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^{13}C-NMR SPECTRA OF FLUORINATED MOLECULES USING ^{19}F-^{13}C POLARIZATION TRANSFER

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Abstract

^{13}C-NMR spectra of fluorinated molecules are difficult to observe under conventional broad-band proton decoupling. The large coupling constants involved make polarization transfer between fluorine and carbon, using INEPT or DEPT experiments very effective while broad band fluorine decoupling collapses the multiplet pattern.

^{13}C-NMR spectra of fluorinated compounds are difficult to obtain for several reasons. On the one hand, in the absence of directly bound protons, lack of nuclear Overhauser enhancement and slow relaxation rates can give very weak signals. On the other hand, coupling to fluorine reduces even more the intensity and can render spectra very cumbersome to interpret. The same problems would appear in protonated molecules but are solved in a routine way by using two types of double resonance techniques: broad-band decoupling collapses the multiplet pattern and the sensitivity is increased by dipolar interactions (nOe) or by polarization transfer between scalarly coupled protons and carbons [1]. Both approaches can be extended to the observation of ^{13}C-NMR spectra of fluorinated molecules. The use of fluorine broad-band decoupling employing a composite pulse sequence has just been descibed by V.Sklenář and Z.Starčuk [2]. In this paper we describe the use of polarization transfer techniques (DEPT[3] and INEPT[4]) applied to carbon-13 nuclei coupled to fluorine.

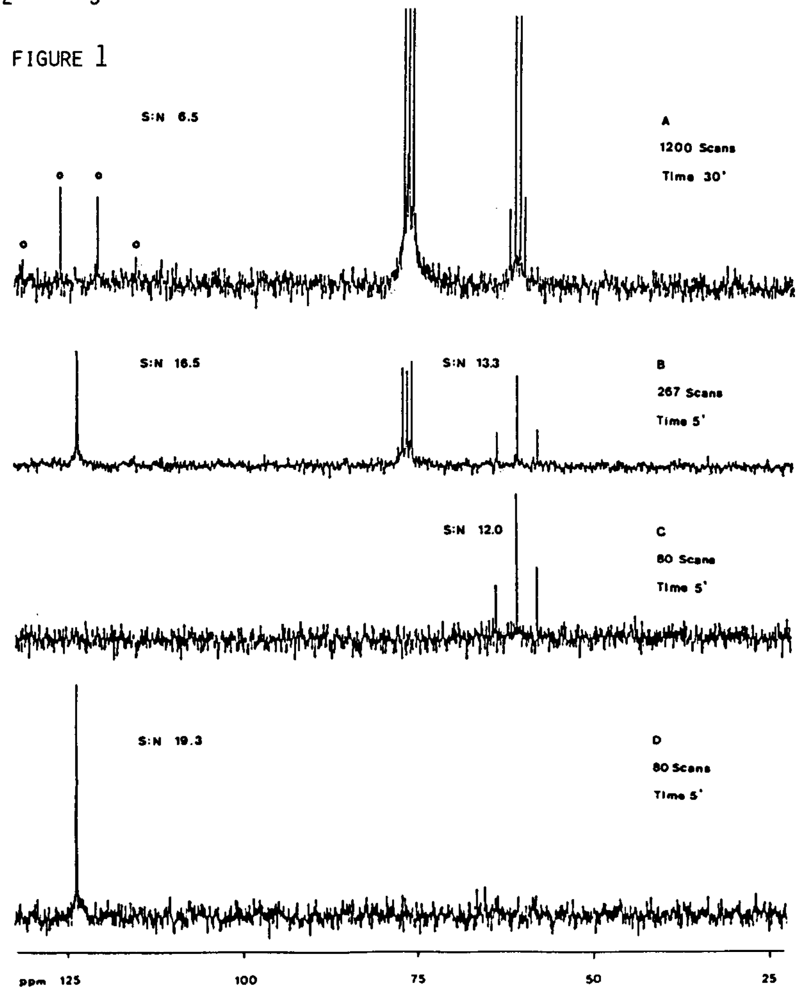
From a theoretical point of view, the sensitivity gain obtained by continuous broad-band fluorine decoupling and by transfer of polarization through scalar coupling is not the same. In a single pulse experiment, the maximum nOe factor $(1+\eta)$ is 2.87 while for an INEPT or DEPT experiment the equivalent enhancement factor would be 4.74. Moreover, further differences are expected because of the requirement for a dipolar relaxation mechanism to obtain the full nOe enhancement. Relaxation mechanisms other than dipole-dipole interactions have been reported for fluorine-19 in fluorocarbons[5,6]. Carbon-13 relaxation in CF_3COOH and CF_3CCl_3 has also been shown to involve significant contributions from mechanisms different from a pure carbon-fluorine dipolar relaxation[7]. Furthermore, fluorocarbons have high affinity for oxygen and in imperfectly degassed samples electron-nuclear relaxation can be the dominant relaxation mechanism[5,7].

In all these cases, nOe enhancements smaller than the theoretical maximum are observed. Conversely, polarization transfer through scalar coupling does not depend on the relaxation mechanism and is expected to give higher enhancements.

When long accumulations are involved, the relaxation time which is relevant to determine the delay between acquisitions is the one of fluorine in the INEPT or DEPT experiments. This is usually much shorter than the one of carbon, and even proton[5], nuclei in the same molecule and allows a shorter recycle time which gives a higher signal-to-noise ratio in the same experimental time.

Polarization transfer experiments between fluorine-19 and carbon-13 appear very attractive also because of the large(> 200 Hz) coupling constants involved for directly bound nuclei. Two bond coupling constants remain relatively large (30-50 Hz) and therefore enhancement of carbons adjacent to the fluorinated position is quite straightforward. Finally the editing possibilities of the DEPT and INEPT experiments can also be applied to the fluorine version to differenciate between CF, CF_2 and CF_3 units. Using proper phase cycling, signals not arising from polarization

FIGURE 1

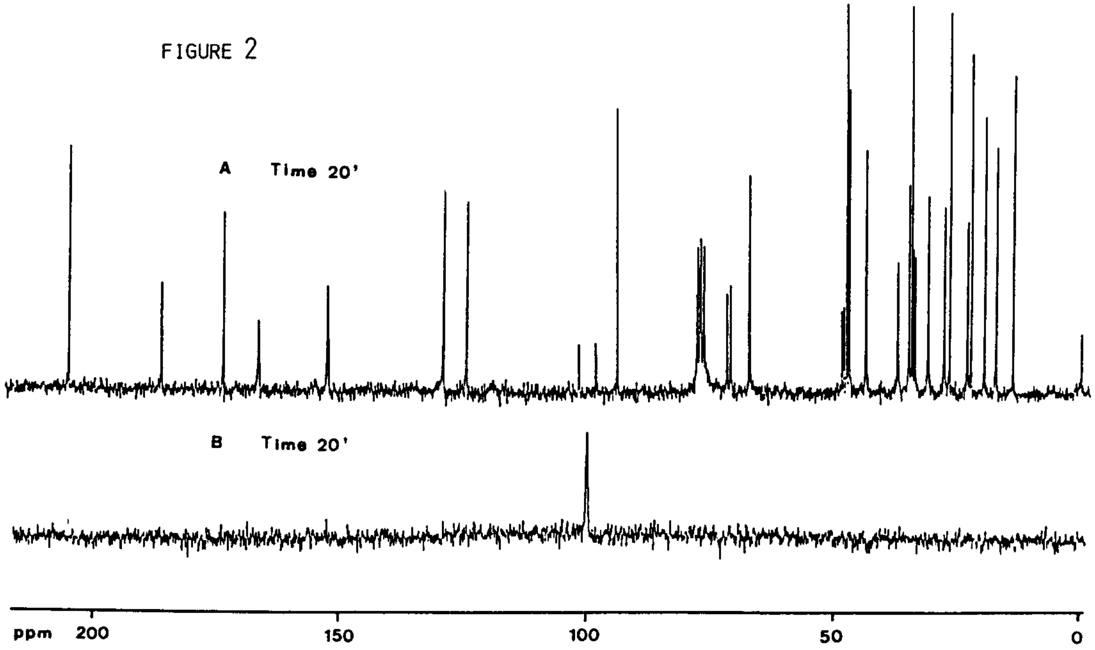


transfer can be eliminated thus providing a great deal of selectivity to monitor only those carbons bound to fluorine in otherwise complex spectra.

Figure 1 shows the 50.3 MHz spectra of a 0.5 M degassed solution of trifluoroethanol obtained under broad-band proton decoupling (a), broad-band fluorine decoupling (b), and polarization transfer using two-bond (35 Hz)(c) and one-bond (277 Hz)(d) coupling constants in a DEPT experiment. As expected, a large increase in the root-mean-square signal-to-noise ratio is observed in carbon 2 when fluorine is decoupled. A comparison between the enhancements obtained by nOe and by scalar polarization transfer favours the latter when fluorine is directly bound to the observed carbon, but the former when a long range coupling constant is involved. This can be due to relaxation during the longer delays associated with the smaller coupling constant, as well as to the effect of fluorine-proton coupling. It should be stressed, nevertheless, that the equivalent proton-carbon DEPT experiment using the two-bond coupling constant would be very difficult because of the much smaller value of the coupling constant between carbon and proton.

Figure 2 shows the 50.3 MHz ^{13}C-NMR spectra of 65 mg of 9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione 17-pentanoate (β-methasone 17-valerate) dissolved in 0.3 mL of $CDCl_3$ (0.45 M) obtained, using a microcell, under broad-band proton decoupling (a) and in a ^{19}F-^{13}C-DEPT (b). This experiment shows both the increased sensitivity in the signal from the fluorinated carbon, even in the presence of a number of unresolved long-range proton couplings, and the selectivity of the method that strongly discriminates against signals not arising from polarization transfer. This feature suggests the use of ^{19}F-^{13}C-DEPT or INEPT to study minor amounts of fluorinated compounds in complex mixtures.

FIGURE 2



We have applied this technique to the study of a termination reaction in solid-phase peptide synthesis by which a trifluoroacetyl group, coming from trifluoroacetic acid used to deprotect the α-amino groups, is irreversibly attached to the end of a growing peptide chain[8]. Gel-phase ^{13}C-NMR with broad-band proton decoupling can be used to monitor the different steps of the synthesis[9] but trifluoroacetyl groups could only be detected using ^{19}F-^{13}C-INEPT. Work in this subject is still under way and it will be published elsewhere.

Experimental Section

Spectra were recorded on a standard Varian XL-200 instrument equiped with a 10 mm broad-band Zens probe. The decoupler coil was tuned to the fluorine frequency and the fluorine transmitter was substituted for the decoupler proton transmitter. The decoupler offset was optimized in a series of esperiments with the decoupler modulation turned off. These experiments also yielded the decoupler power which was found to be of 5 kHz. With this power, the decoupler offset has to be set quite accurately at the proper fluorine frequency. This could cause difficulties if different types of fluorines are present but these problems could probably be solved by using pulsed decoupling after the polarization transfer step.

Trifluoroethanol was from Fluka (puriss) and was degassed by bubling argon during one hour. β-methasone was a kind gift from Dr.A.Messeguer from the Instituto de Química Bio-Orgânica, CSIC, Barcelona.

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