Proton, Carbon-13 and Fluorine-19 NMR Studies of 9,10,11,12-Tetrafluoro-5,6-dihydrobenzo[*b*]naphth[2,1-*f*]oxepin: 'Through-Space' Carbon-Fluorine Coupling Was Revealed

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The ^{1}H, ^{13}C and ^{19}F nmr spectra of 9,10,11,12-tetrafluoro-5,6-dihydrobenzo[*b*]naphth[2,1-*f*]oxepin (**1**) were totally assigned using a combination of two-dimensional nmr techniques. Unequivocal interpretation of the spectral data allowed the complete assignments of the resonances. In addition, the spectra of compound **1** revealed an unusual through-space carbon-fluorine coupling which was further supported by NOE and modeling experiments.

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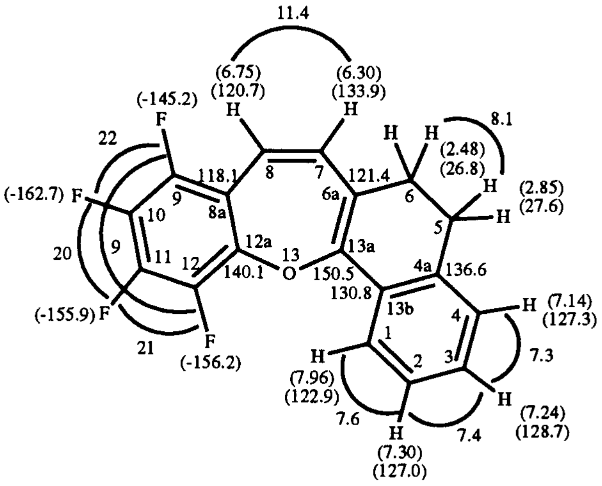
We have recently reported a novel oxepin heterocyclic ring system: namely 9,10,11,12-tetrafluoro-5,6-dihydrobenzo[*b*]naphth[2,1-*f*]oxepin (**1**) [1] and in this article the use of ^{1}H, ^{13}C and ^{19}F 2D experiments to assign the spectra and determine the structure of this compound is reported. In addition, the spectra of compound **1** showed an unusual through-space ^{19}F-^{13}C coupling and the techniques used to elucidate this feature is discussed in detail.



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Proton and fluorine data of compound **1** is given in Table 1. It was clear from chemical shifts and coupling constants that the protons and fluorines could be divided into four separate spin systems with no appreciable coupling between them. The first four protons are clearly on sequential carbons in an aromatic ring. The second spin system is composed of two pairs of aliphatic protons and the third system is two vinyl protons. There is appreciable coupling within each spin system showing that the protons are on adjacent carbons. There is no measurable coupling between different spin systems, they are isolated by at least one non-protonated atom. The fourth spin system consist of four aromatic fluorines which are on adjacent carbon atoms as shown by the size of the fluorine-fluorine coupling constants.

Table 1

Proton and Fluorine Data of Compound 1

Position Spin System 1	Chemical Shift Proton	Fluorine	Coupling
1	7.96		7.6
2	7.24		7.4, 7.6
3	7.30		7.3, 7.4
4	7.14		7.3
Spin System 2			
5,5'	2.85		8.1
6,6'	2.48		8.1
Spin System 3			
7	6.30		11.4
8	6.75		11.4
Spin System 4			
9		-145.2	22, 9
10		-162.7	20, 22
11		-155.9	21, 20
12		-156.2	21, 9

The structure was solved by determining how these four spin systems were linked together. Most of the information for doing this was obtained from ^{1}H-^{13}C one bond and multiple bond correlation's. The data is summarized in Table 2 and includes 38 multiple bond correlations. Of these, the seven key correlations needed to link the spin systems together are shown in Figure 1. The proton on carbon 8 was the only one to show a correlation to a fluorinated carbon. This puts the vinyl group adjacent to the fluorinated aromatic ring, a result confirmed by NOE measurements discussed below. The second vinyl proton (7) showed an important correlation to a non-protonated sp2 carbon with a very large down field shift (C13a) showing that the two vinyl groups are adjacent. This same proton is also correlated to one of the two protonated aliphatic carbons (C6) and those aliphatic protons are in turn correlated to the vinyl carbon (C7). This plus the supporting correlation to C6a, show that the vinyl and aliphatic spin systems are adjacent, separated by a single non-protonated carbon, C6a.

Table 2

Resonance Assignments for Compound 1

Position	Chemical Shift (ppm) Proton	Fluorine	Carbon	Long-Range Correlations
1	7.96		122.9	H3, H1, F12
2	7.24		127.0	H4, H2
3	7.30		128.7	H3, H1
4	7.14		127.3	H5, H4, H2
4a	136.6			H6, H5, H1
5	2.85		27.6	H6, H5, H4
6	2.48		26.8	H7, H6, H5
6a			121.4	H8, H6, H5
7	6.30		133.9	H8, H7, H6
8	6.75		120.7	H8, F9
8a			118.1	H8, H7, F11, F9
9		-145.2	143.0	
10		-162.7	137.9	
11		-155.9	141.6	
12		-156.2	140.3	
12a			140.1	H8
13a			150.5	H7, H6, H1
13b			130.8	H5, H4, H2

The aliphatic protons on C5 are correlated to one of the protonated aromatic carbons (C4) and the corresponding aromatic proton (4) is correlated to C5. This establishes the aromatic system immediately adjacent to the aliphatic spin system. The other end of this aromatic spin system (proton 1) is correlated to C13a which completes the carbon backbone determinations. One oxygen is required from elemental analysis and its position was determined by chemical shifts of carbons 12a and 13a and the need to complete the valence of these carbons.

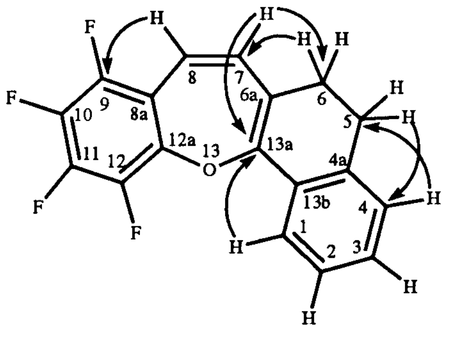

Figure 1. Key proton-carbon correlations needed to link the proton spin systems together.

Once the structure was determined it was obvious that there was an unusual feature in the ^{13}C spectrum. Carbon 1 showed a 5.5 Hz splitting even though the spectrum was fully proton decoupled. This had to be a fluorine coupling but it seemed implausible that a coupling of this size would be transmitted through the intervening six bonds. To investigate this feature further and to complete the fluorine assignments some ^{19}F spectra were taken. The first was a ^{19}F-^{13}C correlation spectrum with the delays optimized for a coupling constant of 270 Hz. This measurement is made with the decoupler nucleus set to fluorine but otherwise it is the same as an ordinary ^{1}H-^{13}C HETCOR. This spectrum allowed the correlation of each fluorine with its directly bonded carbon. The results are included in Table 2 and they help complete the ^{13}C assignments and support the structural assignment made above.

The spectrum shown in Figure 2 is a long range ^{19}F-^{13}C correlation spectrum obtained with conditions optimized for a 6 Hz coupling. The 1D carbon spectrum plotted along the side of the 2D spectrum is a standard proton decoupled ^{13}C spectrum. The 2D data however was collected with ^{19}F decoupling and therefore the 2D spectrum is proton coupled and shows all of the proton splitting. The correlations obtained from this spectrum are given in Table 2 and they support the structure obtained by providing additional data verifying the connection of the F9-F12 and H7-H8 spin systems.

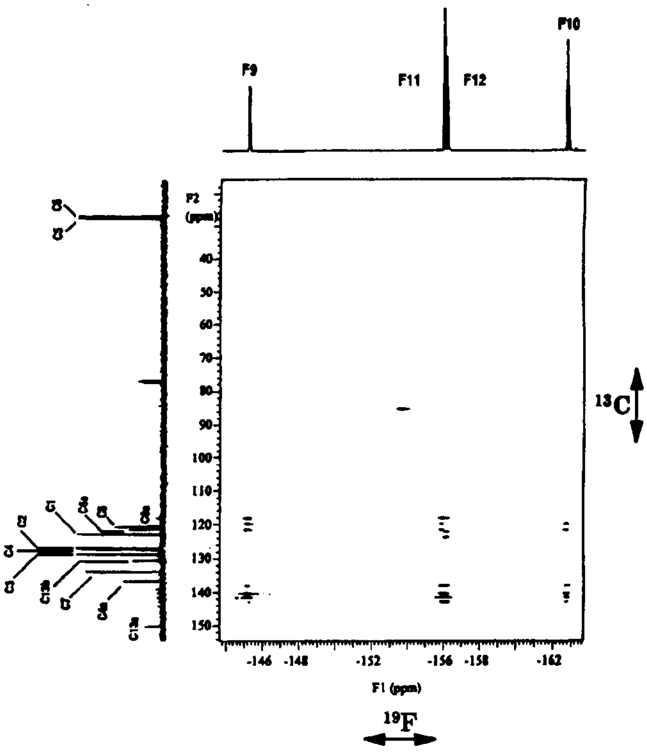

Figure 2. Long-range, ^{19}F-^{13}C heteronuclear chemical shift correlation spectrum of 1 recorded in deuteriochloroform.

Figure 3 is the part of the spectrum which shows the crucial correlation between F12 and C1. The peak of interest is split into a doublet by the one bond proton-carbon coupling as explained above. For that reason it is the center of the two peaks which aligns with C1 and correlates it with F12. This result shows clearly that C1 and F12 are coupled and explains the splitting of C1 in the proton decoupled ^{13}C spectrum is due to fluorine F12. Since F12 and C1 are six bonds apart it seemed implausible that the

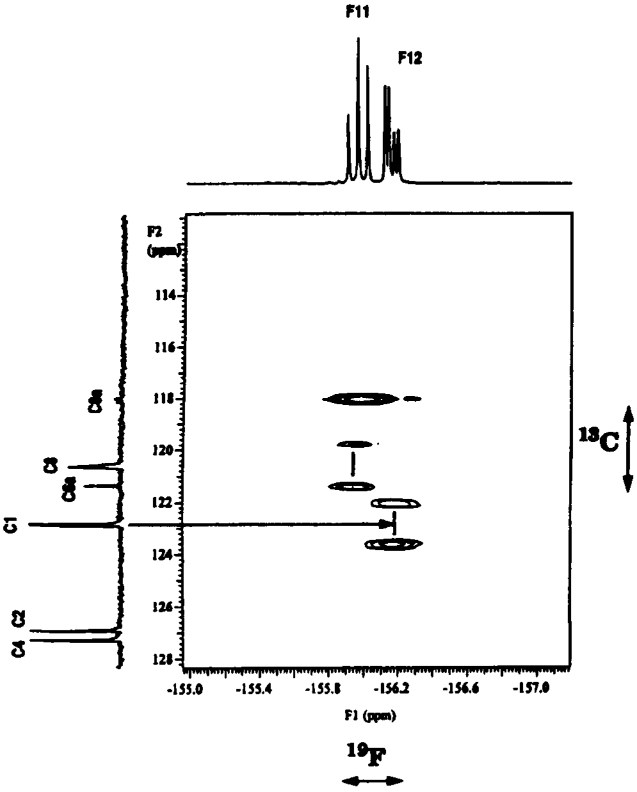

Figure 3. Expansion of long-range heteronuclear chemical shift correlation spectrum of 1 recorded in deuteriochloroform.

5.5 Hz coupling was a through bond coupling. While through space fluorine-carbon couplings are quite unusual, they are by no means unprecedented [2,3,4,5]. In fact, they are known to be quite strong when the fluorine and the proton on the affected carbon are close together in space.

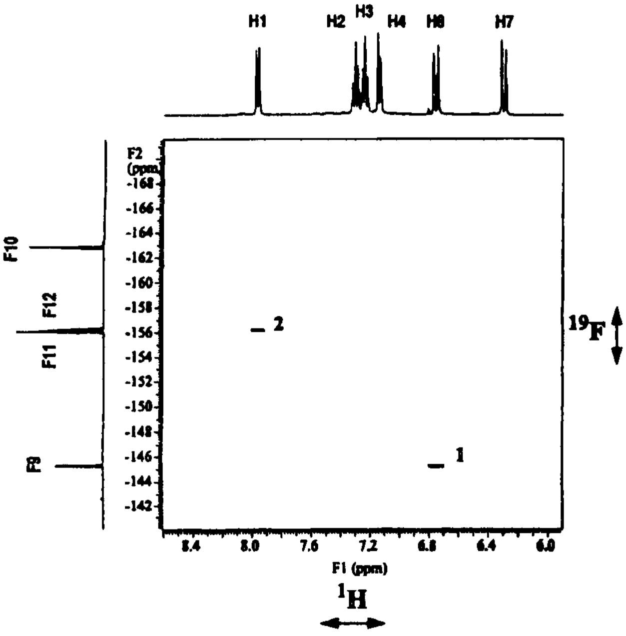

Figure 4. ^{1}H-^{19}F HOESY spectrum of 1 recorded in deuteriochloroform.

To check on ^{1}H-^{19}F spatial proximity a ^{19}F-^{1}H 2D NOE spectrum using the HOESY sequence was obtained. The full spectrum is shown in Figure 4 and it has two correlations. Peak 1 correlated H8 with the fluorine previously assigned to F9 based on ^{1}H-^{13}C long range correlations. This NOE supports that assignment and the immediate proximity of the F9-F12 and H7-H8 spin systems.

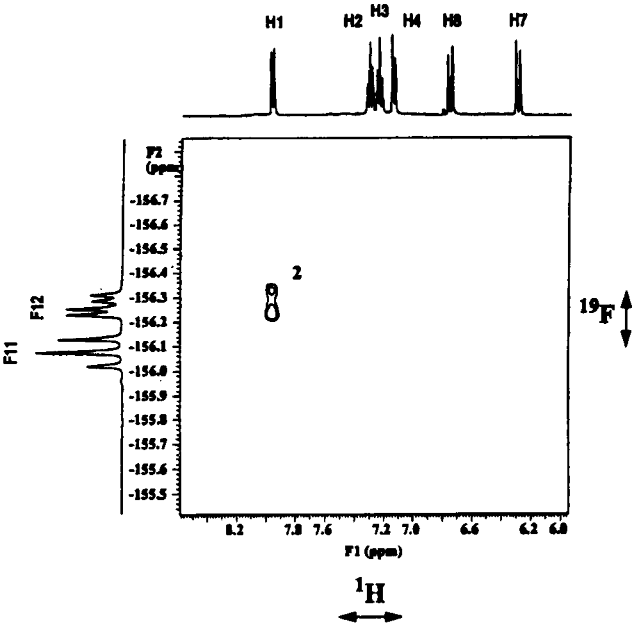

Figure 5. Expansion of ^{1}H-^{19}F HOESY spectrum of 1 recorded in deuteriochloroform.

Figure 5 is an expansion just showing the second NOE and that it in fact correlates H1 and F12. This verifies one of the requirements of the through space mechanism, namely that the fluorine and the proton on the carbon showing the through space interaction must be close together in space. The key correlations involving fluorine are summarized in Figure 6.

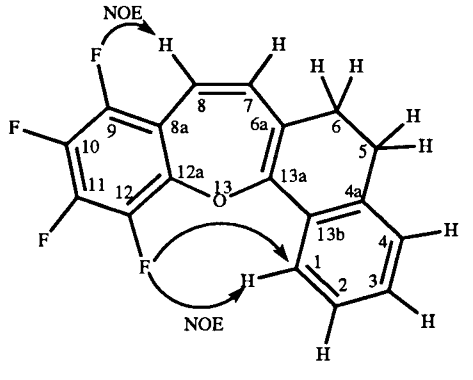

Figure 6. Key fluorine correlations of 1, two ^{1}H-^{19}F NOE's and a ^{19}F-^{13}C heteronuclear correlation.

To further probe this through space mechanism this molecule was modeled using SYBYL6.04 [6]. The key feature of the structure is that there is substantial puckering at the oxygen atom with the result that F12 and H1 are actually very close together (MM3 = 2.449A). This is well within the proximity required for the direct through-space interaction between the fluorine lone pair (donor) orbital and the σ^* (acceptor) orbital of the C-H bond which is believed to be the major contributor to the coupling.

In conclusion, the total assignment of the novel heterocyclic oxepin ring system **1** was determined using ^{1}H-^{13}C multiple bond correlations. The unusual through-space ^{19}F-^{13}C coupling was observed and verified through ^{19}F-^{13}C hetcor and ^{1}H-^{19}F NOESY experiments, along with molecular modeling to further support this phenomena.

EXPERIMENTAL

HOESY spectra [7] were collected using the pulse sequence D1 - PP_1 - t1 - PP_2 - MIX - PW - AT where PP_1 and PP_2 are fluorine 90 degree pulses. The proton pulse PW was set to a 90 degree pulse. The acquisition consisted of 128 increments of t1. The delay D1 was 4 seconds and the mixing time MIX was 1.5 seconds.

The fluorine-carbon HETCOR spectrum was taken using a standard HETCOR pulse sequence [8,9]. The decouple nucleus was set to fluorine, 64 t1 increments were used and recycling delay was 3 seconds. The delays were optimized for a 270 Hz fluorine-carbon coupling constant. For the longer range fluorine-carbon HETCOR, the delays were optimized for a one bond coupling constant of 270 Hz and a long rang coupling constant of 6 Hz. For the long range HETCOR 128 increments of t1 were used. The samples were dissolved in deuteriochloroform and the HOSEY and fluorine-carbon HETCOR spectra were measured on a Varian XL-300 using a Nalorac four nucleus probe (^{1}H, ^{19}F, ^{13}C, and ^{31}P) at a temperature of 25°.

The HC-COSY used heteronuclear COSY sequence which was an adaptation of the standard HC-COSY [10] using a low pass filter [11].

The pulse sequence was Dl - PP_1 - D2 - PW_1 - t1 - PP_2 - D4 - PW2 - D5- where PP_1 and PP_2 are fluorine 90 degree pulses and PW_1 and PW_2 are carbon 90 degree pulses. The relaxation delay D1 was 2 seconds, the low pass filter delay D2 was 3.3 milliseconds, the delay D3 used to evolve the smaller coupling constants was 62 milliseconds, and a refocusing delay D5 of 30 milliseconds was used. The delay included in the coherence transfer step D4 was 15 milliseconds. Since the desired proton magnetization during this delay time was longitudinal spin order it was possible to apply a 8 millisecond homospoil pulse during this 15 millisecond delay to minimize unwanted magnetization. The spectra were collected fully coupled, the carbon pulses were 14 microseconds, the proton pulses were 100 microseconds and 200 increments of t1 were used to digitize the F1 dimension. The data was collected on a Varian XL-400 spectrometer.

Modeling of this molecule was done using SYBYL6.04 [6]. Structures were generated using CONCORD3.0 [12] cleanup and optimized using both semi-empirical quantum mechanics and force field methods. For the semi-empirical quantum mechanics, optimization was performed using MOPAC93 [13] with the AM1 Hamiltonian and PRECISE keyword. For the force field calculations, MM3(92) [14] was employed. Missing torsional parameters were generated using our in-house automated parameter generation program [15].

REFERENCES AND NOTES

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