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Computational ^{19}F NMR. 2. Organic compounds†

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Fluorine-19 NMR chemical shifts have been calculated for a wide variety of fluorinated organic molecules by relativistic density functional methods. The study includes, along with common fluorine-containing functional groups, several fluorinated biologically active molecules or models thereof. These calculations further showcase the predictive power of DFT-NMR, and illustrate how they can be used to assign ^{19}F spectra for the structure determination of organofluorine compounds.

Introduction

Organofluorine chemistry finds widespread applications in several areas of chemistry and materials chemistry.[1] For example, fluorinated drugs are valuable in pharmaceutical chemistry owing to several favorable characteristics; in fact, many current drugs contain one or more fluorine atoms, 5-fluorouracil being probably the best known example.[2] In materials science, the properties of organofluorine compounds are exploited, *e.g.* per- or poly-fluorinated alkyl chains microsegregate from alkyl or hydrophobic parts[3] allowing for the design of fluorinated surfactants, such as perfluorooctanesulfonic and perfluorooctanoic acids, liquid crystals,[4] ionic liquids[5,6] (including the large number of fluorinated anions[7]) and ionic liquid crystals;[8,9] in crystal engineering by exploiting the strong quadrupolar interactions between aromatic and fluoro-aromatic moieties.[10]

The structural characterization of organofluorine compounds is greatly aided by ^{19}F NMR, alongside with the usual ^{1}H and ^{13}C array of NMR spectroscopic tools. The ^{19}F nucleus has quite favorable NMR properties ($I = 1/2$, 100% natural abundance, high magnetogyric ratio, wide chemical shift range). As a result, ^{19}F NMR is a generally applied tool in such investigations; recent examples can be found in ref. 11 and 12. Often, the relatively small number of fluorine atoms in a given compound makes the assignment of the ^{19}F resonances straightforward. However, in general, the simpler the assignment the less informative is the NMR spectrum for the structural identification of the compound. On the other hand, the presence of several fluorine atoms may render spectral interpretation a non-trivial task.

Quantum chemical protocols based on density functional theory have proven to be of invaluable help in structural identification of organic molecules by comparison of predicted ^{1}H and ^{13}C NMR spectra of putative structures with the experimental data.[13–20] However, the prediction of fluorine chemical shifts by DFT methods is less developed. Indeed, inaccuracies in Kohn–Sham eigenvalues were reported to produce large errors in fluorine shieldings.[21] In a previous work,[22] we provided an overview of the developments in this field and carried out a systematic exploration of the performance of DFT methods for a wide range of fluorinated compounds, including inorganic and simple organic molecules, and showed that the main features of ^{19}F chemical shifts can be predicted across the range spanned by inorganic fluorine compounds (1300 ppm). It should be remarked that in most such cases only one fluorine atom is present and assignment is straightforward. On the other hand, many organofluorine compounds possess several fluorine atoms, often in similar or identical functional groups; obviously, this is the context where ^{19}F NMR would be most helpful for structure elucidation, and the demands on the computational end strictest.

Even though DFT predictions of ^{19}F chemical shift have been successfully applied to the structural identification of fluorinated organic compounds,[23,24] a matching systematic analysis concerning organic fluorine compounds, whose ^{19}F shifts lie in a much smaller range (*ca.* 300 ppm), has not yet been carried out. Therefore, in this work we present the results of DFT calculations of ^{19}F chemical shift for a wide variety of organic compounds and functional groups.

Computational section

All calculations were carried out with ADF and associated routines for NMR shieldings.[25] We have adopted the GGA BLYP functional[26–28] and a triple-zeta, twice-polarized Slater basis set (TZ2P), with the Zero-Order Regular Approximation (ZORA) at the scalar (ZSC) level for the optimization and Spin–Orbit (ZSO) level for the NMR calculation. Calculated shieldings are the sum of the diamagnetic, paramagnetic and spin–orbit terms

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($\sigma = \sigma_d + \sigma_p + \sigma_{SO}$), and chemical shifts are referenced to $CFCl_3$ ($\sigma_{ref} = 120$ ppm)[22] as $\delta_{calc.} = \sigma_{ref} - \sigma$. The results are evaluated from the statistical error of the least-squares regression $\delta_{calc.} = a + b\delta_{exp}$, the Mean Absolute Error ($MAE = \sum_i |\delta_i^{calc.} - \delta_i^{exp}|/n$) and the corrected MAE : CMAE $= |\delta_{calc.} - \delta_{fit}|/n$. The maximum deviation (MD) is the largest difference between an experimental and a calculated point while the corrected maximum deviation (CMD) is the largest distance between a calculated point and its projection on the linear fit line.

Results and discussion

We have selected a wide range of organic fluorinated compounds as shown in Table S1 of the ESI† with the aim of representing the most common environments in which fluorine can be found in organic molecules, and therefore the widest possible range of ^{19}F chemical shifts, from simple monofluorinated alkanes to aromatic compounds, polyfluorinated molecules and systems containing various heteroatoms, such as oxygen, nitrogen, silicon and the other halogens. Substituted benzotrifluorides (Ar–CF_3) were not considered because the ^{19}F shift varies very little (1 ppm at most) with the substituent, and this range was found to be too small compared with the generally attainable accuracy (see below).

The compounds considered have been loosely categorized as in ref. 29 (although the classification is blurred), as follows (R_F denotes an organofluorine group). (a) Fluoromethanes (−272 to 19 ppm); (b) fluoroethanes (−239 to −64.5 ppm); (c) fluoroethylenes (−205 to −66 ppm); (d) primary (RCH_2F, −232 to −206 ppm), (e) secondary (R_2CHF, −213 to −165 ppm) and (f) tertiary (R_3CF, −182 to −127 ppm) monofluorides; (g) primary ($RCHF_2$, −129 to −110 ppm) and (h) secondary (R_2CF_2, −149 to −84 ppm) geminal difluorides; (i) trimethylsilyl fluorides ($Me_3Si–R_F$, −277 to −58 ppm); (j) trifluoromethyl derivatives (CF_3, −93 to −49 ppm); (k) trifluoroacetyl and trifluoromethanesulfonyl derivatives ($CF_3C(O)$ and CF_3SO_2, −84 to −53 ppm); (l) monosubstituted fluorobenzenes (X–C_6H_4–F, −166 to −94 ppm); (m) other fluorobenzenes (−166 to −108 ppm); (n) miscellaneous compounds ($H_3Si–R_F$, PhO–R_F, PhS–R_F, −265 to −43 ppm). Experimental data were taken from ref. 29 and 30.

Chemical shifts therefore span a range of about 300 ppm, from the most shielded resonance of $(CH_3)_3SiCH_2F$ (−277 ppm) to the most deshielded one CF_2I_2 (18.6 ppm). This range, while much smaller than the full range including inorganic compounds (*ca.* 1300 ppm) is still wide if compared with the variation in functional groups. Given the large number of compounds investigated, numerical data are presented only in the ESI (Table S1a–n†) for brevity.

The general correlation between calculated and experimental chemical shifts is shown in Fig. 1. Broadly speaking, the performance of the computational protocol is satisfactory: for the 256 data considered, the overall correlation overestimates the shift by 15% with an offset of −17 ppm, and a mean absolute error of 35 ppm, *i.e.* 10% of the range considered.

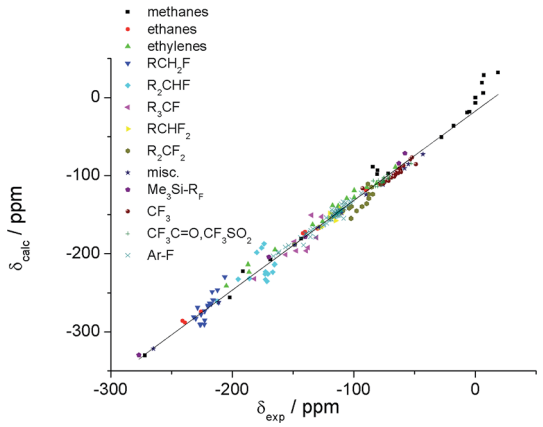


Fig. 1 Correlation between calculated and experimental ^{19}F chemical shifts. Solid line: linear fitting $\delta_{calc.} = a + b\delta_{exp}$. $a = -17 \pm 1$ ppm, $b = 1.15 \pm 0.01$, $R^2 = 0.9808$, MAE = 34.6 ppm, MD = 67.5 ppm, CMAE = 6.2 ppm, CMD = 37.6 ppm. The compounds are categorized as (see text): methane, ethane and ethylene derivatives; primary (RCH_2F), secondary (R_2CHF) and tertiary (R_3CF) monofluorides; primary ($RCHF_2$) and secondary (R_2CF_2) geminal difluorides; trimethylsilyl fluorides ($Me_3Si–R_F$); trifluoromethyl groups (CF_3); trifluoroacetyl and trifluoromethanesulfonyl derivatives ($CF_3C{=}O$, CF_3SO_2); aryl fluorides (Ar–F) and miscellaneous compounds. Data in Table S1.†

Some issues arise immediately. (a) Almost all the categories indicated above have overlapping shift ranges; therefore such indicators are not of major importance for the evaluation of these results. (b) While the correct range of shift is always predicted, the scatter of data points is noticeable.

Since the data set includes a diverse array of functionalities, we will discuss some of the classes of organofluorine compounds separately to highlight their issues. Several factors deserve analysis, *i.e.* relativistic effects caused by the heavy halogens Br and I, solvent, steric and conformational effects. These will be discussed in turn; however, whereas the classification mentioned above is chemically intuitive, it is more meaningful to dissect the data starting from the compounds that, in principle, present fewer problems in connection with the computed results. The discussion will then begin with fluoroarenes (l)–(n), which are conformationally rigid (although they may include polar substituents) and contain only light atoms. Conformational effects are best highlighted by firstly referring to rigid compounds, for which a single conformation is sufficient, and excluding both heavy halogens (which may be subject to relativistic effects) and polar functional groups (which are likely to show specific solvent effects).

Polyfluorinated benzenes (n)

These compounds are ideally suited for a computational validation, being completely rigid and non-polar while at the same time spanning a sizable 58 ppm range. Indeed, an excellent correlation is obtained (Fig. 2). Some items (tri-, tetra-fluorobenzenes and pentafluorobenzene) feature two or three signals from chemically non-equivalent fluorine atoms differing by at least 10 ppm, which are always predicted in the correct order.

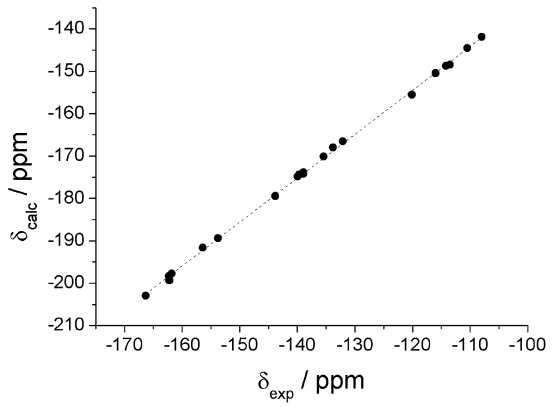


Fig. 2 Correlation between calculated and experimental ^{19}F chemical shifts for polyfluorobenzenes. $\delta_{calc.} = a + b\delta_{exp}$: $a = -30.2$ ppm, $b = 1.036$, $R^2 = 0.9993$, MAE = 35 ppm, CMAE = 0.4 ppm, MD = 37 ppm, CMD = 1 ppm. Data in Table S1(n).†

Fluoroarenes (l) and (m)

O*rtho*-, *meta*- and *para*-substituted fluorobenzenes were considered, including derivatives with polar, strongly solvated substituents. If one firstly considers the full group, only a fair correlation is obtained. It is then helpful to dissect the results according to the pattern of substitution: in *ortho* and *para* derivatives one expects a strong influence of the substituents, which should be attenuated in the *meta* position. *Ortho*-substituted fluorobenzenes (Fig. 3a), particularly those with a hydrogen-bond donor substituent (OH, COOH, NHR) show the highest deviation from the correlation line (*ca.* 10 ppm). It is likely that solvent effects contribute to the conformer population, which in turn affects the ^{19}F shift. Steric effects are also operating, as highlighted by the comparison with *para* derivatives (Fig. 3c) where the correlation is much better. The results for *meta* derivatives (Fig. 3b) are hardly correlated with experiment, because the spread of chemical shifts is only 4–5 ppm, *i.e.* below the attained statistical accuracy. Therefore no information, other than the correct prediction of the range, can be gained (for the same reason, we did not investigate benzotrifluorides).

Fluoromethanes (a)

The chemical shifts of fluoro(halo)methanes span the entire range of $\delta(^{19}F)$, from −271.9 ppm (CH_3F) to 18.6 ppm (CF_2I_2). Thus, starting from CH_3F, introduction of a fluorine (CH_2F_2) causes a strong deshielding ($\Delta\delta = 128$ ppm), the maximum effect being reached for CF_4 ($\Delta\delta = 210$ ppm). However, even a single iodine atom causes an 80 ppm deshielding in CH_2FI; in the series CF_2X_2 (X = F, Cl, Br, I) δ increases as −62, −6.8, 6.5, 19 ppm. Hence, iodine has the largest deshielding effect. The data are shown in Fig. 4. The correlation is only of fair quality despite the obvious rigidity of the compounds. The largest deviations occur for $\delta > -100$ ppm, *i.e.* in the region where Br and I fluorides resonate.

When dealing with compounds containing heavy atoms such as Br or I, it is important to recall that strong relativistic effects

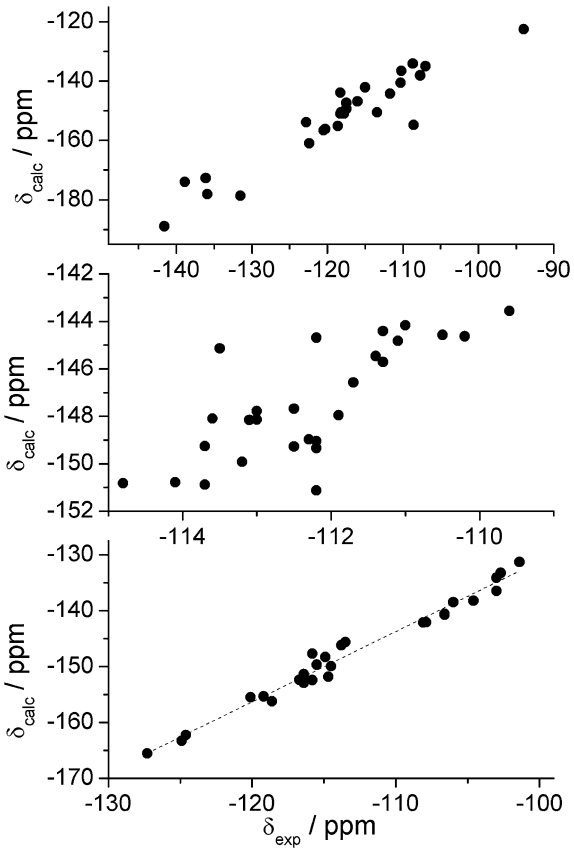


Fig. 3 Correlation between calculated and experimental ^{19}F chemical shifts for (top to bottom) *ortho*, *meta* and *para* monosubstituted fluorobenzenes. Fitting parameters for *para* derivatives: $\delta_{calc.} = a + b\delta_{exp}$: $a = -5.05$ ppm, $b = 1.261$, $R^2 = 0.9752$, MAE = 34 ppm, CMAE = 1 ppm, MD = 38 ppm, CMD = 3 ppm. Data in Table S1(l) and (m).†

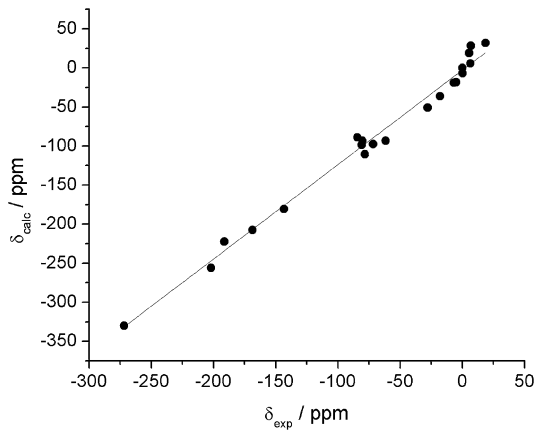


Fig. 4 Correlation between calculated and experimental ^{19}F chemical shifts of fluorohalomethanes. Solid line: linear fitting $\delta_{calc.} = a + b\delta_{exp}$. $a = -3 \pm 3$ ppm, $b = 1.21 \pm 0.03$, $R^2 = 0.9856$, MAE = 20.6 ppm, MD = 58.2 ppm, CMAE = 9.1 ppm, CMD = 22.7 ppm. Data in Table S1(a).†

may arise in the resonance frequencies of other nuclei; large shielding effects (*i.e.* very negative chemical shifts compared to those for analogues with light atoms) are often found for atom nuclei directly bonded to a heavy atom; *e.g.* $\delta(^{13}C) = -293$ ppm

in CI_4, often called "normal halogen effect". In such cases, inclusion of spin–orbit coupling in the Hamiltonian is mandatory.[31–36] The magnitude of σ_{SO} can be traced to the *s* character of the bond between the light and the heavy atom.[31,32] However, contrary to what happens with ^{13}C, relativistic effects on ^{19}F shifts in the F–C–X arrangement of fluoromethanes are only modest; the spin–orbit contribution to the shielding (σ_{SO}) amounts to 1–5 ppm, *i.e.* 5% of σ at most, as expected for bonds with small *s* character. In any case, $\sigma_{SO} > 0$ like in the case of ^{13}C, as expected for high-lying occupied orbitals with π local symmetry of the bond connecting the heavy atom and the observed nucleus.[37,38] The small absolute values of σ_{SO} do not warrant a more detailed analysis.

Indeed, the spread of shieldings observed is essentially due to changes in the paramagnetic term (σ_p). Therefore, ^{19}F shifts, even in polyiodoalkanes, are hardly affected by heavy-atom effects and can be predicted with fair accuracy even without taking relativistics into account. This recognition opens the possibility of running non-relativistic calculations with other software as well.

Miscellaneous rigid compounds

This subset of data, comprising methane and ethylene derivatives, secondary and tertiary monofluorides, some primary geminal difluorides, and trimethylsilyl fluorides (see Fig. 5) exhibits a higher correlation coefficient ($R^2 = 0.99$), and the main statistical parameters are somewhat improved (CMAE = 4 ppm). This indicates that conformational issues play some role in general. However, the largest deviations are observed for rigid molecules such as 1-fluorobicyclo[2.2.1]heptane, 1-fluorobicyclo[2.2.2]octane and cyclohexyl fluoride, where conformational effects can hardly be invoked.

Conformationally flexible compounds

This heterogeneous category includes fluoroethanes (b), all monofluorides (d)–(f) and geminal difluorides (g) and (h), trifluoromethyl (j), trifluoroacetyl and trifluoromethanesulfonyl (k) derivatives. For all such compounds, the ^{19}F shift was calculated only for a single conformation obtained by geometry optimization. Remarkably, the correlation for fluoroethanes is good across 176 ppm, probably owing to the limited number of significant conformations. For monofluorides the correlation is rather poor, owing in part to the small shift range spanned (<50 ppm). The remaining categories give fair or good correlations, each spanning 30–50 ppm. These however include many polar molecules, for which one can expect strong medium effects on ^{19}F shifts. Two significant outliers are CF_3NH_2 and $(CF_3)_2C(OH)_2$; for these unstable or strongly polar compounds the experimental conditions under which the spectra were obtained may have to be carefully evaluated; for this reason they are not included in the correlation of Fig. 6.

Overall, with few exceptions the theoretical level we have adopted can, at least, pinpoint the correct range of ^{19}F chemical shift in a wide variety of organofluorine compounds. The predictions are understandably better if one only considers structurally related, rigid, non-polar molecules. Whereas such problems are invariably encountered in all investigations of NMR chemical shifts, such effects are prominent in the case of ^{19}F.

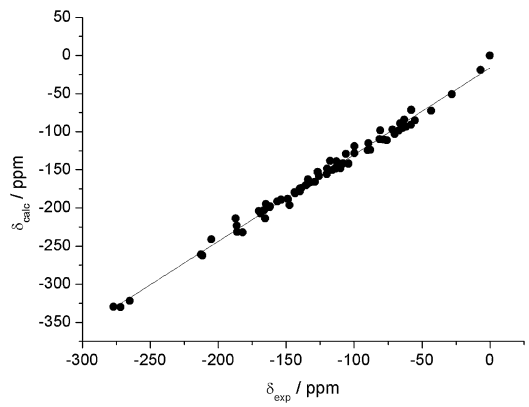


Fig. 5 Correlation between calculated and experimental ^{19}F chemical shifts of miscellaneous rigid compounds. Solid line: linear fitting $\delta_{calc.} = a + b\delta_{exp}$. $a = -16 \pm 2$ ppm, $b = 1.14 \pm 0.01$, $R^2 = 0.9908$, MAE = 33.5 ppm, MD = 58.2 ppm, CMAE = 4.0 ppm, CMD = 13.6 ppm. See text for data sources.

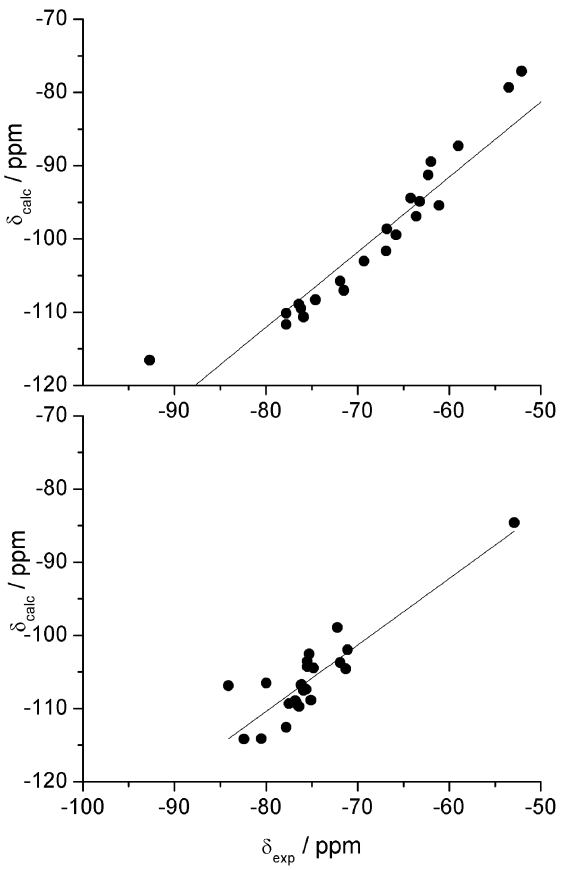


Fig. 6 Correlation between calculated and experimental ^{19}F chemical shifts. Top: 1,1,1-trifluoroethanes and miscellaneous CF_3-compounds. Solid line: linear fitting $\delta_{calc.} = a + b\delta_{exp}$. $a = -30 \pm 5$ ppm, $b = 1.03 \pm 0.08$, $R^2 = 0.8877$. Bottom: trifluoroacetyl and trifluoromethanesulfonyl compounds. Solid line: linear fitting $\delta_{calc.} = a + b\delta_{exp}$. $a = -38 \pm 8$ ppm, $b = 0.9 \pm 0.1$, $R^2 = 0.7658$. See text for data sources.

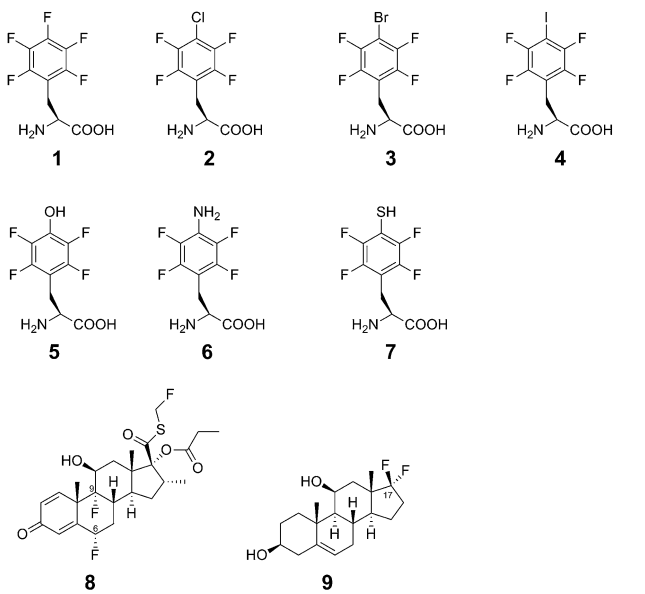
While there is room for improvement, even at this stage it seems possible to address issues in the structural chemistry of fluorine compounds; hereafter we shall present some examples of application in problems related to biological chemistry and drug development. Several fluorinated drugs have been synthesized[2] and ^{19}F NMR spectroscopy is a powerful tool to trace their metabolism, owing to the ease of detection and to the absence of natural sources of fluorine in biological fluids and tissues which may interfere or overlap with the resonances of interest. On the other hand, ^{19}F can also be used in structural assignment of novel drugs as it has been shown recently in ref. 39 and 40.

Fluorophenylalanines and fluorinated steroids

Fluorinated aminoacids are often incorporated in synthetic proteins to improve their stability.[41] Qin *et al.*[39] have synthesized a series of *para*-substituted tetrafluorophenylalanines and investigated their ^{19}F spectroscopic signatures. Their chemical shifts in chloroform range from about −120 to −160 ppm (small solvent effects have been observed in methanol and will not be considered). In Scheme 1 we show the model systems **1–7** used for the calculations (the *Fmoc* and *Boc* protecting groups have not been considered).

Ampt *et al.*[40] have used ^{19}F NMR spectroscopy for the identification of fluorinated steroids, including the drug fluticasone propionate (**8**) and a challenging derivative with two diastereotopic fluorine atoms (**9**). These two compounds have also been investigated computationally herein.

Experimental and calculated chemical shifts are collected in Table 1, while the correlation is shown in Fig. 7. The correlation for the fluorophenylalanines is particularly good; the three resonances that are slightly offset compared to the others are those of the fluorine nuclei in the *meta* position of compounds **5**, **6** and **7**, where hydrogen bonding to the *para* substituent may play some role, but all signals are predicted in the correct sequence. It is noteworthy that the fitting line of this subset of data is very close to the fitting line of the calibration set shown in Fig. 1. We can therefore inspect the outcome of the application of the linear relation derived from the calibration set. If we estimate the chemical shift, δ_{est}, using the linear fitting parameters of Fig. 1 and the DFT predicted values for the set of fluorophenylalanines and fluorinated steroids (*i.e.* assuming that the experimental chemical shifts are unknown) we obtain the values reported in Table 1. The agreement is very good, the MAE being just 1.8 ppm, and even the relatively small difference between *ortho* and *meta* fluorine nuclei in **2** is correctly predicted. Therefore the computational protocol appears



Scheme 1 Fluoroalanines and fluorinated steroids.

Table 1 Experimental and calculated ^{19}F chemical shifts of fluoroalanines and fluorinated steroids **1–9**

Compound	δ_{exp}	σ	$\delta_{calc.}$	δ_{est} [a]
1 o	−142.0	300.0	−180.0	−141.7
1 m	−161.5	322.3	−202.3	−161.1
1 p	−154.4	315.0	−195.0	−154.8
2 o	−141.3	299.3	−179.3	−141.1
2 m	−140.7	297.5	−177.5	−139.6
3 o	−140.8	298.3	−178.3	−140.3
3 m	−133.0	289.0	−169.0	−132.2
4 o	−140.2	297.3	−177.3	−139.4
4 m	−120.1	274.4	−154.4	−119.5
5 o	−144.8	302.5	−182.5	−144.0
5 m	−163.4	328.0	−208.0	−166.1
6 o	−145.3	304.7	−184.7	−145.8
6 m	−161.5	326.5	−206.5	−164.7
7 o	−142.2	300.7	−180.7	−142.3
7 m	−137.3	298.4	−178.4	−140.4
8 F9α	−164.6	320.3	−200.3	−159.4
8 F6α	−186.7	356.8	−236.8	−191.1
8 SCH_2F	−192.0	358.7	−238.7	−192.7
9 F17α	−100.8	259.3	−139.3	−106.3
9 F17β	−113.6	272.9	−152.9	−118.2

[a] Chemical shifts estimated using the linear fitting parameters of Fig. 1 and the reported σ values.

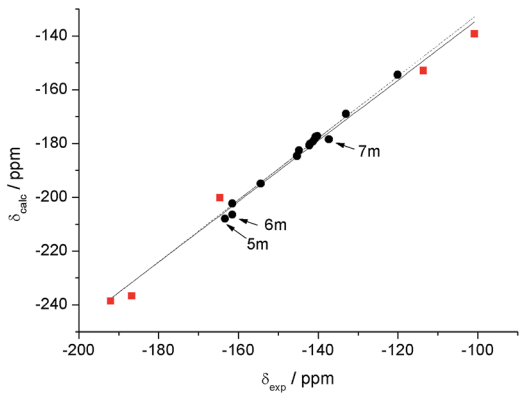


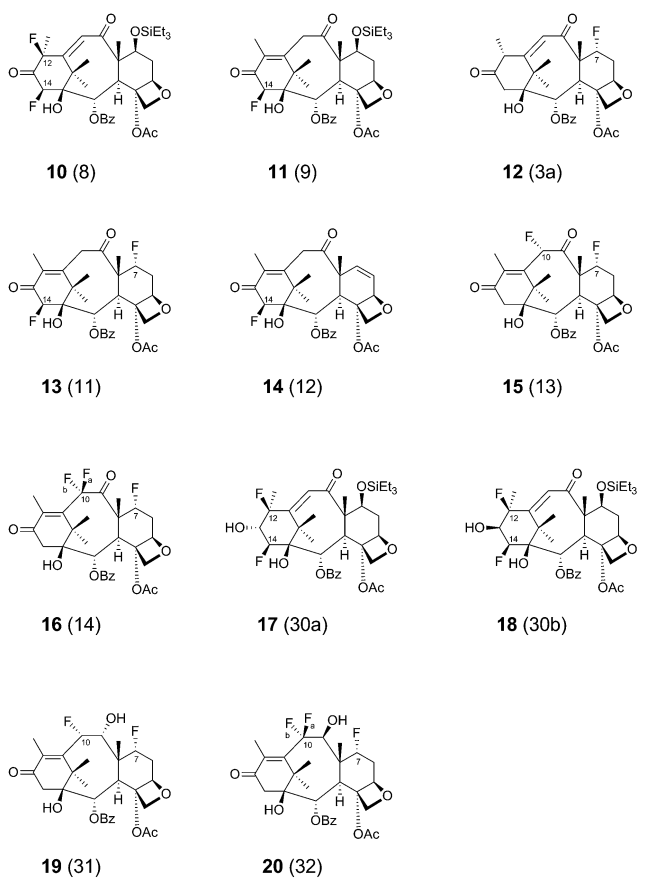
Fig. 7 Correlation between calculated and experimental ^{19}F chemical shifts of *para*-substituted tetrafluorophenylalanines **1–7** (black circles) and fluorinated steroids **8** and **9** (red squares). Solid line: linear fitting $\delta_{calc.} = a + b\delta_{exp}$. $a = -21.1 \pm 4.5$ ppm, $b = 1.13 \pm 0.03$, $R^2 = 0.9861$. Dotted line: linear fitting of the complete calibration set of Fig. 1.

sufficiently robust for practical applications and assignments of ^{19}F resonances in organic molecules.

Fluorinated taxoids

As a further application we will consider some fluorinated taxoid compounds, effective against cancer, that have been recently investigated by Nicolaou and Valiulin.[42] The compounds selected are shown in Scheme 2; in some cases they were obtained as mixtures. Although ^{1}H and ^{13}C NMR were sufficient to identify the structures, ^{19}F NMR would have been a valuable help; experimental ^{19}F data are not available. Therefore, we present these data as a possible application to the structural elucidation of new fluorinated biologically active compounds.

Compounds **10** and **11** were obtained in mixture in similar yield; compounds **13**, **14** and **15** were also obtained in mixture by reacting **12** with Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane); **16** was obtained from **15** and exhibits a germinal F_2 pair; **17** and **18** were obtained in *ca.* 1 : 2 mixture by reducing **10**; **19** and **20** were obtained by reduction of **15** and **16**, respectively.[42] Hence, this set of molecules offers an intriguing selection of similar chemical environments of fluorine atoms to test the capability of the computational protocol to discriminate the different resonances. The results are reported in Table 2.



Scheme 2 Fluorinated taxoids. Compound numbers in parentheses are those of the original paper (ref. 42).

Table 2 Calculated ^{19}F chemical shifts of fluorinated taxoids **10**–**20**[a]

Compound[a]		$\delta_{calc.}$	δ_{est}[b]
10 (8)	F12	−162.6	−126.6
	F14	−257.8	−209.4
11 (9)	F14	−232.8	−187.7
12 (3a)	F7	−207.2	−165.4
13 (11)	F7	−206.2	−164.5
	F14	−232.8	−187.6
14 (12)	F14	−231.9	−186.9
15 (13)	F7	−203.7	−162.3
	F10	−213.9	−171.2
16 (14)	F7	−212.5	−170.0
	F10a	−123.9	−93.0
	F10b	−127.8	−96.3
17 (30a)	F12	−158.1	−122.7
	F14	−241.9	−195.6
18 (30b)	F12	−184.6	−145.7
	F14	−253.0	−205.2
19 (31)	F7	−207.5	−165.7
	F10	−246.6	−199.7
20 (32)	F7	−208.4	−166.4
	F10a	−117.2	−87.1
	F10b	−120.3	−89.8

[a] Compound numbers in parentheses are those of the original paper (ref. 42). [b] Chemical shifts estimated using the linear fitting parameters of Fig. 1 and the reported σ values.

In addition to the DFT predicted values we also report in Table 2 the estimated "experimental" values based on the linear regression of the calibration set of Fig. 1. Fluorine at position 14 (F-14) exhibits a significant variation from **10** to **11** and from **10** to **17** and **18**, while in **11**, **13** and **14** (which differ in a remote position compared to position 14), the chemical shift of F-14 is essentially constant around −187 ppm. Geminal fluorines in **16** and **20** are quite similar; a deshielding of about 6 ppm is observed in the calculated values upon reduction of the carbonyl in position 9 of **16** to give compound **20**. Interestingly, the reduction of the same carbonyl in the analogous compound **15** (where there is only one fluorine in position 10 of the carbon skeleton) to obtain **19**, causes a large shielding of about 30 ppm of the fluorine in position C10, in contrast to the effect observed in the **16**/**20** pair. Finally, depending on the arrangement of the hydroxyl on carbon C13 a significant shift is observed in both F-12 and F-14 when comparing compound **10** with **17** and **18**. Therefore, DFT predictions allow to distinguish the slightly different chemical environments of fluorine in these compounds (or mixtures thereof), and can be envisioned as a valuable help in their structure determination.

Conclusions

The calculation of ^{19}F chemical shifts in organic molecules can be performed with the BLYP functional with satisfactory accuracy; overall, the data are correlated with experiment to within 6 ppm, *i.e.* with an error comparable with the typical spread of experimental data. The influence of relativistic effects on fluoromethanes substituted with heavy halogens (Br, I) has been examined and found to be modest. The attainable accuracy

strongly depends on the conformational flexibility; hence, in rigid compounds such as fluorobenzenes the data define correlation lines with corrected mean absolute errors of <1 ppm, except where steric effects are present. The computational protocol has then been tested for the prediction of experimental fluorine chemical shifts first on a set of organic compounds recently investigated, whose NMR data were available, and found to perform very well. Then it has been employed for the prediction of $\delta(^{19}F)$ of fluorinated taxol derivatives for which experimental data are not available. The chemical shifts derived either from the DFT calculations or from the empirical correlation parameters show an appreciable distribution of values which would allow an easy identification of the taxol derivatives even in mixtures.

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