a concise but thorough introduction to fluorine NMR itself and, just as importantly, to learn how the presence of fluorine substituents can enhance the efficacy of both proton and carbon NMR as tools for structure characterization.

Simply speaking, the purpose of this little book is to provide you, the working organic chemist, with virtually everything you need to know about fluorine NMR, including an understanding of the impact of fluorine substituents upon proton and carbon NMR.

This book is primarily intended for use by academic and industrial organic chemists, most of whom will have interests in fluorinated

compounds of potential pharmaceutical and agrochemical interest. Such compounds are for the most part what I will call "lightly" fluorinated, that is, containing one or at most a few fluorine-containing substituents, with the emphasis being on isolated fluorine substituents, CF_2 groups, and trifluoromethyl substituents. However, virtually all fluorine-containing substituents that might be of interest, including C_2F_5 and SF_5, will be discussed. More heavily fluorinated compounds will not be totally ignored, but the emphasis will be upon the lightly fluorinated species.

Hopefully, this book will work both to provide an introduction to the novice and as a resource for those chemists who are more experienced in working with fluoro-organic compounds. As you will soon notice, the book has not been written by an NMR "specialist," but rather has been written for working organic chemists *by* a working organic chemist.

This book would not have been possible without the encouragement of my wife, Jing, the critical technical assistance of Dr. Ion Ghiviriga in obtaining and interpreting NMR spectra, and the able assistance of my current and past research group members who synthesized key model compounds and who, along with Dr. Ghiviriga, obtained all spectra that appear in this book. They include Dr. Ying Chang, Dr. Wei Xu, Lianhao Zhang, and Henry Martinez.

William R. Dolbier, Jr.

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 textbooks.[1–8] There are also a number of recent reviews on the subject of fluorine in medicinal chemistry.[9–13]
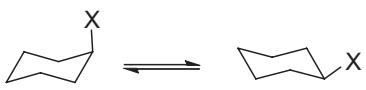
1.1.1. Steric Size

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 as to the comparative steric impact of various fluorinated substituents on the equilibrium between axial and equatorial substitution in cyclohexane.[14]

1.1.2. Polar Effects

Fluorine is, of course, the most electronegative atom on the periodic table. σ_p and F values (the "pure" field inductive effect) provide

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

$$-\Delta G^\circ \ (\text{kcal/mol}^{-1}) = A \ \text{value}$$

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$_2$F	1.6
C$_2$H$_5$	1.8	CHF$_2$	1.9
i-C$_3$H$_7$	2.2	CF$_3$	2.4
Ph	2.8	C$_2$F$_5$	2.7

TABLE 1.2. Substituent Effects: σ_P and *F* Values

Substituent	σ_P	*F*	Substituent	σ_P	*F*
H	[0]	[0]	CH$_2$F	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$_2$F$_5$	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$_2$CF$_3$	0.09	0.15

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).[15]

1.1.3. Effect of Fluorine Substituents on the 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 and carboxylic acids, as well as the effect it has on the basicity of amines (Tables 1.3–1.5).

TABLE 1.3. Carboxylic Acid Acidity[1,2]

XCH_2CO_2H	pK_a
X = H	4.8
X = F	2.6
X = NO_2	1.5
X = CF_3	2.9
X = CF_3CH_2	4.2
CF_3CO_2H	0.2

TABLE 1.4. Alcohol Acidity[1,2,6]

Alcohol	pK_a
CH_3CH_2OH	15.9
CF_3CH_2OH	12.4
$(CF_3)_2CHOH$	9.3
$(CF_3)_3COH$	5.4

TABLE 1.5. Amine Basicity[1]

XCH_2NH_2	pK_b
X = CH_3	3.3
X = CH_2CF_3	5.3
X = CF_3	8.3

1.1.4. Effect of Fluorinated Substituents on the 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 following equation (Scheme 1.1), where P values are the octanol/water partition coefficients.

Representative π values

$$CH_3 (0.56), CF_3 (0.88), OCF_3 (1.04), SF_5 (1.23), SCF_3 (1.44)$$
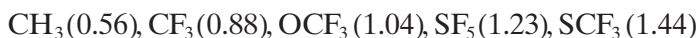
As a measure of the impact of fluorine on a molecule's lipophilicity, the π value of a CF_3 group is 0.88, as compared to 0.56 for a CH_3 group.

<u>**Scheme 1.1**</u>

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

$$SO_2CH_3 < OH < NO_2 < OCH_3 < H < F < Cl < SO_2CF_3 < CH_3 < SCH_3 < CF_3 < OCF_3$$
$$< SF_5 < SCF_3 < C_2F_5$$
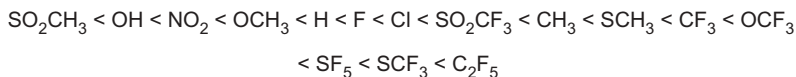
1.1.5. Other Effects

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.[9]

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 past 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[16]

Aside from carbon and hydrogen, ^{19}F 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 usually first order. The nuclear spin quantum number for fluorine is $\frac{1}{2}$ 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.

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

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 (~+20 ppm), sulfonylfluorides (δ ~+60), 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 the highest field chemical shift for an organofluorine compound at −268 ppm. Chapter 2 will provide 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 derive from spectra obtained by the author at the University of Florida. All data from the literature were obtained via searches using MDL Crossfire Commander or SciFinder Scholar. 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 is some variation 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 will be preferred, with chemical shifts being reported to the nearest parts per million (except occasionally when comparisons within a series from a common study are reported). When multiple values have been reported in the literature, the author will use his judgment regarding choice of the value to use in the book.

1.2.2. Coupling Constants

Fluorine spin–spin coupling constants to other fluorine nuclei, to neighboring hydrogen nuclei, and to carbons 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 will be discussed in each of the subsequent chapters that describe the different structural situations of fluorine substitution.

Spin–spin coupling constants will be reported throughout this book as absolute values of $|J|$ in hertz, 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 for the most part will not be cited. It is assumed that if such references are required, the reader can find them by a quick search using either MDL Crossfire Commander or SciFinder Scholar. The author found MDL Crossfire Commander the superior database for locating specific NMR data.

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CHAPTER 2

AN OVERVIEW OF FLUORINE NMR

2.1. INTRODUCTION

If one wishes to obtain a fluorine NMR spectrum, one must of course first have access to a spectrometer with a probe that will allow observation of fluorine nuclei. Fortunately, most modern high field NMR spectrometers that are available in industrial and academic research laboratories today have this capability. Probably the most common NMR spectrometers in use today for taking routine NMR spectra are 300 MHz instruments, which measure proton spectra at 300 MHz, carbon spectra at 75.5 MHz and fluorine spectra at 282 MHz. Before obtaining and attempting to interpret fluorine NMR spectra, it would be advisable to become familiar with some of the fundamental concepts related to fluorine chemical shifts and spin-spin coupling constants that are presented in this book. There is also a very nice introduction to fluorine NMR by W. S. and M. L. Brey in the Encyclopedia of Nuclear Magnetic Resonance.[1]

For those new to the field of fluorine NMR, there are a number of convenient aspects about fluorine NMR that make the transition from proton NMR to fluorine NMR relatively easy. With a nuclear spin of $\frac{1}{2}$ and having almost equal sensitivity to hydrogen along with sufficiently long relaxation times to provide reliable integration values, ^{19}F nuclei

provide NMR spectra that very much resemble proton spectra, with the additional benefit of having a much broader range of chemical shifts, which means that one usually will not encounter overlapping signals in compounds that contain multiple fluorine-containing substituents, and thus most spectra will be first order. Also, since it is not usual to employ proton decoupling when obtaining fluorine NMR spectra, one will observe not only coupling between proximate fluorine substituents, but also between fluorine nuclei and proton nuclei, with the magnitude of geminal and vicinal F–F and F–H coupling constants generally being larger than the respective H–H spin-spin coupling constants.

As is the case for ^{1}H spectra, but not for ^{13}C spectra, the intensities of individual signals in ^{19}F NMR spectra constitute an accurate measure of the relative number of fluorine atoms responsible for such signals.

Because today the majority of organic chemists who make fluoroorganic compounds work in pharmaceutical and agrochemical industries, and such people are primarily interested in lightly fluorinated molecules, the emphasis in this book will be the NMR analysis of compounds containing one, two or three fluorine atoms or bearing substituents containing a limited number of fluorines, with the goal of understanding how the chemical shifts and spin-spin couplings of such substituents are affected by the structural environment in which they exist.

2.2. FLUORINE CHEMICAL SHIFTS

The observed resonance frequency of any NMR-active nucleus depends in a characteristic manner upon the magnetic environment of that nucleus. The effective field strength (B_{eff}) felt by the nucleus of an atom that has magnetic moment differs from the imposed field (B_0) in the following manner (eq. 2.1)

$$B_{eff} = B_0 - \sigma B_0 \qquad (2.1)$$

where σ is the dimensionless *shielding constant*

This shielding constant, σ, is made up of three terms (eq. 2.2)

$$\sigma = \sigma_{dia} + \sigma_{para} + \sigma^{i} \qquad (2.2)$$

The diamagnetic term, σ_{dia}, corresponds to the opposing field resulting from the effect of the imposed field upon the electron cloud surrounding the nucleus. In this case, electrons closer to the nucleus give rise to greater shielding than distant ones.

The paramagnetic term, σ_{para}, derives from the excitation of p-electrons by the external field, and its impact is opposite to that of diamagnetic shielding. The term, σ^i, derives from the effect of neighboring groups, which can increase or decrease the field at the nucleus. σ can also be affected by intermolecular effects, in most cases deriving from interaction of the solvent.

In the case of proton spectra, only s-orbitals are present. Thus, only σ_{dia} is important, whereas, in contrast, the paramagnetic term, σ_{para}, is dominant in determining the relative shielding of fluorine nuclei. Thus, the "normal" intuitions regarding "shielding" that most chemists have acquired while working with ^{1}H NMR generally do not apply when it comes to predicting relative chemical shifts in ^{19}F NMR. For example, the fluorine nucleus of $ClCH_2CH_2F$ is slightly more highly shielded ($\delta_F = -220$) than that of CH_3CH_2F ($\delta_F = -212$).

There are other notable differences between fluorine and proton NMR spectra. For example, the effects of anisotropic magnetic fields, such as those generated by ring currents, are relatively much less important for fluorine than for proton NMR. Thus the ranges of vinylic and aromatic fluorine chemical shifts overlap completely. Also notable is the much greater sensitivity of single carbon-bound F-substituents to environment than carbon-bound CF_2 or CF_3 substituents. Single fluorine chemical shifts, which encompass vinylic, aryl, and saturated aliphatic fluorine substituents, range between about -70 ppm and -238 ppm, whereas the similar range for CF_2 groups is -80 to -130 ppm, and that of the CF_3 group is even smaller, between about -52 and -87 ppm.

In general, and all other things being equal, the fluorines of a trifluoromethyl group are more deshielded than those of a CF_2H or $R-CF_2-R'$ group, which are themselves more deshielded than a single fluorine substituent (Scheme 2.1).
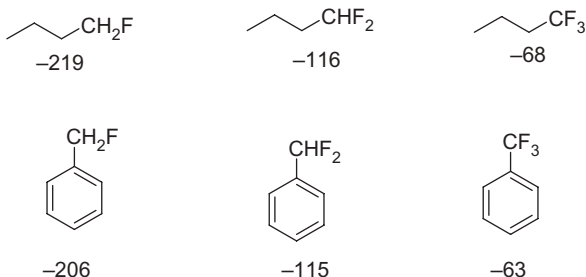
Scheme 2.1

TABLE 2.1. Impact of α-Halogen Substitution on Fluorine Chemical Shifts

X	CH$_3$	F	Cl	Br	I
δ, CF$_3$X	−65	−62	−33	−21	−5
δ, HCF$_2$X	−110	−78	−73	−70	−68
δ, H$_2$CFX	−212	−143	−169	—	−191

TABLE 2.2. Impact of α-Chalcogen Substitution on Fluorine Chemical Shifts

Y	F	OPh	SPh	SePh
CF$_3$Y, δ	−62	−58	−43	−37
HCF$_2$Y, δ	−79	−87	−96	−94
H$_2$CFY, δ	−143	−149	−180	—

Some illustrative trends in chemical shift exist for the effect of α-halogen or α-calcogen substitution on a fluorinated carbon. Trends in chemical shift derived from α-halogen-substitution on CF$_3$, CF$_2$H, and CH$_2$F groups are variable, depending on the group, with CF$_3$ and CF$_2$H being increasingly deshielded by F < Cl < Br < I (opposite the trend observed for proton chemical shifts), with this trend being more pronounced for CF$_3$. In contrast, the CH$_2$F group is increasingly *shielded* going from F to I (Table 2.1).

Likewise, the analogous α-chalcogen substitution only exhibits a consistent deshielding trend for the CF$_3$ group (F < OPh < SPh < SePh), with shielding effects being observed for both the CF$_2$H and CH$_2$F groups (Table 2.2).

2.2.1. Steric Deshielding of Fluorine

Another significant and not infrequently encountered impact on fluorine chemical shifts is the deshielding influence of a physically proximate alkyl group upon CF$_3$ groups, CF$_2$ groups, and aromatic C–F (based upon limited data, there does not appear to be significant effect on CH$_2$F groups).[2] Under circumstances such as those depicted in Scheme 2.2 below, where structurally all other factors are equal except for the steric interaction of the alkyl group with the fluorinated group, one observes significant deshielding in the presence of this steric interaction. This deshielding is understood to occur only when there is direct overlap of the van der Waals radii of the alkyl group and that of the fluorine, and the deshielding is thought to be the result of van der Waals forces of the alkyl group restricting the motion of electrons on the fluorine and thus making the fluorine nucleus respond to the magnetic field as if the electron density were lowered.