

A Chemical Shift Additivity Method for the Prediction of Fluorine-19 Chemical Shifts in Fluoroaromatic Compounds

Michael J. Fifolt, Stanley A. Sojka, Roger A. Wolfe, and Daniel S. Hojnicky

Occidental Chemical Corporation, Grand Island Technology Center, Grand Island, New York 14072

Joseph F. Bieron and Frank J. Dinan*

Department of Chemistry, Canisius College, Buffalo, New York 14208

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An empirical, substituent chemical shift based additivity method is described for the a priori prediction of ^{19}F chemical shifts in tri- and tetrasubstituted fluoroaromatic compounds. The method is shown to correlate experimental and calculated ^{19}F chemical shifts with coefficients of correlation of 0.977 and 0.988 in two deuterated solvents. It is also demonstrated to be largely free of concentration and hydrogen bonding effects over a 500-fold concentration range and to be free from "ortho effects", which characteristically interfere with ^{19}F chemical shift predictions.

Introduction

Fluorine NMR spectroscopy is a widely used analytical procedure. The ^{19}F nucleus is ideally suited for study by the NMR technique. Its high natural abundance and favorable gyromagnetic ratio afford it 83% of the sensitivity observed in proton NMR, and its wide chemical shift range exceeds that which is characteristic of ^{13}C NMR.¹

Despite the power and utility of this method there are no published additivity rule relationships that allow quick and convenient estimation of ^{19}F chemical shifts in the manner that is so widely and efficiently used for the estimation of ^{13}C chemical shifts.^{2,3} Rather, published compilations of ^{19}F chemical shift data are ordered based upon functional group type (ex. CF_2 , CF_3).^{4,5} This organizational style is not as versatile or convenient as the chemical shift additivity approach.

Studies that relate the chemical shift of ^{19}F in fluoroaromatic compounds to a variety of theoretical parameters have appeared in the literature for some time. Pioneering studies in the field have demonstrated that these chemical shifts can be correlated with the resonance effects of para substituents in para-disubstituted fluorobenzenes⁶ and the inductive effects of meta substituents in meta-disubstituted fluorobenzenes.⁷ No successful correlation of ^{19}F chemical shifts with ortho substituents is reported, presumably due to the steric and hydrogen-bonding interactions that can occur between these substituents and the adjacent fluorine atom. These studies, while of substantial theoretical interest, are of limited utility since they apply only to simple and sharply restricted classes of fluoroaromatic compounds.

Another approach to the prediction of ^{19}F chemical shifts involves their calculation using semiempirical methods. Characteristically, this methodology attempts to utilize such parameters as charge densities and bond orders to establish multiple regression equations that account for

^{19}F chemical shifts. In a typical study of this type a series of multiple regression equations were developed which, in the optimal case, predicted ^{19}F chemical shifts with a standard error of 6.2 ppm.⁸

A frequently encountered problem with semiempirical and theoretical methods that attempt to predict ^{19}F chemical shifts in fluoroaromatic compounds is their inability to account for so called ortho effects.⁸ This problem is encountered with compounds that have a polar substituent ortho to the ring fluorine atom. This steric arrangement results in intramolecular electrical field effects, which substantially and unpredictably influence the chemical shift of the ^{19}F atom. Interactions of this type result in substantial deviations between experimentally determined and calculated ^{19}F chemical shift values. This is a general phenomenon and is characteristic of calculations of this type.

Inspection of the data presented in Tables II and III clearly indicates that this problem is not significant when the substituent chemical shift based, additivity effect approach is utilized. The deviation between calculated and experimental values for compounds having polar substituents ortho to the fluorine atom is small and not significantly different from those deviations observed for compounds that do not have this steric arrangement.

A recent theoretical study maintains that ^{19}F chemical shifts are actually a measure of the induced orbital paramagnetism at the fluorine atom, but makes no attempt to predict these chemical shifts on an a priori basis.⁹

An even more recently reported approach to the prediction of ^{19}F chemical shifts utilizes a computerized data base.¹⁰ This procedure, while promising, is presently limited; it deals only with perfluorinated compounds. Additionally, the data utilized to prepare this data base were gathered from the chemical literature over the period 1961-1981, and are, therefore, subject to differences arising from variations in instrument parameters, solvent effects, concentration differences, sample purity, etc. These factors combine to limit the applicability and accuracy of the method.

Each of these theoretical and semiempirical approaches to the prediction of ^{19}F chemical shifts has shortcomings. These are particularly obvious when they are compared to the chemical shift additivity relationships that are

(1) *Varian Instruments NMR Table*; Copyright 1968 by Varian Associates.

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Table I. Fluorine-19 Substituent Chemical Shift Values for Disubstituted Fluoroaromatic Compounds

compound	¹⁹ F chemical shifts				substituent chemical shifts (SCS) ^a							
	ortho (acetone)	ortho (DMSO)	meta (acetone)	meta (DMSO)	para (acetone)	para (DMSO)	ortho (acetone)	ortho (DMSO)	meta (acetone)	meta (DMSO)	para (acetone)	para (DMSO)
difluorobenzene	-139.7	-138.8	-110.6	-109.5	-120.0	-118.8	-25.5	-26.1	3.2	3.1	-6.3	-6.2
fluoroacetanilide	-125.6	-124.6	-112.8	-111.8	-120.3	-119.4	-11.8	-12.0	1.0	0.8	-6.5	-6.8
fluoroacetophenone	-110.6	-110.0	-113.1	-112.0	-107.1	-105.9	3.2	2.6	0.7	0.6	6.7	6.7
fluoroaniline	-136.3	-134.9	-115.6	-113.5	-129.7	-129.4	-22.5	-22.2	-1.9	-0.9	-15.9	-16.8
fluoroanisole	-136.1	-135.3	-112.6	-111.4	-125.2	-124.0	-22.3	-22.7	1.2	1.3	-11.4	-11.4
fluorobenzaldehyde	-122.4	-120.7	-112.6	-111.6	-104.3	-103.2	-8.6	-8.1	1.2	1.0	9.5	9.4
fluorobenzamide	-113.6	-113.3	-113.4	-112.6	-109.8	-109.2	0.2	-0.7	0.4	0.1	4.0	3.4
fluorobenzoic acid	-110.0	-110.1	-113.3	-112.2	-107.2	-106.5	3.8	2.5	0.5	0.4	6.6	6.1
fluorobenzoyl chloride	-109.5	-	-113.6	-	-101.8	-	4.3	-	0.2	-	12.0	-
fluorobenzonitrile	-108.6	-107.9	-110.9	-110.0	-104.0	-102.8	5.2	4.7	2.9	2.6	9.8	9.8
fluorobenzotrifluoride	-115.8	-115.4	-111.4	-110.3	-108.0	-106.8	-2.0	-2.8	2.4	2.3	5.8	5.8
fluorobromobenzene	-108.1	-107.7	-110.8	-110.0	-115.6	-114.7	5.7	4.9	2.9	2.6	-1.8	-2.1
fluorochlorobenzene	-116.3	-115.9	-111.2	-110.3	-116.7	-115.2	-2.5	-3.2	2.6	3.5	-2.4	-2.6
fluoroiodobenzene	-94.4	-106.2	-110.9	-110.3	-114.8	-114.2	19.4	6.4	2.9	2.3	-1.1	-1.5
N-(fluorophenyl)-methanesulfonamide	-126.1	-124.1	-112.0	-111.2	-118.9	-118.5	-12.3	-11.5	1.7	1.4	-5.1	-5.9
N-(fluorophenyl)tri-fluoroacetamide	-123.5	-120.3	-	-111.1	-116.8	-116.0	-9.7	-7.6	-	1.5	-3.0	-3.3
N-(fluorophenyl)tri-fluoromethane-sulfonamide	-123.0	-124.7	-	-110.7	-115.4	-	-9.2	-12.1	-	1.9	-1.6	-
fluoronitrobenzene	-119.7	-119.0	-110.4	-109.5	-103.6	-102.4	-6.0	-6.4	3.4	3.1	10.2	10.2
fluorophenol	-138.0	-136.3	-113.2	-112.1	-126.8	-125.0	-24.3	-23.7	0.6	0.5	-13.0	-12.4
fluorotoluene	-118.4	-117.3	-114.9	-113.7	-119.2	-118.0	-4.6	-4.7	-1.1	-1.1	-5.4	-5.3
fluorophenylisocyanate	-123.6	-122.6	-112.2	-111.3	-116.5	-115.6	-9.8	-10.0	1.6	1.3	-2.7	-3.0
N-(fluorophenyl)-phthalimide	-120.0	-118.6	-	-	-	-	-6.2	-6.0	-	-	-	-

^aSCS values were calculated by subtracting the ¹⁹F chemical shift for fluorobenzene in the appropriate solvent (-113.8 ppm in acetone-*d*₆ and -112.6 ppm in DMSO-*d*₆) from the ¹⁹F chemical shift measured for the substituted fluorobenzene derivative.

Table II. Experimental vs Calculated ^{19}F Chemical Shift Values in Acetone- d_6

no.	compound	exptl	calcd	deviation ^{a,b}	
1	4-chloro-2-fluoroacetanilide	-123.0	-122.3	-0.7	
2	(2,4-difluorophenyl)acetanilide	(C-2)	-123.1	-125.4	2.3
		(C-4)	-116.5	-117.1	0.6
3	(3,4-difluorophenyl)acetanilide	(C-3)	-137.9	-138.8	0.9
		(C-4)	-145.8	-146.3	0.5
4	2,5-difluoroaniline	(C-2)	-142.3	-142.6	0.3
		(C-5)	-119.6	-121.9	2.3
5	2,6-difluoroaniline	-133.2	-133.1	-0.1	
6	2-amino-3-fluorobenzoic acid	-136.5	-135.8	-0.7	
7	2,6-difluorobenzonitrile	-105.9	-105.4	-0.5	
8	2-amino-5-fluorobenzotrifluoride	-133.0	-131.7	-1.3	
9	3-amino-4-fluorobenzotrifluoride	-135.5	-133.9	-1.6	
10	4-amino-3-fluorobenzotrifluoride	-131.3	-130.5	-0.8	
11	5-amino-2-fluorobenzotrifluoride	-129.0	-127.3	-1.7	
12	3-chloro-4-fluorobenzotrifluoride	-110.5	-111.2	0.7	
13	4-fluoro-3,5-dinitrobenzotrifluoride	-120.4	-119.9	-0.5	
14	2,3-dimethylfluorobenzene	-121.9	-119.5	-2.4	
15	3,4-dimethylfluorobenzene	-119.2	-120.3	1.1	
16	1-bromo-2,5-difluorobenzene	(C-5)	-117.3	-117.1	-0.2
17	2,4-difluorophenol	(C-2)	-133.4	-134.9	1.5
		(C-4)	-124.4	-123.6	-0.8
18	4,5-difluorophthalic anhydride	-123.7	-126.0	2.3	
19	<i>N</i> -(2,6-difluorophenyl)phthalimide	-117.7	-117.3	-0.4	
20	5-fluorosalicylic acid	-125.0	-126.5	1.5	
21	<i>N</i> -(2,4-difluorophenyl)methanesulfonamide	(C-2)	-113.1	-115.7	2.6
		(C-4)	-120.0	-122.8	2.8
22	<i>N</i> -(2,4-difluorophenyl)(trifluoromethyl)acetanilide	(C-2)	-118.0	-120.3	2.3
		(C-4)	-111.4	-113.6	2.2
23	<i>N</i> -(2,6-difluorophenyl)(trifluoromethyl)acetanilide	-118.4	-120.3	1.9	
24	<i>N</i> -(2,4-difluorophenyl)trifluoromethanesulfonamide	(C-2)	-117.3	-119.8	2.5
		(C-4)	-109.9	-112.2	2.3
25	<i>N</i> -(2,6-difluorophenyl)trifluoromethanesulfonamide	-117.5	-119.8	2.3	

^a Calculated by subtracting the calculated ^{19}F chemical shift value from the experimental value. ^b Standard deviation = 1.65 ppm.

widely used for the prediction of ^{13}C chemical shifts with good accuracy from readily available empirical data.

Experimental Section

The ^{19}F NMR spectra used in this study were obtained on either a Bruker NR-270AF or a Bruker NR-100AF spectrometer. An internal deuterium field-frequency lock was used throughout. Samples were prepared as 0.15 M solutions in either acetone- d_6 or dimethyl sulfoxide- d_6 (DMSO- d_6) to which 0.5% fluorobenzene was added as an internal standard. The fluorobenzene was referenced to CFCl_3 . A 4.0- μs pulse was repeated 16 times with a delay time of 20 s. The sweep width and offset were adjusted to accommodate all of the sample resonances. Substituent chemical shift values were determined relative to a measured value of -113.8 ppm for fluorobenzene in acetone- d_6 and -112.6 ppm for DMSO- d_6 . All compounds used in this study were either commercially available (Aldrich Chemical Co.) or were prepared by using standard literature procedures. Chemical shift values were found to be reproducible to within ± 0.1 ppm.

Results and Discussion

We have developed an empirically based chemical shift additivity relationship that allows ^{19}F chemical shifts to be calculated in a manner similar to that commonly used for ^{13}C chemical shift predictions. This procedure has been applied to fluoroaromatic compounds and allows their ^{19}F chemical shifts to be calculated with good accuracy in a wide variety of tri- and tetrasubstituted compounds. This relationship has been demonstrated to be valid in two solvent systems and to be largely independent of concentration over a wide range. It is also free of "ortho effects", which often interfere with ^{19}F chemical shift predictions.

The data in Table I indicate the effects which a wide variety of common substituent groups have on the ^{19}F chemical shift in ortho-, meta-, and para-substituted fluoroaromatic compounds in acetone- d_6 and DMSO- d_6 . The effect of the substituent on the chemical shift is termed the substituent chemical shift (SCS). It is deter-

mined for each substituent group by subtracting the chemical shift for fluorobenzene (in the appropriate solvent) from that of the substituted fluoroaromatic derivative.

The SCS values obtained in this manner were used to calculate the ^{19}F chemical shift for a series of tri- and tetrasubstituted fluoroaromatic compounds. This was accomplished by summing the appropriate SCS values with the fluorobenzene ^{19}F chemical shift observed in the solvent being used. For example, the ^{19}F chemical shift calculated for 4-chloro-2-fluoroaniline in DMSO- d_6 was determined by summing: $-112.6 + (-22.2) + 3.5 = -131.4$ ppm. These values, obtained from Table I are, respectively, the chemical shift for fluorobenzene, the SCS value for an ortho amino group, and the SCS value for a para chloro group in DMSO- d_6 solvent. In order to assess the accuracy with which this procedure allows ^{19}F shifts to be estimated, the calculated shifts were compared to experimentally observed ^{19}F chemical shifts determined on the same tri- and tetrasubstituted compounds.

Tables II and III compare the experimentally determined ^{19}F chemical shift values with those calculated as described above. Subtraction of the calculated values from the experimentally observed ^{19}F chemical shift values afforded the deviations listed in these tables. A standard deviation was calculated from these values for each of the two solvents used; 1.65 ppm in acetone- d_6 , and 1.49 ppm in DMSO- d_6 .

The correlations between experimental and observed ^{19}F chemical shifts clearly demonstrate that the SCS additivity based approach allows accurate a priori predictions of ^{19}F chemical shifts in a wide variety of tri- and tetrasubstituted fluoroaromatic compounds. The accuracy that is characteristic of this approach is clearly illustrated in the correlation between experimental and calculated ^{19}F chemical shifts, which is shown in Figures 1 and 2.

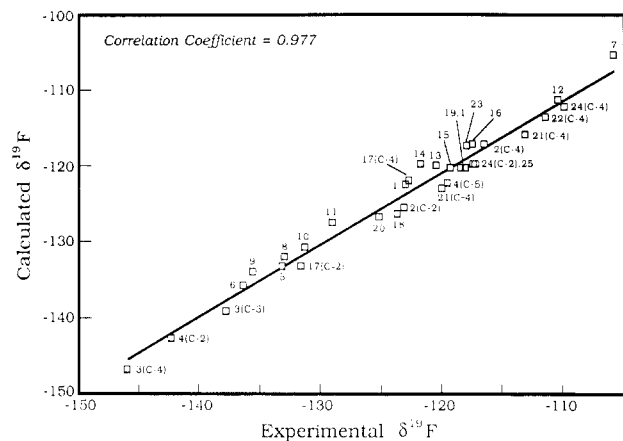


Figure 1. Experimentally observed vs calculated ^{19}F chemical shifts in acetone- d_6 .

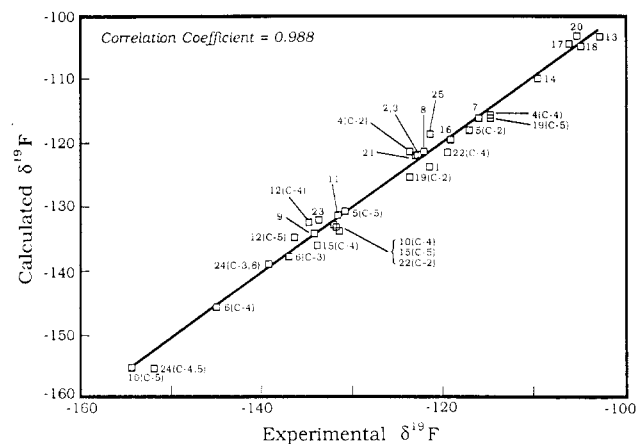


Figure 2. Experimentally observed vs calculated ^{19}F chemical shifts in DMSO- d_6 .

Figure 1 shows this correlation for the compounds listed in Table III. The coefficient of correlation for these data, which were obtained in acetone- d_6 , is 0.977. Figure 2 presents the data that were obtained in DMSO- d_6 and are listed in Table II. The coefficient of correlation for these data is 0.988.

The solvents selected for use in this study, acetone- d_6 and DMSO- d_6 , were chosen because of their ready availability and, particularly in the case of DMSO, their ability to dissolve a wide range of polar and nonpolar compounds. These selection criteria were judged to be most important since the solvent dependency of ^{19}F chemical shifts has been shown to be small. It has previously been demonstrated that the ^{19}F chemical shift of a wide variety of disubstituted fluoroaromatic compounds varied by approximately 1 ppm when their ^{19}F NMR spectra were determined in a series of 19 solvents ranging in polarity from cyclohexene to a methanol-water mixture.⁶

Comparison of the ^{19}F chemical shifts obtained in this study when the same compound was run in both acetone- d_6 and DMSO- d_6 confirmed this observation. Six experimentally determined ^{19}F chemical shifts which were obtained in both of these solvents differed by an average of 1.9 ppm.¹¹

The effect of concentration on chemical shift is of importance since, if significant, sample concentration could influence the magnitude of experimentally obtained chemical shift values. This variable was investigated in

Table III. Experimental vs Calculated ^{19}F Chemical Shift Values in DMSO- d_6

no.	compound	exptl	calcd	deviation ^{a,b}
1	4-chloro-2-fluoroacetanilide	-121.6	-124.0	2.4
2	2-cyano-2-fluoroacetanilide	-123.0	-122.0	-1.0
3	2-fluoro-4-(trifluoromethyl)acetanilide	-123.1	-122.1	-1.0
4	(2,4-difluorophenyl)acetanilide	(C-2) -119.4	-121.5	2.1
		(C-4) -114.8	-116.3	1.5
5	(2,5-difluorophenyl)acetanilide	(C-2) -117.0	-118.0	1.0
		(C-5) -130.9	-130.8	-0.1
6	(3,4-difluorophenyl)acetanilide	(C-3) -137.0	-137.9	0.9
		(C-4) -144.9	-145.5	0.6
7	3-fluoro-4-methylacetanilide	-116.0	-116.5	0.5
8	2-fluoro-4-nitroacetanilide	-122.3	-121.5	-0.8
9	3-fluoroanthranilic acid	-134.3	-134.5	0.2
10	4,5-difluoroanthranilic acid	(C-4) -131.5	-133.6	2.1
		(C-5) -154.5	-155.2	0.7
11	4-chloro-2-fluoroaniline	-131.7	-131.4	-0.3
12	2-carboxamido-4,5-difluorobenzoic acid	(C-4) -134.8	-132.6	-2.2
		(C-5) -136.4	-134.9	-1.5
13	2-chloro-4-fluorobenzotrifluoride	-102.5	-103.4	0.9
14	3-chloro-4-fluorobenzotrifluoride	-109.4	-110.1	0.7
15	3-chloro-4,5-difluorobenzotrifluoride	(C-4) -133.9	-136.2	2.3
		(C-5) -131.9	-132.9	1.0
16	4-fluoro-3,5-dinitrobenzotrifluoride	-119.0	-119.6	0.6
17	1-bromo-2,6-difluorobenzene	-105.8	-104.6	-1.2
18	1,4-dibromo-2-fluorobenzene	-104.5	-105.1	0.6
19	2,5-difluoronitrobenzene	(C-2) -123.5	-125.2	1.7
		(C-5) -114.7	-115.7	1.0
20	5-fluoro-2-nitrotoluene	-104.9	-103.5	-1.4
21	2-chloro-4-fluorophenol	-123.7	-121.5	-2.2
22	2,4-difluorophenol	(C-2) -131.7	-133.2	1.5
		(C-4) -122.7	-121.9	-0.8
23	4,5-difluorophthalic acid	-133.5	-132.2	-1.3
24	tetrafluorophthalic acid	(C-3,6) -139.1	-139.0	-0.1
		(C-4,5) -151.9	-155.2	3.3
25	3,6-difluorophthalic anhydride	-121.5	-118.6	-2.8

^a Calculated by subtracting the calculated ^{19}F chemical shift value from the experimental value. ^b Standard deviation = 1.49.

both solvents and found not to be significant.

A series of ten ^{19}F chemical shift measurements were made at equally spaced concentration intervals in acetone- d_6 and DMSO- d_6 solutions of 2-fluoroaniline. These measurements were carried out over a 500-fold concentration range; from 50 to 0.1 weight percent. The observed chemical shifts varied by only 0.1 ppm in each solvent and demonstrated the concentration effect to be of little importance.

This concentration/chemical shift study also has implications for the presence or absence of hydrogen-bonding effects on observed chemical shifts in the two solvents tested. Whereas intramolecular hydrogen bonding, which can be present in 2-fluoroaniline, is independent of concentration, intermolecular hydrogen bonding is a concentration-dependent phenomenon.

A previous study of fluorobenzene derivatives established that ^{19}F chemical shift differences of from 8 to 25

(11) Compounds 1, 2, 12, and 17, Table I; compounds 1, 4, 14, and 22, Table II.

ppm are observed between the protonated and non-protonated forms of these compounds.¹² Given the relatively great magnitude of these chemical shift differences and the small chemical shift range observed over the 500-fold concentration range measured, it seems reasonable to conclude that intramolecular hydrogen bonding does not significantly influence the measured ¹⁹F chemical shifts in the solvents utilized here.

It is clear from these data that this SCS-based additivity method effectively predicts ¹⁹F chemical shifts in fluoroaromatic compounds. The extent to which this method would apply to other types of fluoroorganic compounds has yet to be determined, but is clearly an area for future investigation.

Registry No. *o*-Difluorobenzene, 367-11-3; *m*-difluorobenzene, 372-18-9; *p*-difluorobenzene, 540-36-3; *o*-fluoroacetanilide, 399-31-5; *m*-fluoroacetanilide, 351-28-0; *p*-fluoroacetanilide, 351-83-7; *o*-fluoroacetophenone, 445-27-2; *m*-fluoroacetophenone, 455-36-7; *p*-fluoroacetophenone, 403-42-9; *o*-fluoroaniline, 348-54-9; *m*-fluoroaniline, 372-19-0; *p*-fluoroaniline, 371-40-4; *o*-fluoroanisole, 321-28-8; *m*-fluoroanisole, 456-49-5; *p*-fluoroanisole, 459-60-9; *o*-fluorobenzaldehyde, 446-52-6; *m*-fluorobenzaldehyde, 456-48-4; *p*-fluorobenzaldehyde, 459-57-4; *o*-fluorobenzamide, 445-28-3; *m*-fluorobenzamide, 455-37-8; *p*-fluorobenzamide, 824-75-9; *o*-fluorobenzoic acid, 445-29-4; *m*-fluorobenzoic acid, 455-38-9; *p*-fluorobenzoic acid, 456-22-4; *o*-fluorobenzoyl chloride, 393-52-2; *m*-fluorobenzoyl chloride, 1711-07-5; *p*-fluorobenzoyl chloride, 403-43-0; *o*-fluorobenzonitrile, 394-47-8; *m*-fluorobenzonitrile, 403-54-3; *p*-fluorobenzonitrile, 1194-02-1; *o*-fluorobenzotrifluoride, 392-85-8; *m*-fluorobenzotrifluoride, 401-80-9; *p*-fluorobenzotrifluoride, 402-44-8; *o*-fluorobromobenzene, 1072-85-1; *m*-fluorobromobenzene, 1073-06-9; *p*-fluorobromobenzene, 460-00-4; *o*-fluorochlorobenzene, 348-51-6; *m*-fluorochlorobenzene, 625-98-9; *p*-fluorochlorobenzene, 352-33-0; *o*-fluoroiodobenzene, 348-52-7; *m*-fluoroiodobenzene, 1121-86-4; *p*-fluoroiodobenzene, 352-34-1; *N*-(*o*-fluorophenyl)methanesulfonamide, 98611-90-6; *N*-(*m*-fluorophenyl)methanesulfonamide, 35980-20-2; *N*-(*p*-fluorophenyl)methanesulfonamide, 35980-24-6; *N*-(*o*-fluorophenyl)-

trifluoroacetamide, 61984-68-7; *N*-(*m*-fluorophenyl)trifluoroacetamide, 35980-21-3; *N*-(*p*-fluorophenyl)trifluoroacetamide, 35980-25-7; *N*-(*o*-fluorophenyl)trifluoromethanesulfonamide, 23383-98-4; *N*-(*m*-fluorophenyl)trifluoromethanesulfonamide, 23384-01-2; *N*-(*p*-fluorophenyl)trifluoromethanesulfonamide, 23384-00-1; *o*-fluoronitrobenzene, 1493-27-2; *m*-fluoronitrobenzene, 402-67-5; *p*-fluoronitrobenzene, 350-46-9; *o*-fluorophenol, 367-12-4; *m*-fluorophenol, 372-20-3; *p*-fluorophenol, 371-41-5; *o*-fluorotoluene, 95-52-3; *m*-fluorotoluene, 352-70-5; *p*-fluorotoluene, 352-32-9; *o*-fluorophenyl isocyanate, 16744-98-2; *m*-fluorophenyl isocyanate, 404-71-7; *p*-fluorophenyl isocyanate, 1195-45-5; *N*-(*o*-fluorophenyl)phthalimide, 568-95-6; *N*-(*m*-fluorophenyl)phthalimide, 19357-20-1; 4-chloro-2-fluoroacetanilide, 59280-70-5; (2,4-difluorophenyl)acetanilide, 399-36-0; (3,4-difluorophenyl)acetanilide, 458-11-7; 2,5-difluoroaniline, 367-30-6; 2,6-difluoroaniline, 5509-65-9; 2-amino-3-fluorobenzoic acid, 825-22-9; 2,6-difluorobenzonitrile, 1897-52-5; 3-amino-5-fluorobenzotrifluoride, 393-39-5; 3-amino-4-fluorobenzotrifluoride, 535-52-4; 4-amino-3-fluorobenzotrifluoride, 69409-98-9; 5-amino-2-fluorobenzotrifluoride, 2357-47-3; 3-chloro-4-fluorobenzotrifluoride, 78068-85-6; 4-fluoro-3,5-dinitrobenzotrifluoride, 393-76-0; 2,3-dimethylfluorobenzene, 443-82-3; 3,4-dimethylfluorobenzene, 452-64-2; 1-bromo-2,5-difluorobenzene, 399-94-0; 2,4-difluorophenol, 367-27-1; 4,5-difluorophthalic anhydride, 18959-30-3; *N*-(2,6-difluorophenyl)phthalimide, 120371-26-8; 5-fluorosalicyclic acid, 345-16-4; *N*-(2,4-difluorophenyl)methanesulfonamide, 98611-91-7; *N*-(2,4-difluorophenyl)(trifluoromethyl)acetanilide, 98651-71-9; *N*-(2,6-difluorophenyl)(trifluoromethyl)acetanilide, 98634-00-5; *N*-(2,4-difluorophenyl)trifluoromethanesulfonamide, 23384-22-7; *N*-(2,6-difluorophenyl)trifluoromethanesulfonamide, 98611-93-9; 2-cyano-2-fluoroacetanilide, 829-81-2; 2-fluoro-4-(trifluoromethyl)acetanilide, 88288-14-6; (2,5-difluorophenyl)acetanilide, 398-90-3; 3-fluoro-4-methylacetanilide, 458-10-6; 2-fluoro-4-nitroacetanilide, 348-19-6; 3-fluoroanthranilic acid, 825-22-9; 4,5-difluoroanthranilic acid, 83506-93-8; 4-chloro-2-fluoroaniline, 57946-56-2; 2-carboxamido-4,5-difluorobenzoic acid, 83506-92-7; 2-chloro-4-fluorobenzotrifluoride, 94444-58-3; 3-chloro-4,5-difluorobenzotrifluoride, 77227-99-7; 1-bromo-2,6-difluorobenzene, 64248-56-2; 1,4-dibromo-2-fluorobenzene, 1435-52-5; 2,5-difluoronitrobenzene, 364-74-9; 5-fluoro-2-nitrotoluene, 446-33-3; 2-chloro-4-fluorophenol, 1996-41-4; 4,5-difluorophthalic acid, 18959-31-4; tetrafluorophthalic acid, 652-03-9; 3,6-difluorophthalic anhydride, 652-40-4.

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Perfluoro- and Polyfluorosulfonic Acids. 21. Synthesis of Difluoromethyl Esters Using Fluorosulfonyldifluoroacetic Acid as a Difluorocarbene Precursor

Qing-Yun Chen* and Sheng-Wen Wu

Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu, Shanghai, China

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Difluoromethyl alkanoates **5** and fluorinated and nonfluorinated alkanesulfonates **9** were synthesized in moderate yields by the reaction of alkali metal salts of acids with fluorosulfonyldifluoroacetic acid (**3**) in acetonitrile under mild conditions. The presumed intermediate anion $\text{FO}_2\text{SCF}_2\text{CO}_2^-$ generates CF_2 by elimination of SO_2 , CO_2 , and F^- . The esters are formed by insertion of CF_2 into the O-H of the acid, whereas HCF_3 is formed by the competing capture of F^- . Organic acids can be used indirectly in the reaction in the presence of inorganic salts such as Na_2SO_4 and KCl , with comparable yields of difluoromethyl esters.

Introduction

Difluorocarbene is a useful intermediate for synthesizing organofluorine compounds.¹ Although several methods

for generating CF_2 are known,² there is a need for more readily available CF_2 precursors. In our study of the synthesis and reactions of perfluoro- and polyfluoroalkanesulfonic acids, we have discovered a new series of

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