

Long-Range Intrinsic and Equilibrium Deuterium Isotope Effects on ^{19}F Chemical Shifts

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Deuterium isotope effects on ^{19}F chemical shifts caused by deuteration at OH or NH groups have been determined for intramolecularly hydrogen bonded compounds including fluorinated *o*-hydroxyacyl aromatics, enamines, *o*-hydroxyazo and hydrazo compounds. The *o*-hydroxyazo and hydrazo compounds represent tautomeric and non-tautomeric cases. Deuterium isotope effects on fluorine chemical shifts for *o*-hydroxyacyl aromatics are found to parallel deuterium isotope effects at the carbon *ipso* to fluorine. For the azo and hydrazo compounds very long-range effects are seen formally over ten bonds. Through-space effects are observed in the case of spatially close nuclei like 2-fluorobenzamide-*N*- α .

The isotope effects on ^{19}F chemical shifts can, in *p*-fluorophenyl substituted cases, be used to monitor the change in equilibrium upon deuteration and therefore to estimate the importance of hydrogen bonds.

Deuterium isotope effects on ^{19}F chemical shifts have been investigated in carbenium ions,^{1–4} acyl fluorides,⁵ fluoroethylenes⁶ and fluorobenzenes.⁷ Long-range deuterium isotope effects on fluorine chemical shifts have been studied in bicyclo compounds in order to elucidate the mechanism.⁸ In the latter compounds with large distances between deuterium and fluorine, it was found that the effect occurs through the σ -electron skeleton. ^{19}F is a very sensitive nucleus both regarding detection and chemical shifts; therefore, ^{19}F chemical shifts have been used with success to monitor tautomeric equilibria.^{9,10}

Solvent deuterium isotope effects on ^{19}F chemical shifts have also proved very useful.^{11,12} In that context compounds with exchangeable OH or NH groups next to fluorine were investigated.¹² It is interesting to compare isotope effects due to intramolecular hydrogen bonds and solvent isotope effects. Recently, 2-fluorobenzamide has been examined and a rather large 'through-space' isotope effect was established, caused by deuterium substitution at the nearby amide group¹³ and hence of orbital overlap type. As outlined above, a number of different mechanisms, possibly dependent on distance but also on hydrogen bonding, exist. Elucidation of these intrinsic isotope effects is, furthermore, important as the intrinsic contribution must be known in order

to use deuterium isotope effects as a gauge of equilibrium situations.

Deuterium isotope effects on chemical shifts are defined as $n\Delta X(\text{D}) = \delta X(\text{H}) - \delta X(\text{D})$, where X is the observed nucleus, D is the heavier isotope (in this case deuterium) and *n* is the number of intervening bonds between the nuclei in question and the isotope.

Deuterium isotope effects on ^{13}C chemical shifts have been studied in a large number of intramolecularly hydrogen-bonded cases and this type of isotope effect shows systematic trends.^{14–20} In conjugated systems they are transmitted over many bonds²⁰ and the mechanism has been discussed.²¹ The charge separation in hydrogen-bonded systems is of great interest.²² ^{19}F chemical shifts are very sensitive to electric field effects.^{23,24} It is clearly of interest to compare the isotope effects on carbon, $n\Delta C(\text{XD})$, with isotope effects on ^{19}F chemical shifts, $n+1\Delta F(\text{D})$, in the same compounds. A correlation between these parameters may be very useful in determining one parameter when the other is known, but also in order to understand the mechanism better.

Equilibrium isotope effects have also been studied in detail^{25,26} and Bordner *et al.*²⁷ have raised the question of the functional form of the change in the equilibrium constant as a consequence of deuteration. They suggested the unusual functional form $K^{\text{D}} = K^{1+\alpha}$ in which K^{D} is the equilibrium constant for the deuterated compound. This has been confirmed in β -diketones²⁸ and in

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β -thio ketones.²⁹ Fluorinated *o*-hydroxyazo compounds provide a very good test set as the three mono-fluorinated compounds have equilibrium constants between one and three at 300 K.

The present investigation covers deuterium isotope effects on ^{19}F chemical shifts of fluorinated *o*-hydroxyacyl aromatics, acetanilides, amides, enamines, *o*-hydroxyazo and hydrazo compounds. The hydroxyazo and hydrazo compounds represent both tautomeric and non-tautomeric cases, some of which serve as models for the estimation of standard values for the azo and hydrazo cases.

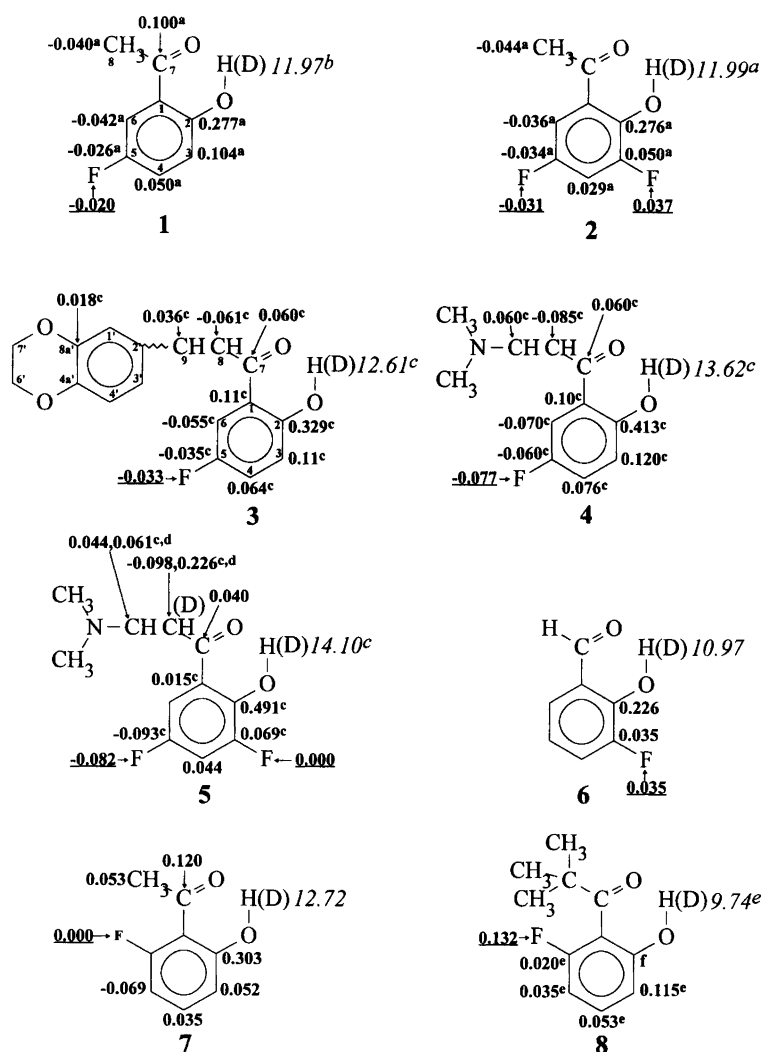
Results and discussion

XH chemical shifts, deuterium isotope effects on ^{19}F and ^{13}C chemical shifts are given in Scheme 1. ^{13}C chemical shifts and $J(\text{C},\text{F})$ coupling constants are given in Table 1 and the ^{19}F chemical shifts are given in Table 2.

Deuterium isotope effects on fluorine chemical shifts, $^n\Delta\text{F}(\text{XD})$.

o-Hydroxy acyl aromatics. The deuterium isotope effects on ^{19}F chemical shifts over four bonds are positive for **2** and **6** and zero for **5**. The isotope effects over six bonds, $^6\Delta\text{F}-5(\text{OD})$ are negative, whereas the effects over five bonds, $^5\Delta\text{F}-5(\text{OD})$, are small except for **8**. A comparison of $^{n+1}\Delta\text{F}(\text{OD})$ with $^n\Delta\text{C}(\text{OD})$ for **1**–**7**, **9** and **10** revealed that the signs and also the magnitudes of the two types of isotope effect are very similar. The only exception is $^4\Delta\text{F}-3(\text{OD})$ of **5**, which is zero. This parallel behaviour underlines either that the fluorine chemical shift depends on the perturbation in a manner different from that of ^{13}C or that an alternation in the effect,^{17,30} as suggested for the ^{13}C isotope effects, does not occur. An explanation for non-alternation is possibly the transmission of $^4\Delta\text{F}(\text{D})$ through the σ -electron skeleton.

The value observed for **8** is clearly unusual. This is



Scheme 1

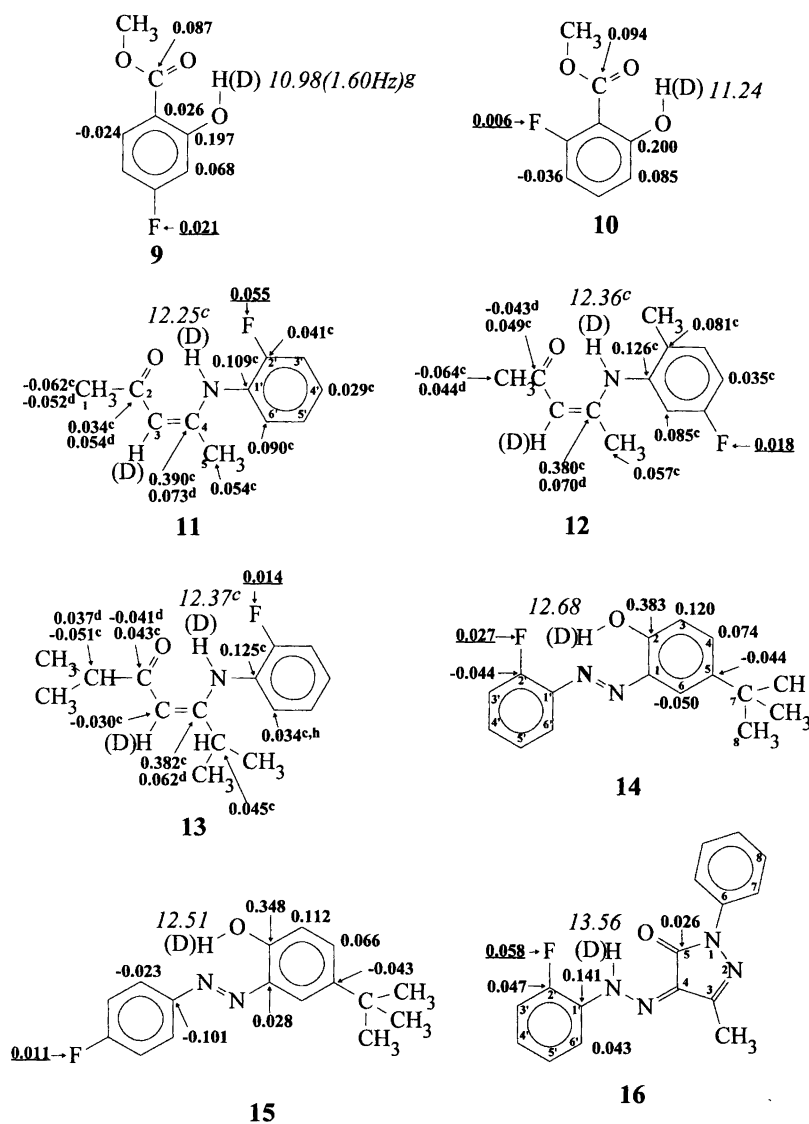
most likely related to strain isotope effects expected for such systems.³¹

Compounds with NH-Ph fragments. These compounds are divided into two groups, those having the NH group taking part in intramolecular hydrogen bonding, **11–13**, **16–21** and those which do not, **26–28**. **18** and **19** have, in addition a non-hydrogen-bonded NH group remote from the fluorine. The $^4\Delta\text{F}-2'(\text{ND})$ isotope effects are rather similar in the localized hydrogen bonded cases except for **13** and all the values are close to 0.060 ppm. This is only half the size of the isotope effect observed for the tautomeric compound, **25**. The lack of $^5\Delta\text{C}(\text{ND})$ isotope effects observed for the acetanilide and hydrazones can be ascribed to the lack of resonance-assisted hydrogen bonds (RAHB) in the former. If this is so, it is unusual that $^6\Delta\text{F}(\text{D})$ of **19**, **21**, **28**, and to a certain extent **31**, are large and positive, which suggests a different origin of the isotope effect. The relatively

large value of $^n\Delta\text{F}(\text{D})$ for the *o*-fluoro compounds, **26** and **29**, compared with the *m*- and *p*-fluoro compounds, **27**, **28**, **30** and **31** might be a consequence of the close proximity of the NH(D) and the fluorine in the *o*-fluoro compounds.³² That proximity plays a role for this kind of isotope effect has been demonstrated for **29**. In this case the isotope effect on the fluorine chemical shift for the proximate ND is 0.138 ppm, whereas it is only 0.016 ppm for the ND pointing away from the fluorine.¹³ Furthermore, the close proximity of NH and F in **29** is ascertained by observation of large through-space H-F coupling.³² It is also notable that **27** does not show an isotope effect. Close proximity has also been claimed as the cause of a large $^3\Delta\text{F}(\text{D})$ effect of fluorobenzene-2-*d*.⁷

As mentioned above, $^4\Delta\text{F}(\text{D})$ of **13** is much smaller than for **11**. The same is found for $^3\Delta\text{C}-2(\text{ND})$ and $^3\Delta\text{C}-6(\text{ND})$. This is not the case for either $^2\Delta\text{C}-1(\text{ND})$ or $^2\Delta\text{C}-1'(\text{ND})$, although this had been suspected.³³

$\text{D}_2\text{O}:\text{H}_2\text{O}$ solvent isotope effects on the fluorine shift



Scheme 1 (cont.)

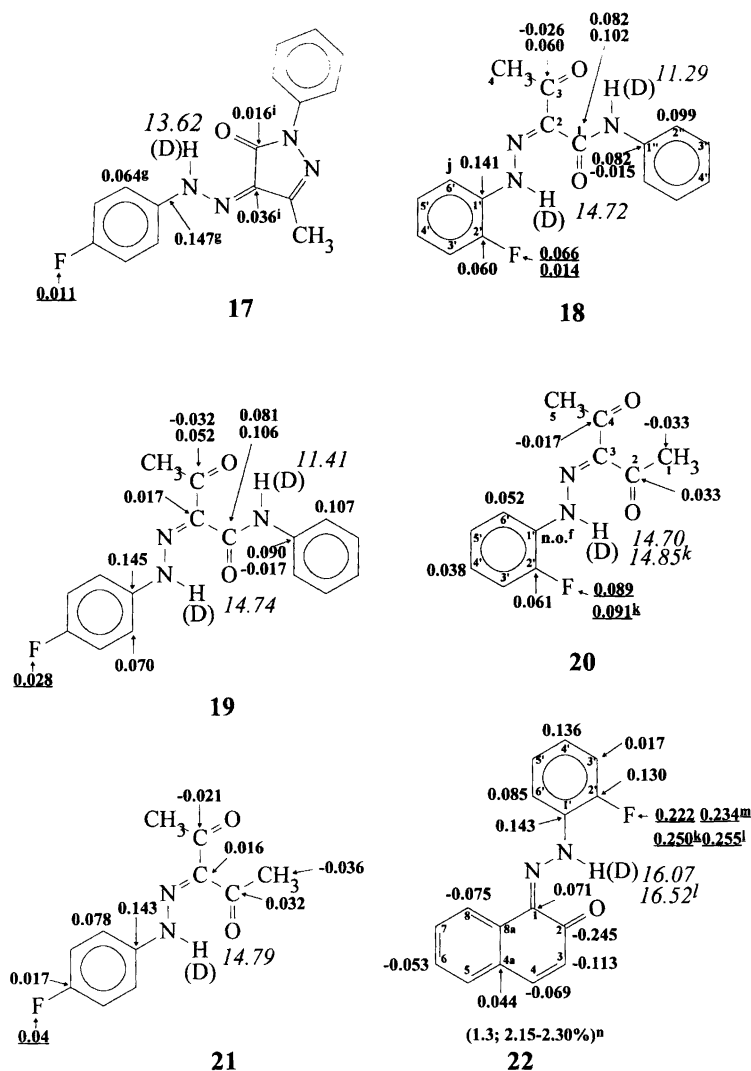
of **29** are actually larger (0.199 ppm),¹² than that observed in CDCl₃ (0.138 ppm). This is in line with the previous conclusion, that the intramolecular contribution in H₂O:D₂O is small.¹²

Extraordinarily long-range isotope effects on fluorine, formally over eight bonds, are seen from the amide-like NH group of **18**. A similar, but smaller effect was seen for **19**, in which the distance is longer.

Azo compounds. The isotope effect seen in **15** is exceptional. If it is transmitted through bonds, the pathway is over ten bonds. However, another transmission pathway might be via the hydrogen bond. Similar effects are, in principle, seen for $\Delta C(XD)$, but not to the same extent. The generally small isotope effects confirm that no tautomeric equilibrium is involved (see later), so **14** and **15** can safely be used as models for azo compounds. The value for **14** is larger than that for **15**, in good agreement with the smaller number of bonds.

General effects. ¹⁹F chemical shifts. The ¹⁹F chemical shifts of the *o*-acyl aromatics fall within three different ranges: F-3 substituted at ca. -135 ppm, F-5 substituted at ca. -117 ppm and F-6 substituted at ca. -105 ppm, with compound **8** again falling outside at -100.2 ppm.

For the NH compounds, F-2 substitution leads to ¹⁹F shifts at ca. -132 ppm, with corresponding values of the enaminones at ca. -123 ppm. For F-4 substitution, the values are ca. -117 ppm (Table 2). The values mentioned for the NH compounds, including hydrazo compounds, are different from those found for azo compounds. For F-2 substituted azo compounds the values are ca. -125.1 ppm and for F-4 substituted isomers -109.5 ppm, as indicated by the model compounds, **14** and **15** (Table 2). The values for the azo compounds are known to be influenced by substituents.³⁴ The values found for hydrazo compounds confirm those found by Lycka^{9,10} and therefore make possible the use of ¹⁹F chemical shifts to estimate the amounts of hydrazo



Scheme 1 (cont.)

and azo forms of hydrazo-azo tautomeric equilibria⁹ (see later).

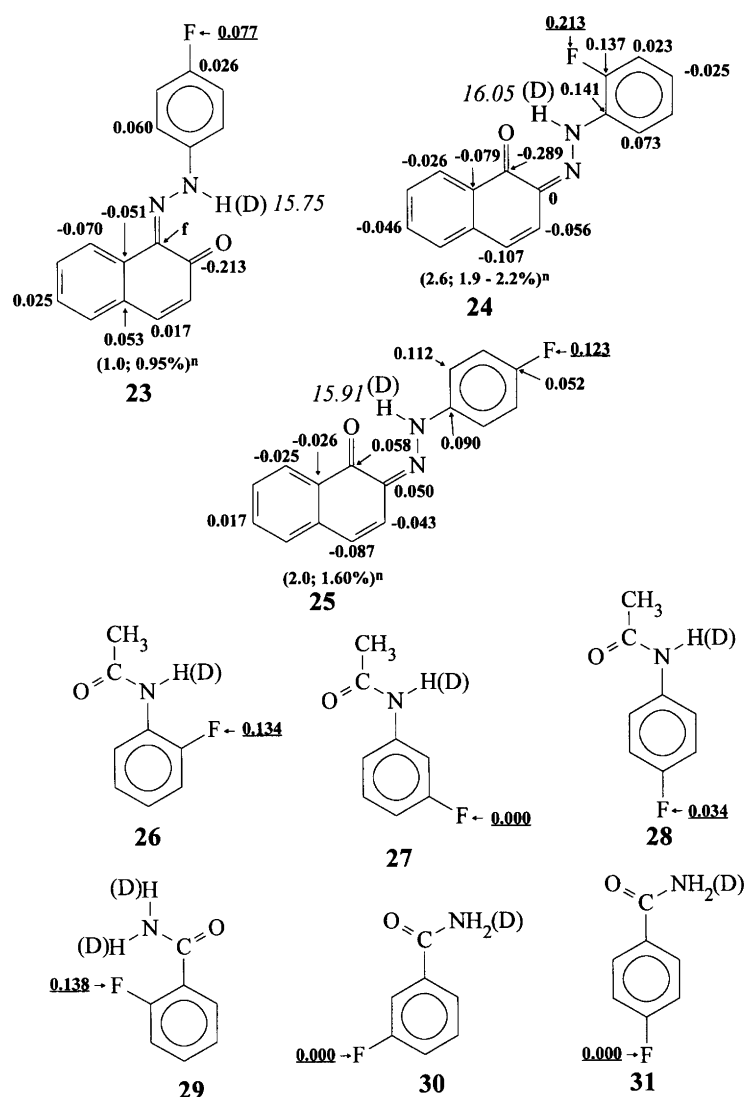
It has been demonstrated that, in certain cases, $^n\Delta\text{X}(\text{D})$ simply reflects the chemical shift of X.²¹ A proportionality was found between $^7\Delta\text{F}(\text{D})$ and δF of deuteriated 4-fluorophenylethyl carbonium ions.⁴ No such trend is seen for **1**, **2**, **31**, **17** and **21** (Scheme 1).

$^1J(\text{C},\text{F})$. For fluorinated compounds, $^1J(\text{C},\text{F})$ (Table 1) couplings give information about the double bond character of the C-F bond^{35,36} and consequently about delocalization of the fluorine lone-pair. The $^1J(\text{C},\text{F})$ couplings are seen to vary in **1**–**10** according to the fluorine position: $^1J(\text{C-6},\text{F}) > ^1J(\text{C-4},\text{F}) > ^1J(\text{C-3},\text{F}) > ^1J(\text{C-5},\text{F})$. For the NH compounds the variation in $^1J(\text{C},\text{F})$ is much smaller and a nearly constant value is

found for both *o*- and *p*-fluorinated compounds. For the *ortho*-case a larger coupling is found for the azo than for the hydrazo case. $^1J(\text{C},\text{F})$ couplings are therefore a possible way of determining the position of azo-hydrazo tautomeric equilibria (see later).

Tautomeric equilibria. The determination of equilibrium constants in the tautomeric compounds can be based on chemical shifts of nuclei sensitive to the difference between the azo and hydrazo forms. The nuclei should at the same time be isolated from local changes in the structure. Lycka *et al.*³⁷ have tested the use of C-1', C-2' and C-4' of phenyl rings and for fluorine substituted compounds, $\delta^{19}\text{F}$.^{9,10} Both $\delta^{15}\text{N}$ ⁹ and $^1J(\text{N},\text{H})$ ³⁸ are also useful, but were not used in this investigation.

In the present study an investigation was carried out



Scheme 1. $^n\Delta\text{F}(\text{XD})$ and $^n\Delta\text{C}(\text{D})$, X=O or N and OH, ^1H chemical shifts (in italics). Hydrogen bonds are not shown for clarity. ^aFrom Ref. 17. ^bGiven as 12.29 ppm in Ref. 17. ^cFrom Ref. 33. ^dIsotope effect due to deuteration at carbon. ^eTaken from Ref. 30. ^fNot observed. ^gCoupling constants. ^hAssignment based on carbon, fluorine coupling constant. ⁱTemperature 230 K. ^jOverlap prevented determination. ^kTemperature 250 K. ^lTemperature 225 K. ^mTemperature 280 K. ⁿValues in brackets are equilibrium constants, $K = [\text{hydrazone form}]/[\text{azo form}]$ and % change in equilibrium constant due to deuteration.

Table 1. ^{13}C chemical shifts (ppm) obtained at 300 K in CDCl_3 using TMS as an internal reference and C_1F coupling constants in parentheses.

Compounds	C-1	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
1	119.0 ^a (5.7)	158.4 ^a (~0)	119.6 ^a (7.5)	124.8 ^a (23.2)	—	154.6 ^a (236.7)	115.3 ^a (23.0)	203.5 ^a (2.3)	26.4 ^a	—	—	—	—	—	—	—
2	120.2 ^a (3.8) ^b ; 7.4 ^b	147.7 ^a (13.1) ^b ; 3.3 ^b	151.5 ^a (251.7) ^b ; 11.4 ^b	111.2 ^a (21.2) ^b ; 27.2 ^b	—	153.4 ^a (10.3) ^b ; 241.4 ^a	110.7 ^a (4.2) ^b ; 22.9 ^b	204.0 ^a (N.R.) ^a	27.0 ^a	—	—	—	—	—	—	—
6 ^d	122.2 (3.3)	149.6 (12.5)	150.8 (248.9)	122.6 (17.5)	—	119.3 (6.2)	128.4 (3.5)	196.3 (2.6)	—	—	—	—	—	—	—	—
7	N.O. ^f	163.9 (4.7)	114.3 (6.6)	136.2 (12.7)	—	106.1 (24.5)	163.4 (256.1)	203.0 (3.3)	32.4 (11.4)	—	—	—	—	—	—	—
9	109.3 (2.7)	163.9 (14.2)	104.4 (24.0)	167.4 (254.0)	—	107.3 (22.4)	132.2 (11.5)	170.1	52.4	—	—	—	—	—	—	—
10	102.5 (13.1)	162.9 (3.5)	113.2 (3.9)	135.2 (12.0)	—	106.8 (23.3)	162.3 (260.5)	169.8 (3.8)	52.5	—	—	—	—	—	—	—
14	137.6	150.5	117.9	131.4	—	142.9	129.9	34.2	31.4	—	N.O. ^f	159.1 (257.1)	117.0 (25.6)	132.4 (8.1)	124.6 (3.5)	117.2 (6.4)
15	136.8	150.3	117.7	130.9	—	143.0	129.6	34.1	31.4	—	147.3 (2.9)	124.1 (8.7)	116.4 (22.8)	164.3 (252.4)	116.4 (22.8)	124.1 (8.7)
16 ^g	—	—	148.2	129.5	—	157.5	137.7	118.3	128.7	—	129.9 (9.2)	151.7 (246.9)	115.7 (17.9)	125.5 (7.5)	124.9 (3.7)	115.8 (1.0)
18 ^h	162.7	127.6	199.6	26.2	—	—	—	—	—	—	130.4 (9.1)	152.2 (246.9)	116.1 (12.0)	125.4 (4.7)	125.1 (3.5)	115.9 (4.8)
19 ⁱ	162.8	125.9	199.1	25.8	—	—	—	—	—	—	137.8 (2.8)	117.0 (7.8)	116.3 (22.8)	160.1 (245.3)	116.3 (22.8)	117.0 (7.8)
20	31.7	197.9	134.5	197.0	—	26.6	—	—	—	—	N.O. ^f	152.1 (246.9)	116.0 (17.9)	125.9 (7.3)	125.2 (3.6)	116.4 (3.3)
21	31.6	198.0	133.3	196.9	—	26.6	—	—	—	—	137.9 (2.3)	117.7 (7.6)	116.6 (22.8)	160.6 (247.0)	116.6 (22.8)	117.7 (7.6)
22	131.0	173.4	125.1	140.7	128.2	128.6	126.1	128.9	121.8	133.4	132.8 (8.7)	153.9 (250.7)	116.1 (18.4)	127.3 (7.6)	125.0 (3.7)	117.0 (0.8)
23	129.9	166.2	123.3	138.8	128.2	128.6	125.4	128.7	121.6	133.4	143.0 (3.2)	121.2 (8.6)	116.6 (23.6)	162.5 (249.6)	116.6 (23.6)	121.2 (8.6)
24	175.8	134.0	128.1	122.0	137.2	127.7	132.7	127.1 ^j	126.5 ^j	130.5	131.6 (8.8)	153.1 (249.1)	115.9 (18.1)	126.3 (7.3)	125.1 (3.8)	116.7 (0)
25	169.6	132.7	128.1	120.9	136.9	127.6	131.8	126.2	126.3	129.3	141.2 (2.8)	120.1 (8.2)	116.5 (23.2)	161.9 (248.3)	116.5 (23.3)	120.1 (8.2)

^aRef. 17. ^bCoupling to F-3. ^cCoupling to F-5. ^d ^{13}C chemical shift for 3-5 and 11-13 are given in Ref. 33; for 8 in Ref. 31. ^eN.R., not resolved. ^fN.O., not observed. ^gC-9, 125.0; C-10, 11.6. ^hC-1', 137.2; C-2', 120.9; C-3', 129.1; C-4', 124.9. ⁱC-1', 124.9. ^jMay be interchanged.

Table 2. ^{19}F chemical shifts (in ppm) relative to $^{19}\text{FCl}_3\text{C}$ at 300 K.

Compound	$\delta^{19}\text{F}$	Compound	$\delta^{19}\text{F}$
1	-124.56	17	-116.57 ^c
2	-131.84 ^a - 122.02 ^b	18	-132.42
3	-124.78	19	-117.32
4	-126.42	20	-132.49
5	-134.30 ^a - 124.48 ^b	21	-116.54
6	-137.17	22	-129.52
7	-105.12	23	-113.05 ^d
8	-100.21	24	-130.62
9	-101.73	25	-114.16 ^e
10	-105.59	26	-132.19
11	-122.97	27	-112.04
12	-106.95	28	-118.54 ^f
13	-122.40	29	-138.46
14	-125.12	30	-139.78
15	-109.51	31	-144.13
16	-132.84		

^aF-3. ^bF-5. ^cRef. 9 found -116.60 and -116.47 at 310 K and 290 K, respectively. ^dRef. 9 found 113.03 at 310 K and 290 K. ^eRef. 9 found -114.13 and -114.17 at 310 K and 290 K, respectively. ^fRef. 39 found -119.67.

of the variation of the parameters in the model compounds especially those serving as models for the hydrazone forms, namely ^{19}F chemical shift and $^1J(\text{C},\text{F})$ couplings. These data revealed that $^1J(\text{C},\text{F})$ couplings are constant for the NH type compounds and sufficiently different from those of the azo model compound, 14, to be useful.

A similar comparison of $\delta\text{C}-2'$ and $\delta\text{C}-4'$ of the hydrazone models (16, 18 and 20 for *o*-fluoro-substituted and 17, 19 and 21 for the *p*-substituted) revealed that for the *o*-substituted compound both C-2' and C-4' showed a large difference between the hydrazone and the azo forms, whereas for the *p*-substituted form only C-2' showed sufficient difference. C-1' was not included as this resonance is not always observed and the chemical shift of C-6' turned out not to be very useful.

Compounds 22, 23 and 25 show tautomerism⁹ and so does 24 judging from the present data. The deuterium isotope effects on the ^{19}F chemical shifts of 22 were found to be temperature-sensitive in line with the change in the equilibrium constant towards more hydrazone form at lower temperatures.^{9,10} $^n\Delta\text{C}(\text{XD})$ isotope effects contain both the intrinsic and the equilibrium contributions. The intrinsic isotope effects on the *p*-fluorine are very small in the azo form (15) and small in the hydrazone form (17 and 21). The chemical shift difference of the fluorine in the *ortho*-position between the azo and the hydrazone forms can be estimated to be 7.06 ppm and similarly to be 7.62 ppm for the *p*-form. The small intrinsic contributions to the isotope effect at the fluorine, as described above, makes the isotope effect on the fluorine chemical shifts a very suitable probe for estimating changes in the equilibrium upon deuteration. For the *o*-fluoro compounds 22 and 24, the correction due to the intrinsic contribution can be estimated as the

weighted average of the values for **14** and **16**. The mean value 0.043 is considerably larger than that for the *p*-fluorine case. The changes in the equilibrium upon deuteration of the OH/NH proton are given in Scheme 1.

Compound **24** has not previously been investigated. The proportion of the hydrazone can be estimated from the ¹⁹F chemical shift^{9,10} to be 72%.

Deuteration leads in all cases to more of the most stable tautomer, demonstrating the dominant role of the hydrogen bond in the tautomeric equilibrium. However, from a comparison of the equilibrium constants with the change in equilibrium upon deuteration, no complete correlation exists between these two parameters. We observe for both pairs, **22**, **23** and **24**, **25** the largest change in the equilibrium upon deuteration is for the compound with the largest equilibrium constant.

Conclusions

The intrinsic deuterium isotope effects on ¹⁹F chemical shifts can be divided into three groups: (i) those of intramolecularly hydrogen bonded OH groups: $\Delta F(D)$ isotope effects are roughly proportional to those of the attached carbon and are of the same sign; (ii) longer-range effects, which are typically through σ -bonds; (iii) proximity effects, which are through-space (orbital overlap of non-bonded atoms) and lead to rather large positive isotope effects.

In *p*-fluorophenyl substituted cases, the isotope effects on ¹⁹F chemical shifts can be used effectively to monitor the change in equilibrium of, e.g., tautomeric systems upon deuteration and hence to estimate the importance of hydrogen bonding.

Experimental

Compounds. Compounds **1**, **2**, **6**, **29–31** were purchased from Aldrich, Weinheim, Germany and **3–5** from Maybridge Chemical Company, Tintagel, UK. Compound **7** was synthesized from 6-fluoro-2-methoxybenzonitrile as described for **8**.³¹ Compound **7** contained traces of *o*-hydroxyacetophenone. Compounds **9** and **10** were synthesized from the corresponding acid by esterification with methanol using H₂SO₄ as catalyst at room temperature for 5 h. The reaction mixture was neutralized and extracted with ether. Compounds **7**, **9** and **10** were red oils obtained in small amounts. Their identities were confirmed by ¹H and ¹³C NMR spectra³³ and mass spectra: [*m/z* (%)] for **7**, 154 (39), 139 (100), 83 (19), 57 (10), 43 (11); for **9**, 170 (41), 139 (20), 138 (100), 110 (69), 83 (17), 82 (14), 81 (10), 57 (17); for **10**, 170 (55), 139 (36), 138 (100), 110 (91), 83 (19), 82 (15), 57 (16). Compounds **11** and **13** were prepared by condensation from the corresponding β -diketones and *o*-fluoroaniline and **12** from the corresponding 2-methyl-5-fluoroaniline.³³ The compounds were distilled and recrystallized before use. **14–18** and **22–25** were prepared as described earlier in Ref. 10 and **19–21** were synthesized analogously

to the published procedure.⁴⁰ Compounds **26–28** were prepared by mixing the appropriate fluoroanilines with excess of acetic anhydride and the solid product were separated and recrystallized from ethanol. **29** and **31** were synthesized as described earlier.³⁴

NMR. The ¹³C NMR spectra of deuteriated species were recorded in CDCl₃ on a Bruker AC 250 NMR spectrometer at 62.896 MHz with a digital resolution of 0.55 Hz per point. Chemical shifts are measured relative to internal SiMe₄. Spectra were recorded at 300 K, for samples in CDCl₃ unless otherwise stated. Spectra of both deuteriated and non-deuteriated species, and of mixtures of the two species, were recorded for all compounds. Most low-temperature spectra were recorded for samples in CD₂Cl₂.

¹⁹F NMR spectra were recorded at 235.35 MHz in 10 mm tubes with a resolution of 0.6 Hz/point. ¹⁹F chemical shifts were referenced to CFCl₃.

Most of the compounds were deuteriated by dissolving the compounds in a mixture of CH₃OH and CH₃OD, and then evaporating the solvent off under reduced pressure. The degree of deuteration could easily be varied this way. **5**, **11**, **12** and **13** all showed incorporation of deuterium at C-2.

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