High-Resolution Fluorine-19 NMR spectra of Solid Fluorinated Organic Compounds

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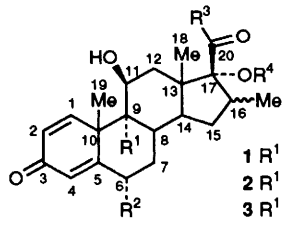
It is demonstrated herein that a combination of high-power proton decoupling and magic angle spinning can give acceptable high-resolution ^{19}F NMR spectra of simple solid multi-fluorinated organic molecules, as exemplified by three fluorosteroids.

The advent of techniques for obtaining high-resolution NMR spectra of solids, developed slowly from the implementation of magic angle spinning in 1958, has had an immense effect on a wide range of chemical problems in the last decade. The combination of high-power proton decoupling, cross polarisation and magic angle spinning (MAS) now allows spectra of most spin = ½ nuclei in solids to be obtained routinely. Proton and fluorine NMR usually require the use of magic-angle spinning with multiple-pulse sequences (CRAMPS), which is somewhat more technically challenging, but such experiments are also now readily implemented. However, there remains a case of difficulty, namely that of ^{19}F NMR in organic compounds which also contain many protons. This requires high-power proton decoupling, in addition to magic-angle spinning (and, for abundant fluorines, multiple-pulse operation). Because the ^{1}H and ^{19}F frequencies are relatively close (within 6%), this presents a problem, though lower-power proton decoupling has been routinely used for many years in solution-state NMR and a pioneering experiment on a static single crystal was reported[1] in 1987. To our knowledge, the only previous publications[2,3] in this area for solids have either been in polymer chemistry, or have involved only monofluorinated compounds[4,5] so that fluorine chemical shift differentiation was not studied. Some earlier relevant experiments[6,7] used only fast magic-angle spinning and have been reviewed.[8]

We give here what we believe to be the first examples of proton-decoupled MAS fluorine spectra of solid organic compounds of pharmaceutical interest involving more than one fluorine atom per molecule. The compounds examined are the steroids **1–3**. Compounds **1** and **2** have the methyl substituent at C-16 in the α position, whereas for **3** it is β.

We have deliberately chosen systems in which the fluorines are well-separated, so that there are only modest (F,F) dipolar interactions. This obviates the need for multiple-pulse operation, *i.e.* magic-angle rotation at modest speeds suffices to average such homonuclear coupling. However, compounds **1–3** contain three, two and one fluorines per molecule respectively. Fig. 1 shows the spectra for **1** and **2**, while Table 1 correlates the results for all three spectra, comparing the chemical shifts with those for the solution state.

The proton decoupling is effective even for the CHF and CH_2F fluorines. It can be seen that although linewidths are still substantial, the large chemical shift range for ^{19}F results in good dispersion so that closely-related chemical environments can be distinguished. At the spinning speeds used (*ca.* 10 kHz), spinning sidebands have been largely suppressed for the aliphatic cases examined. However, lower speeds should enable shielding tensor components to be derived from spinning sideband analysis. It is, however, already evident that the fluorine of the sidechain in **1** has a somewhat larger shielding anisotropy than the ring fluorines. The differences in chemical shifts between solution and solid states are modest, but may suggest no significant hydrogen-bonding effects and only small changes in molecular conformation induced by crystal packing forces. For compounds **1** and **3** only a single resonance can be observed for each fluorine (within the attainable resolution), indicating that the crystallographic asymmetric unit consists of a single molecule, in agreement with X-ray diffraction results where known. However, for compound **2** two signals, of unequal intensity, are observed [Fig. 1(*b*)] for each of the fluorines (in one case not entirely resolved). A second sample of **2**, from a different batch,



1 $R^1 = R^2 = F$, $R^3 = SCH_2F$, $R^4 = COEt$
2 $R^1 = R^2 = F$, $R^3 = SH$, $R^4 = H$
3 $R^1 = F$, $R^2 = H$, $R^3 = CH_2OH$, $R^4 = COBu^n$

Table 1 Fluorine-19 NMR data for three fluorinated steroids

	Solution state[a]	Solid state		
Compound	δF	δF	linewidth/Hz	Assignment
1	−165.52	−165.6	197	CF
	−187.38	−187.9	200	CHF
	−191.72	−192.3	200	CH_2F
2	−163.87	−165.2	210	CF
		−166.5[b]	[c]	
	−186.08	−180.1[b]	240	CHF
		−183.4	222	
3	−166.75	−171.4	143	CF

[a] In $CDCl_3$ for **1** and **3**, but $[^2H_6]$DMSO for **2**. [b] Weak peaks assigned to a polymorphic form. [c] Shoulder.

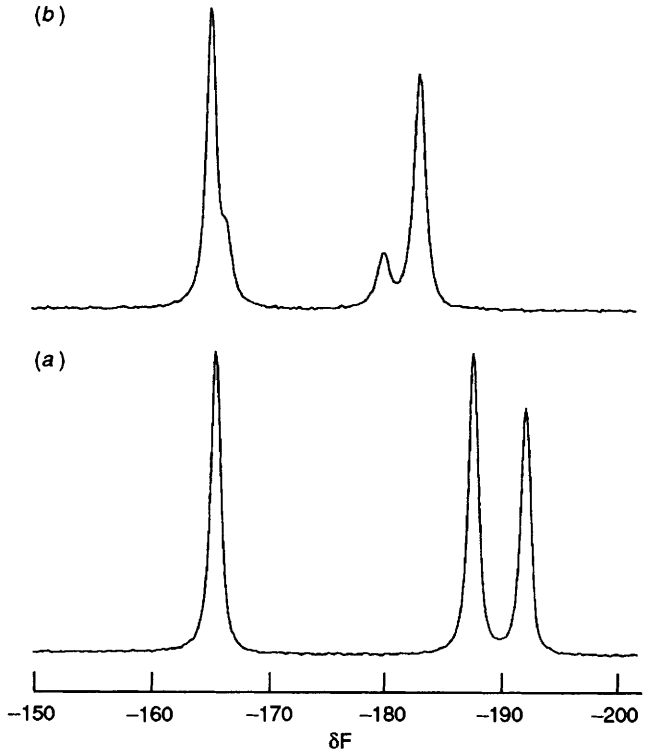


Fig. 1 Fluorine-19 spectra at 188.3 MHz of solid fluorinated steroids, using magic-angle spinning and proton decoupling: (*a*) Compound **1**; (*b*) Compound **2**

showed the same signals but with very different relative intensities. We interpret this as showing that the powder sample examined consisted of a mixture of polymorphs or pseudopolymorphs. This represents a result of pharmaceutical importance, which is not accessible by solution-state NMR. The separation of the shifts between the polymorphs is significant (3.5 ppm for F-6).

We believe these results demonstrate that it is now feasible to study ^{19}F NMR of solid fluorinated organic molecules, though for molecules containing many fluorines, multiple-pulse techniques may also be necessary.

The reported experiments used entirely commercial equipment, unlike the earlier work on fluorinated polymers. A Chemagnetics CMX 200 spectrometer was employed, with a Chemagnetics MAS probe which accepted rotors 4 mm in outside diameter. Typical operating conditions were: pulse duration 1.9 μs; MAS rate *ca.* 10 kHz; recycle delay 30 s; number of transients 32. Each spectrum took only 16 minutes to acquire. Spectra have also been obtained with $^{1}H \rightarrow {}^{19}F$ cross polarisation. Chemical shifts were referenced externally to $CFCl_3$ at 0 ppm using a static replacement rotor.

Note added in proof: Very recently we have become aware of similar experimental results, as yet unpublished, by Hagaman and coworkers.

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Footnotes

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