

Determination of size and sign of hetero-nuclear coupling constants from 2D ^{19}F – ^{13}C correlation spectra

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ABSTRACT

Fluorinated organic compounds have become increasingly important within the polymer and the pharmaceutical industry as well as for clinical applications. For the structural elucidation of such compounds, NMR experiments with fluorine detection are of great value due to the favorable NMR properties of the fluorine nucleus. For the investigation of three fluorinated compounds, triple resonance 2D HSQC and HMBC experiments were adopted to fluorine detection with carbon and/or proton decoupling to yield F–C, F–C{H}, F–C{C_{acq}} and F–C{H,C_{acq}} variants. Analysis of E.COSY type cross-peak patterns in the F–C correlation spectra led, apart from the chemical shift assignments, to determination of size and signs of the J_{CH} , J_{CF} , and J_{HF} coupling constants. In addition, the fully coupled F–C HMQC spectrum of steroid **1** was interpreted in terms of E.COSY type patterns. This example shows how coupling constants due to different nuclei can be determined together with their relative signs from a single spectrum. The analysis of cross-peak patterns, as presented here, not only provides relatively straightforward routes to the determination of size and sign of hetero-nuclear J-couplings in fluorinated compounds, it also provides new and easy ways for the determination of residual dipolar couplings and thus for structure elucidation. The examples and results presented in this study may contribute to a better interpretation and understanding of various F–C correlation experiments and thereby stimulate their utilization.

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1. Introduction

The interest in fluorinated organic compounds has become increasingly important not only within the polymer industry but also within the pharmaceutical industry and for clinical applications [1–4]. For the characterization of chemical structures and thus of those fluorinated compounds, NMR spectroscopy plays a pivotal role; this holds true as well for the analysis of configurations and for the determination of the tacticity of polymers [5–7]. While fluorine NMR has been used for 50 years to correlate chemical shifts and coupling constants to structures of fluorinated compounds, the application of residual dipolar couplings (RDCs) based on fluorine couplings is still a novelty [8–10]. Although proton and carbon NMR are used more commonly for structure elucidation, fluorine NMR has several benefits as recently summarized

[11]. The ^{19}F nucleus has various favorable properties for NMR experiments, such as a high sensitivity which is comparable to that of protons, its natural abundance of 100% and its large spectral dispersion [12–14]. 2D fluorine NMR has long been hampered by instrument limitations, but with modern instrumentation its use can become routine and hence has been growing steadily [4,15–21].

We became interested in the full exploitation of the information content of 2D ^{19}F – ^{13}C correlation spectra when we performed studies to assign diastereotopic fluorine substituents and to elucidate the configuration of fluorinated steroids such as compound **1** of Fig. 1 [11]. In the following study, we selected, along with **1**, compounds **2** and **3** as illustrative examples for the analysis of ^{19}F – ^{13}C correlation spectra (Fig. 1). Compounds **2** and **3** are potentially interesting in the field of polymerization reactions [22,23].

Newmark and Webb studied fluorinated compounds using different types of HSQC and HMBC experiments [17]. In their spectral analysis, the ^1H – ^{19}F coupling present in one of the spectra was considered a spectral complication and also ‘missing’ correlations were mentioned. However, these absent correlations are the result of a reduced multiplet, also known as the E.COSY pattern, and in

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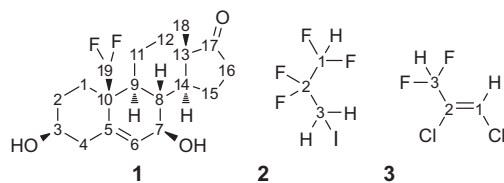


Fig. 1. Structures and numbering of compounds 1–3.

fact provide additional information permitting the determination of the relative sign of couplings [4,24–28].

In this study, we will analyze the coupling patterns in cross-peaks in ^{19}F – ^{13}C HMQC, HSQC and HMBC spectra of the fluorinated compounds **1**, **2**, and **3**. For the small model compounds, the correlation signals in the HSQC experiment shall be interpreted by using proton and/or carbon decoupling. For this purpose, the H–C{N} HSQC and HMBC experiments are translated to the equivalent F–C{H/C} experiments. Extraction of the spectral parameters is demonstrated exemplarily for compounds **2** and **3**. As a more complex example, the fully coupled F–C HMQC of the steroid **1** is interpreted in terms of the E.COSY pattern. Therefore, a full analysis of the signal multiplicity is carried out. In summary, numerous coupling constants together with their signs are obtained, information which can be further exploited for the elucidation of the compounds structure and stereochemistry.

2. Results and discussion

Compounds **2** and **3** are used as models for the illustrative analysis of F–C correlation spectra. The full determination of the hetero-nuclear couplings of compounds **2** and **3** presented here by us led to a re-assignment of the previously reported partial set of couplings [29,30]. For this complete assignment, ^1H , ^{13}C and ^{19}F spectra were recorded and chemical shifts and couplings determined. They are given in the supplementary information. NMR data of compound **1** have been published recently [11]. We present here a complete assignment of hetero-nuclear couplings in terms of size and sign determined via a single fully-coupled 2D F–C NMR spectrum.

The use of triple resonance 2D sequences, e.g. H–N/C{C_{acq},N_{acq}} HSQC that is an HSQC with H–N or H–C correlation, H acquisition and decoupling of ^{13}C and ^{15}N during acquisition, is a method common to protein or nucleic acid NMR [31,32]. We will use the following notation for these triple resonance 2D sequences: F–C{H,C_{acq}}: F–C correlation with F acquisition and decoupling of H during the whole pulse sequence and C decoupling during acquisition. In brief, the first letter indicates the nucleus on which acquisition takes place, the second letter the indirect dimension, between curly brackets decoupling is indicated such that without a subscript the decoupling is turned on during the whole sequence, while the subscript ‘acq’ means that decoupling is only turned on during the acquisition. It is straightforward to apply these triple resonance 2D pulse sequences to fluorine detection, provided the NMR spectrometer has a suitable probe and frequency configuration. A triple resonance HSQC sequence with fluorine detection and carbon correlation and optional proton and carbon decoupling during acquisition (F–C{H,C_{acq}} HSQC) is exemplarily shown in Fig. 2. Several investigators have published on utilization of 2D F–C and 3D F–H–C correlation spectra [5–7,19,20,33,34] but this is – to the best of our knowledge – the first report on a triple resonance version of the HSQC used with fluorine detection. For a F–H{C,H_{acq}} HSQC the proton and carbon channels would need to be exchanged. However, the F–H{C,H_{acq}} HSQC is of lesser importance for small molecules because it does not detect proton-free carbons.

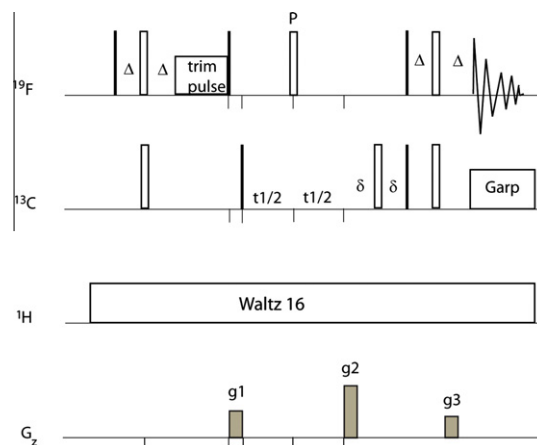


Fig. 2. Pulse sequence diagram for 2D ^{19}F – ^{13}C HSQC with ^{13}C and ^1H decoupling. Solid and open pulses are 90° and 180° pulses respectively. Alternatively the sequence can be run without the trim pulse.

F–C{H,C_{acq}} HMBC and F–C{H} HMBC, providing F–C correlations over multiple bonds, are of considerable value and straightforward to implement.

As a general observation, even the experimentally simpler variants of the triple resonance 2D sequences, simpler with respect to the hardware configuration of the spectrometer, are still not used to its full advantage. As will be demonstrated, the use of triple resonance experiments is very useful to simplify a spectrum by a combination of different ways of decoupling, but can also be used to attribute the couplings and determine their size and sign in a fully coupled spectrum by analyzing the E.COSY cross-peak patterns, as shown in the current investigation.

The ‘fully coupled’ ^{19}F – ^{13}C HSQC of compound **2** (F–C HSQC) is shown in Fig. 3. We define ‘fully coupled’ as a spectrum recorded with decoupling modes turned off resulting in the maximum number of couplings visible from the pulse sequence. It is immediately possible to distinguish the signals of the fluorine atoms at carbon 1 from those at carbon 2, since the signals corresponding to the fluorine atoms at position 1 show an extra splitting, $^2J_{\text{HF}}$, and displacement due to the geminal proton, when compared to the other fluorine atoms’ signals in the spectrum.

The enlarged region in Fig. 3 presents different decoupled versions of the F–C HSQC. The ‘fully’ ^1H , ^{13}C -coupled F–C HSQC spectrum (F–C HSQC; blue) shows four cross-peaks, while in the fully ^1H , ^{13}C decoupled F–C HSQC spectrum (F–C{H,C_{acq}} HSQC, black) only one signal is observed. The ^{13}C decoupled spectrum that is ^{13}C decoupled during acquisition (F–C{C_{acq}} HSQC) is shown in green¹ and the spectrum that is ^1H decoupled in the indirect and acquisition dimensions (F–C{H} HSQC) is given in red. For the acquisition of the four spectra under investigation, the pulse sequence in Fig. 2 was used. Decoupling on the proton and carbon channels, with carbon decoupling only during acquisition, was selected according to the target spectrum type and was achieved by setting the decoupling either to a finite value or turned off. Note further that the 180° fluorine pulse marked P in Fig. 2 eliminates J_{CF} couplings in the carbon dimension, since it decouples ^{19}F in the indirect dimension. Thus, no J_{CF} couplings are observed in this direction in any of the four subspectra.

In most cases, the resulting correlations are E.COSY patterns and the decoupling simplifies the splitting pattern on the F–C correlation peak. By spectral comparison of the four spectra, it is then quite easy to determine the origin of all the couplings. The carbon

¹ For interpretation of color in Figs. 2–6, the reader is referred to the web version of this article.

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