# Non-equivalence of vicinal proton-fluorine coupling constants in a $CF_3$ -CH<sub>2</sub> group

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The proton magnetic resonance spectrum of the tetrahydropyranyl ether of 2,2,2-trifluoroethanol has been measured in several solvents and at different temperatures. Analysis of the ABX<sub>3</sub> pattern produced by the trifluoroethyl group revealed a unique feature. Under all conditions, it was found that the vicinal coupling constants  $J_{AX}$  and  $J_{BX}$  had different magnitudes. This non-equivalence is interpreted as evidence that the C—H<sub>A</sub> and C—H<sub>B</sub> bonds of the trifluoroethyl group differ electronically. A possible relation between this finding and the anomeric effect is discussed. In contrast to the above results, the tetrahydropyranyl ether of ethanol showed equal vicinal proton–proton coupling constants in the ethyl group.

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# INTRODUCTION

In connection with another problem, we have prepared the tetrahydropyranyl ether of 2,2,2-trifluoroethanol (I). The proton magnetic resonance spectrum of this compound exhibited a surprising and unique feature. From an analysis of the ABX3 pattern produced by the trifluoroethyl group, it was found that the vicinal proton-fluorine coupling constants  $J_{AX}$  and  $J_{BX}$  were not equal. Such a non-equivalence of vicinal coupling constants in an ABX<sub>3</sub> system is, to our knowledge, without precedent. There is an erroneous report of such a case in the literature. Finegold (1) concluded from an analysis of the ABX<sub>3</sub> spectrum of diethyl sulfite that the vicinal coupling constants were unequal. However, Kaplan and Roberts (2) later showed this analysis to be wrong, because of the use of a positive sign for the geminal coupling constant. They found that spectra calculated by using a negative sign for  $J_{gem}$  gave a much better agreement with the experimental spectrum. This work, in conjunction with that of Fraser et al. (3), corrected the previous assumption that vicinal and geminal coupling constants had the same sign.



We now report the results of an analysis of the spectra of I measured in several solvents and at different temperatures, all of which yield non-equivalent vicinal coupling constants. We then discuss the significance of this observation and some of its potential applications.

# EXPERIMENTAL

2,2,2-Trifluoroethyl 2-Tetrahydropyranyl Ether

A solution of 9.2 g of 2,2,2-trifluoroethanol in 80 ml of 3,4-dihydro-2H-pyran was cooled in an ice bath. One drop of concentrated hydrochloric acid was added to the cooled solution and the mixture was stirred overnight, during which time the mixture warmed to room temperature. The reaction mixture was diluted with ether, and then washed with a 5% sodium carbonate solution and water. The aqueous washings were extracted with ether and the combined organic phases were dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate distilled at atmospheric pressure. After foreruns of ether and dihydropyran, the liquid which distilled over at 106° was collected and examined by nuclear magnetic resonance (n.m.r.). The spectrum showed no peaks attributable to impurities. The yield was 7.3 g (50% of theoretical).

Anal. Calcd. for  $C_7H_{11}F_3O_2$ : C, 45.64; H, 6.02; F, 30.95. Found: C, 45.45; H, 6.07; F, 30.81.

#### $\alpha$ -Deuterioethanol

A solution of 4.4 g (0.10 mole) of freshly distilled acetaldehyde in 20 ml of anhydrous ether was added dropwise to a flask containing 1.0 g (0.105 mole) of lithium aluminium deuteride<sup>1</sup> in 20 ml of anhydrous ether. The mixture was stirred during the addition and for 2 h afterwards. Water was then added dropwise to the reaction mixture until a white precipitate formed. The precipitate was filtered off and washed with ether, and the filtrates were combined

 $^1\!Purchased$  from Merck, Sharpe and Dohme, Montreal, Quebec.

and dried over anhydrous sodium sulfate. The ether was distilled off and the remaining liquid distilled over at 76–78°. The yield was 2.0 g (43% of theoretical).

#### α-Deuterioethyl 2-Tetrahydropyranyl Ether

By following the same procedure as above, the  $\alpha$ -deuterioethanol was converted into the tetrahydropyranyl ether. The product had b.p. 143–145° (lit. b.p. 146° (4) for the non-deuterated ether). No impurities were detectable from an examination of its n.m.r. spectrum in deuteriochloroform.

The n.m.r. spectra were measured on a Varian DA-60 spectrometer equipped with an external lock. The instrument was always calibrated immediately before use, and the spectra were measured at temperatures above and below room temperature, using the probe assembly described previously (5). All experimental line positions were determined from the average of 10 spectra. The accuracy in the line positions is better than 0.1 c.p.s., which was the largest standard deviation for any line position. The solute concentration was 40% (w/v) for each measurement. The deuterium spin-decoupling experiment was performed with the aid of an N.M.R. Specialties SD-60 spin decoupler.

### RESULTS

The proton magnetic resonance spectrum of I, measured in deuteriochloroform, is shown in Fig. 1a. The complex absorption pattern centered at  $\tau 6.1$  represents the geminal hydrogens of the trifluoroethoxy group. They appear as the AB portion of an ABX<sub>3</sub> system, and are shown in detail in Fig. 1b. Analysis of this 16-line pattern by the method of Fessenden and Waugh (6) gave the following parameters:  $J_{AX} =$ 9.13,  $J_{BX} = 8.77$ ,  $J_{AB} = -12.53$ ,<sup>2</sup> and  $\Delta \nu_{AB} = 8.84$  (all in c.p.s.). The spectrum was then measured in several other solvents and at different temperatures. The parameters obtained from each ABX<sub>3</sub> analysis are listed in Table I. The theoretical line positions calculated from each set agreed to within 0.1 c.p.s. with the corresponding experimental ones, except for the  $-43^{\circ}$ spectrum in CH<sub>2</sub>Cl<sub>2</sub>, which showed considerable line broadening. It is apparent that under each condition of solvent and

temperature  $J_{AX} \neq J_{BX}$ . It is also apparent that the variation in coupling constants with changes in solvent or temperature is quite small.

TABLE I Parameters calculated from the n.m.r. spectra of I

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Solvent	Tem- perature	$\begin{array}{c} J_{\mathrm{H_{A}}-\mathrm{F}} \\ \mathrm{(c.p.s.)} \end{array}$	$J_{\rm H_B-F} \\ ({\rm c.p.s.})$	$\Delta J^*$	$\Delta \nu_{AB}$ (c.p.s.)
CDC1 <sub>3</sub>	$-38^{\circ}_{28^{\circ}}$	$\begin{array}{c} 9.07\\ 9.13\end{array}$	$8.77 \\ 8.77$	$\begin{array}{c} 0.30\\ 0.36 \end{array}$	$9.8\\8.8$
CH <sub>2</sub> Cl <sub>2</sub>	$-43^{\circ}$ $-25^{\circ}$ $28^{\circ}$ $60^{\circ}$ $98^{\circ}$	$\begin{array}{c} 9.35 \\ 9.21 \\ 9.14 \\ 9.01 \\ 9.12 \end{array}$	$8.63 \\ 8.89 \\ 8.89 \\ 8.77 \\ 8.76$	$\begin{array}{c} 0.72 \\ 0.32 \\ 0.25 \\ 0.24 \\ 0.36 \end{array}$	$10.1 \\ 10.0 \\ 9.1 \\ 9.0 \\ 8.5$
Benzene	28°	9.15	8.92	0.23	15.0
Acetone	28°	9.33	9.12	0.21	6.6

\*The accuracy of the non-equivalence in the coupling constants. The reason is as high as that of the individual coupling constants. The reason is as follows. The AB portion of the ABX<sub>3</sub> system consists of four AB subspectra. If  $J_{H_A}$ - $F > J_{H_B}$ -F, then the separation between the more intens in the separation between the more intens in the separation terms of each AB subspectral quartet decreases with increasing field. (This is visually detectable in Fig. 1b.) The separation changes by twice the value of the non-equivalence as long as  $\Delta \nu_{AB}$  is greater than 8 c.p.s. We therefore feel that all the data in this table are accurate to within 0.1 c.p.s., except for the spectral measurements at  $-43^{\circ}$  in CH<sub>2</sub>Cl<sub>2</sub>, where the accuracy is only 0.3 c.p.s. because of line broadening.

We then examined the spectrum of the tetrahydropyranyl ether of ethanol (II) to see if the vicinal proton-proton coupling constants in the ethyl group of this compound would also be non-equivalent. The ethyl group gives rise to an ABC<sub>3</sub> spectrum. Unfortunately, the analysis of such a pattern is too complex to allow the detection of asymmetry of the same magnitude as observed in I. We therefore chose to determine the two vicinal coupling constants by another method. A racemic mixture of  $\alpha$ -deuterioethanol, prepared by the reduction of acetaldehyde with lithium aluminium deuteride, was converted by reaction with dihydropyran into the diastereomeric mixture of tetrahydropyranyl ethers. The n.m.r. spectrum of this mixture was measured during simultaneous irradiation of the deuterium nuclei. The absorption of the CH<sub>3</sub>—CH fragments appeared as two AB<sub>3</sub> patterns. Analysis of the A portion of each of these gave  $J_{AB}$ . In this manner  $J_{CH_3-CH}$  was found to be 7.18 c.p.s. for one proton and 7.19 c.p.s. for the other proton attached to the methylene carbon

<sup>&</sup>lt;sup>2</sup>The ABX<sub>3</sub> analysis cannot provide information about the relative signs of  $J_{AX}$  and  $J_{AB}$ . It does show that  $J_{AX}$  and  $J_{BX}$  have the same sign. The latter two are assigned a positive sign on the basis of the work of Mackor and McLean (22), in conjunction with that of Tiers (23) and that of Evans *et al.* (24).



FIG. 1. (a) The n.m.r. spectrum of I measured in deuteriochloroform. (b) The region  $\tau$  5.4–6.7 with the scale expanded fivefold.

atom of the ethyl group. Thus, it appears likely that vicinal proton-fluorine coupling constants are more sensitive than vicinal proton-proton coupling constants to variations in bonding.<sup>3</sup> Alternatively, the greater electronegativity of the  $CF_3$  group over the  $CH_3$  group may be responsible for the appearance of non-equivalent coupling constants in the trifluoroethanol derivative only.

## DISCUSSION

Magnetic non-equivalence is encountered in a wide variety of molecules. Two particular types have been recognized: nonequivalence in the chemical shift sense and

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<sup>&</sup>lt;sup>3</sup>The greater sensitivity of fluorine n.m.r. spectral parameters to small structural differences has already been illustrated in several different ways. For examples, see Manatt (25), Pirkle (26), Gerig and Roberts (27), and Williamson (14).

non-equivalence in the spin-coupling sense. The first type refers to the existence of a chemical shift between protons, methyl groups, or fluorines attached to the same atom, usually carbon. This occurs in molecules containing an asymmetric or pseudo-asymmetric center or in dissymmetric molecules. Many examples are summarized in a recent paper by Horobin *et al.* (7).

Non-equivalence in the spin-coupling sense occurs when two nuclei have identical chemical shifts but are unequally coupled to one or more neighboring nuclei. Examples of this type are 1,1-difluoroethylene (8) and 1-chloro-1-bromoethane (9). In these examples the non-equivalence is readily understood because the two nuclei on the same carbon have differing geometrical relations with either neighboring nucleus.

The remaining situation, in which both chemical shifts and coupling constants are unequal, is also frequently encountered. For example, in cyclohexanol the protons on C-2 are chemically shifted and couple unequally with the single proton on C-1 (10). This is to be expected from a consideration of the well-known Karplus equation.<sup>4</sup> However, the non-equivalent coupling in I cannot be accounted for on the basis of any simple conformational consideration.

Let us first decide what structural requirements will explain the observed nonequivalence. It is known that coupling between nuclei occurs primarily through the bonding electrons (11). Although there is some evidence that coupling between protons and fluorine can occur through space (12, and references therein), this appears to be limited to a few examples in which there have been five intervening bonds between the two nuclei, which allow the nuclei to lie close to one another. There has also been considerable recent evidence that vicinal proton-fluorine coupling constants are strongly dependent upon the dihedral angle  $\phi$  (13–15). Now, in I, the CF<sub>3</sub> group is rotating rapidly on the n.m.r. time scale (otherwise, we would observe an ABXYZ spectrum). This rapid rotation will average out the environment which each

fluorine "sees", making all fluorine atoms equivalent in the chemical shift sense. The only structural feature which can account for non-equivalent couplings to each vicinal hydrogen is the presence of non-equivalent  $C-H_A$  and  $C-H_B$  bonds. Thus, the vicinal proton-fluorine coupling constants provide us with an extremely sensitive method of detecting differences in the bonding electrons of the diastereomeric protons H<sub>A</sub> and  $H_B$ . The non-equivalence could be a result of different dihedral angles between HA and the three fluorines compared with those between  $H_B$  and the three fluorines. An exaggerated representation of such a distortion in the methylene group which would give rise to non-equivalent coupling via non-equivalent dihedral angles is shown in the Newman projection formula below. Alternatively, differences in the bond lengths, H-C-C bond angles, or bond hybridizations, all of which can affect the coupling constant (16), could be responsible for the non-equivalent coupling.



The question now arises as to what causes the difference in the  $C-H_A$  and  $C-H_B$  bonds. Let us consider the most favorable conformation for I (a threedimensional representation is shown below). The CF<sub>3</sub>CH<sub>2</sub>O group has the axial orientation as a result of the anomeric effect (17). The narrow half-band width of the signal for the anomeric proton at  $\tau$  5.2 is direct evidence for the axial CF<sub>3</sub>CH<sub>2</sub>O group. The remaining bonds in this group are assumed to occupy the staggered conformations, in which the bulkiest substituents are *trans* to one another.<sup>5</sup> In this conformation H<sub>A</sub>

1488

<sup>&</sup>lt;sup>4</sup>This topic is discussed at length in ref. 11.

<sup>&</sup>lt;sup>5</sup>The observed temperature independence of nonequivalent coupling constants is not inconsistent with the postulate of a preferred conformation, since the limits of accuracy of our method preclude the detection of changes which are less than 0.1 c.p.s. or 25% of the measured value at room temperature.



occupies a position quite close to the oxygen atom of the ring. It has, in fact, the same position with respect to the ring oxygen as has the axial hydrogen on C-6 with respect to the axial oxygen of the CF<sub>3</sub>CH<sub>2</sub>O group. Perhaps there is some attractive  $O \cdots H$ interaction for this particular geometry which induces a change in the C—H<sub>A</sub> bond and which is also an important factor in producing the anomeric effect! Work is continuing on the investigation of structurally related compounds to obtain evidence bearing upon the above speculations.

It may be of interest to point out the fundamental similarity and difference between the non-equivalence established herein and the non-equivalence in the chemical shift sense. The latter has been shown by the careful studies of Roberts and his coworkers (18) to be due primarily to conformational asymmetry. In theory, non-equivalence of the chemical shifts may also result from intrinsic asymmetry (19, 20); evidence of this was reported last year by Raban (21). The observation of intrinsic asymmetry is evidence for either electronic differences in two C-H bonds (C-F bonds in the compound CF<sub>2</sub>Br-CHBrCl discussed by Raban) or differences in the magnetic environment as a result of bond distortions elsewhere in the molecule. In contrast, non-equivalence of the vicinal couplings is evidence specifically for differences in the C—H bonds.

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