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THE EFFECT OF SUBSTITUENTS ON GEMINAL PROTON-PROTON COUPLING CONSTANTS

by

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PREFACE

Magnetic non-equivalence of diastereomeric methylene protons is a well-known phenomenon in Nuclear Magnetic Resonance. The chemical shift between the two magnetically non-equivalent nuclei is a measure of the difference in the magnetic environments of the two nuclei, and the coupling constant between them reflects their bonding character. Although there has been much work done in determining the origin of magnetic non-equivalence and the factors affecting the magnitude of the chemical shift, relatively little use has been made of the geminal coupling constant. The Karplus relation between vicinal proton-proton coupling constants and ϕ, the dihedral angle between the protons, is a striking example of the usefulness of coupling constants in determining structure in an organic molecule. In contrast, no correlation has been developed for geminal coupling constants. The aim of this thesis is to examine the effect of substituents on geminal proton-proton coupling constants.

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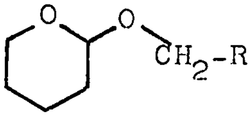
ABSTRACT

The proton magnetic resonance spectra of a series of 2-alkoxytetrahydropyrans of general formula



have been measured. R represents a variety of groups, including para-, meta-, and ortho-substituted phenyl, and several alkyl substituents. The geminal coupling constant, J_{AB}, has been determined in each ether, from the AB pattern produced by the magnetically non-equivalent methylene protons in the alkoxy group. J_{AB} has been found to be dependent on the nature of the substituent.

A study of the solvent dependence of J_{AB} in benzyl 2-tetrahydropyranyl ether has shown an opposite trend in the variation of J_{AB} to that previously reported in the literature.

The proton magnetic resonance spectrum of the 2-tetrahydropyranyl ether of 2,2,2-trifluoroethanol has been measured in several different solvents and at several temperatures. Analysis of the ABX_3 pattern produced by the trifluoroethyl group revealed that the vicinal coupling constants J_{AX} and J_{BX} had different magnitudes. This difference is interpreted as evidence that the $C-H_A$ and $C-H_B$ bonds of the trifluoroethyl group differ electronically. In contrast to the above result, the 2-tetrahydropyranyl ether of ethanol showed equal vicinal proton-proton coupling constants in the ethyl group.

INTRODUCTION

The theory of N.M.R. predicts for two nuclei of spin $\frac{1}{2}$, which are coupled only to each other, a quartet when the two nuclei have different chemical shifts, and a singlet if the chemical shifts of the two nuclei are identical. This quartet is the well-known AB "non-equivalence quartet" and it has been treated extensively in a number of places (1-5).

If we consider the A and B nuclei, they can be oriented in the magnetic field in four possible ways, ranging from the case where both are parallel to the field to the case where both are anti-parallel to the field. These four situations are illustrated in Figure 1 (6).

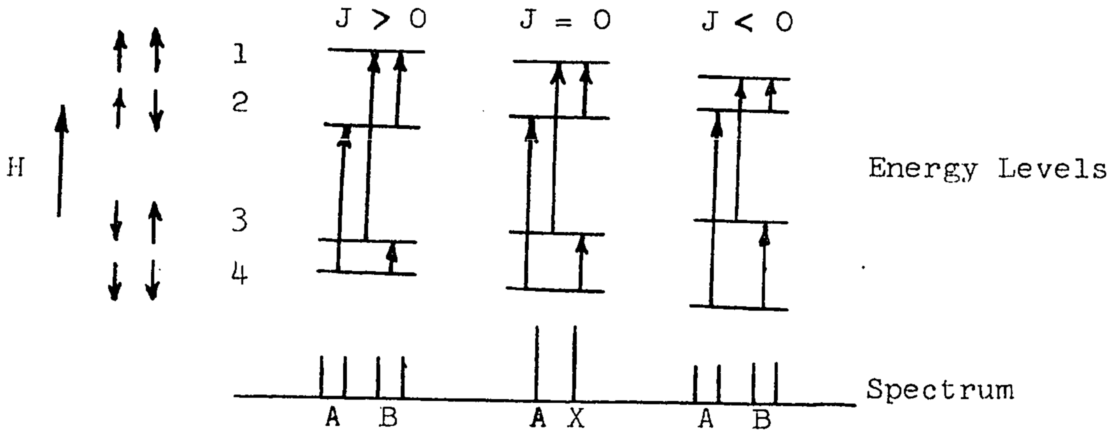


Figure 1. Energy level diagram for two magnetically non-equivalent nuclei of spin $\frac{1}{2}$.

The center portion of Figure 1 corresponds to the case where the coupling between the two nuclei is non-existent. As we can see from the energy level diagram, spacings 1-2 and 3-4 are equal, as are spacings 1-3 and 2-4. There are, therefore, only two different transitions. If, however, the two nuclei are coupled to each other, the energy levels are shifted, resulting in four different transitions. For the case where the anti-parallel arrangement leads to a lower energy than the parallel arrangement, the coupling constant is conventionally referred to as positive, and for the opposite case, as negative. The sign of the coupling constant cannot, however, be determined from the spectrum, even though a negative coupling constant leads to a different arrangement of energy levels than that from a positive coupling constant.

The shape of the AB quartet may vary from four equally intense lines to effectively one single line. This is shown in Figure 2.

If the chemical shift between the A and B nuclei, $\Delta\nu$, is much greater than the coupling constant, J, the spectrum will consist of four equally intense lines. As $\Delta\nu$ becomes of the order of magnitude of J, the intensity relationship between the four lines will change.

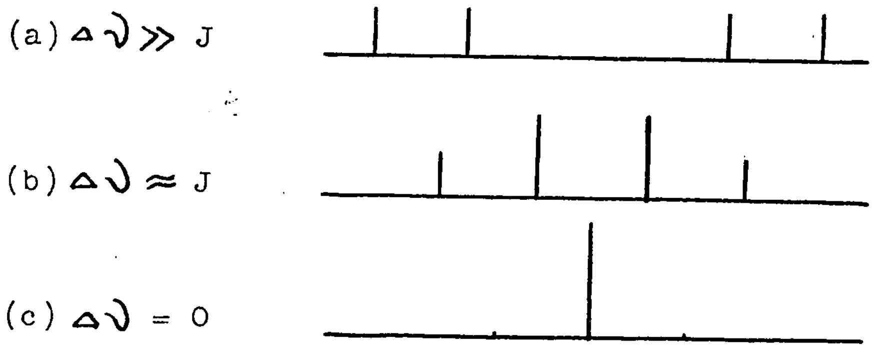


Figure 2. AB patterns for different values of $\Delta\nu_{AB}$.

As $\Delta\nu$ becomes smaller, the two inner lines become more intense, and the two outer lines decrease in intensity. In the limit where $\Delta\nu$ becomes zero, the spectrum collapses to effectively a single line.

A simple analysis of the AB quartet gives both the chemical shift between the A and B nuclei, $\nu_A - \nu_B$, and the absolute value of the coupling constant, $|J_{AB}|$.

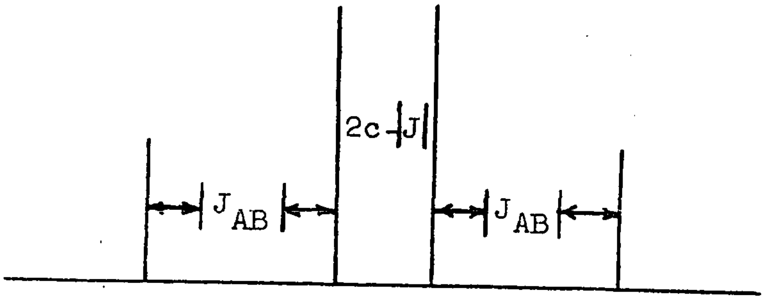


Figure 3. AB non-equivalence quartet.

As shown in Figure 3, $|J_{AB}|$ can be measured directly from the spectrum, and $\nu_A - \nu_B$ can be calculated from equation 1.

$$c = \tfrac{1}{2}\left[(\nu_A - \nu_B)^2 + J_{AB}^2\right]^{\frac{1}{2}} \quad \text{- - - - - - - - - -} \quad (1)$$

The relative intensities of the inner and outer lines are given by equations 2 and 3 respectively.

$$1 + \frac{J_{AB}}{\left[J_{AB}^2 + (\nu_A - \nu_B)^2\right]^{\frac{1}{2}}} \quad \text{- - - - - - - - - - -} \quad (2)$$

$$1 - \frac{J_{AB}}{\left[J_{AB}^2 + (\nu_A - \nu_B)^2\right]^{\frac{1}{2}}} \quad \text{- - - - - - - - - - -} \quad (3)$$

Magnetic Non-equivalence

Magnetic non-equivalence of nuclei can be defined in terms of the chemical shift and in terms of the coupling constant. Two nuclei will be magnetically non-equivalent if they have different chemical shifts or if they are coupled differently to a third nucleus in the molecule. These two types of magnetic non-equivalence bring about three possible situations. The first possibility is that of having different chemical shifts for two nuclei which are coupled equally to every other nucleus in the molecule. This is the most common situation and many examples are given in the literature (7). The second possibility is that of two nuclei with identical chemical shifts but coupled unequally to one or more neighbouring nuclei. This is the case, for example in 1,1-difluoroethylene (8), in which the hydrogens have the same chemical shift but are coupled differently to the fluorines because of the cis and trans relationship between the protons and the fluorines.

The third possibility is that of having nuclei with both different chemical shifts and unequal coupling to one or more neighbouring nuclei. This situation is also fairly common. For example, in cyclohexanol the protons on the 2-carbon atom have different chemical shifts and are coupled unequally to the single proton on the 1-carbon atom (9).

Magnetic Non-equivalence of Geminal Nuclei

The term "geminal" is applied to two nuclei separated by two bonds and linked by another nucleus, usually a carbon atom (e.g. H-C-H). When geminal nuclei occupy geometrically non-equivalent sites in a molecule, they are likely to be magnetically non-equivalent as well, in which case they have different chemical shifts.

Magnetic non-equivalence of geminal nuclei can occur when there is some kind of asymmetry in the molecule. If we consider a 1,1,1,2-tetrasubstituted ethane molecule, three stable conformations about the central C-C bond can be drawn, as shown in Figure 4.

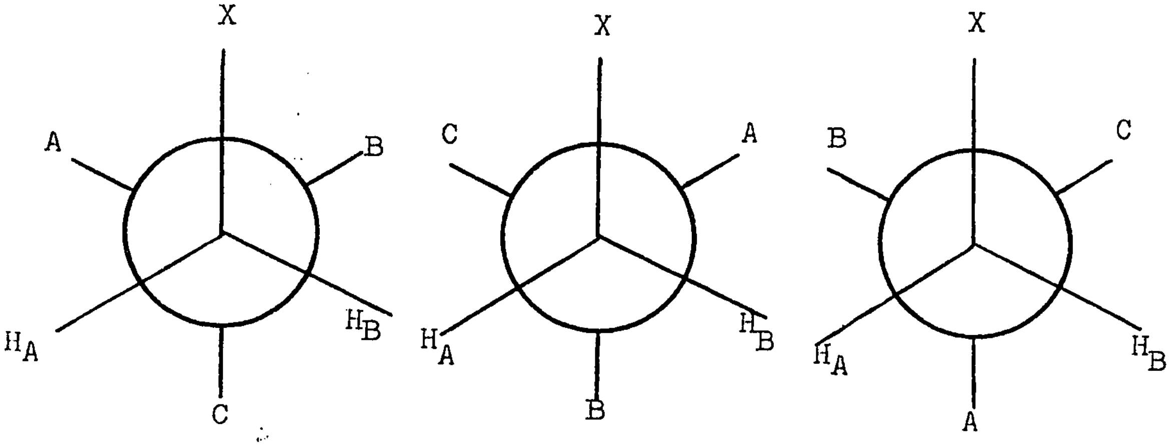


Figure 4. Three stable conformations in 1,1,1,2-tetrasubstituted ethane.

In molecules where A, B, and C are three different substituents, H_A and H_B are usually magnetically non-equivalent. This phenomenon was first interpreted as indicating slow rotation about the central C-C bond (10), since it was thought that rapid rotation would average out the chemical shifts of H_A and H_B. However, the methylene protons in CH_2X-CAAB were shown to have identical chemical shifts (11).

Restricted rotation should also have applied in this case, and the methylene protons should then have been magnetically non-equivalent. It was concluded that the chemical shifts of H_A and H_B are not necessarily averaged by rapid rotation unless the residence times of the molecule in each of the various rotational conformations are equal.

It is generally accepted that in order for geminal nuclei to be magnetically non-equivalent, there must be a source of asymmetry in the molecule, and difference in conformer population. It has been suggested, however, that non-equivalence can in principle still persist when the conformational isomers are all of equal energy (12), or even when the internal rotation is free (13).

Source of Asymmetry

Over the last ten years, magnetic non-equivalence of geminal nuclei has been reported in a vast number of molecules.

Magnetic non-equivalence has been observed for the methylene hydrogens in the ethyl groups of ethers (14), sulfites (15), sulfoxides (16, 12, 17), diethyl sulfide borane (16), diethylmethylammonium iodide (16), and a thiophosphonate (15); for the methylene hydrogens in variously substituted 1,1,1,2-tetrasubstituted ethanes (14, 18, 19); for the fluorine nuclei in the difluoromethylene group of appropriately substituted ethanes (14, 11, 10, 20); for the methyl groups of various systems with an isopropyl skeleton (21-23); and in hindered and bridged biphenyls (24-26).

It is obvious from the previous list of examples where magnetic non-equivalence has been observed that non-equivalence is not restricted to the R-CH_2-C*R'R"R'" type of molecule. First of all, the asterisked carbon need not be asymmetric in the usual sense. If one of the R-stroke groups is R-CH_2, the methylene hydrogens may still be magnetically non-equivalent. The asterisked carbon may also be replaced by other elements such as N, S, or P.

The geminal hydrogens may be replaced by other groups which give n.m.r. signals, such as F or CH_3, and the geminal pair need not be bonded directly to the source of asymmetry, but may be separated from it by a group such as -COO-, $-CH_2-$, or -O-. Finally, magnetic non-equivalence may result from dissymmetry in the molecule, as in the hindered and bridged biphenyls.

Intrinsic Asymmetry

The relative importance of molecular asymmetry itself, and preferences in conformational populations as the cause of magnetic non-equivalence has been discussed in a number of places (3, 27-30). Pople (13) has pointed out that the methylene hydrogens in the 1,1,1,2-tetrasubstituted ethane shown in Figure 4, are non-equivalent in all three possible conformations. Therefore, even assuming equal populations and rapid interconversion of the three conformers, H_A and H_B are always distinct and identifiable.

Gutowsky (29) has suggested that one possible way to show the contribution of "intrinsic asymmetry" to the magnetic non-equivalence is to measure the non-equivalence at room temperature where interconversion of the different conformers is rather slow, and at higher temperatures where the interconversion becomes more rapid.

The non-equivalence should decrease with an increase in temperature until free rotation is achieved. At this temperature, the non-equivalence would be a measure of the intrinsic asymmetry contribution to the non-equivalence. Gutowsky (29) thus obtained a value of 6.7 c.p.s. for the intrinsic asymmetry contribution to the non-equivalence for CF_2 Br-CFBrCl.

Raban (31) has measured the intrinsic asymmetry non-equivalence in the same molecule using a low temperature method, and found a value of 5 c.p.s. At low temperature, the individual spectra of each rotamer shown in Figure 5 can be observed.

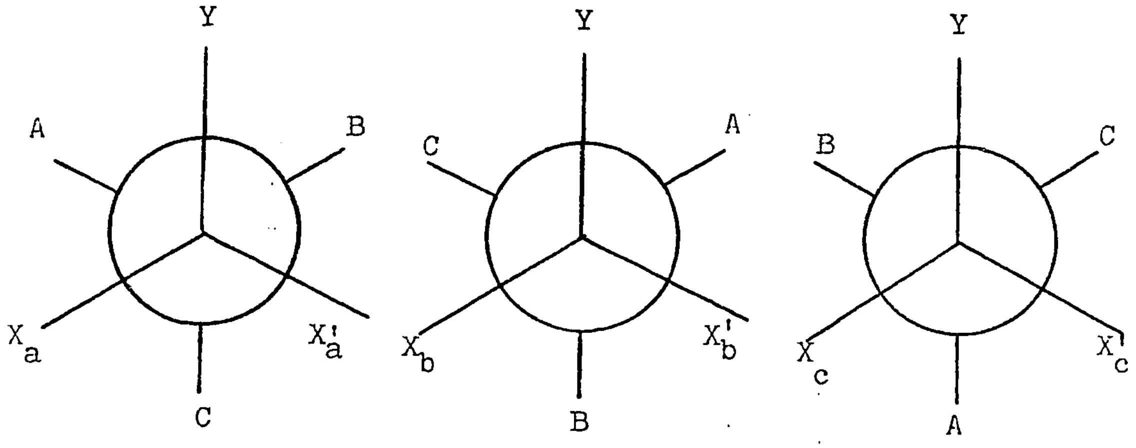


Figure 5. Three stable conformations in $CX_2Y\text{-}CABC$.

Under conditions of rapid rotation and equal population of the conformers, the non-equivalence is due to intrinsic asymmetry. We can see from Figure 5, however, that the environment of X_a is very similar to that of $X_{c'}$. Similarly, $X_{a'}$ and X_b, and $X_{b'}$ and X_c have similar environments. It would then seem that under conditions of rapid rotation and equal population the chemical shifts of X and X' would average to approximately the same value.

This would mean that the intrinsic asymmetry contribution should be near zero. The values measured by Gutowsky and Raban would seem to support this reasoning. However, Raban (31) has calculated a value of 55 c.p.s. for the intrinsic asymmetry non-equivalence in $CF_2Br-CHBrCl$. Raban further points out that the value for $CF_2Br-CFBrCl$ is near zero because of the fortuitous cancellation of large terms of opposite signs. These results then indicate that two nuclei such as X_a and $X_{c'}$ which appear to have similar environments can still have very different chemical shifts, and thus in some cases, the intrinsic asymmetry contribution to the non-equivalence can be substantial.

Although intrinsic asymmetry has been shown to be important in the above cases, the careful studies made by Roberts and co-workers (32, 33) clearly show that non-equivalence is due primarily to conformational preferences in compounds of the general formula $\phi-CH_2-O-CHR'R''$.

Conformational Effects on Magnetic Non-Equivalence

Roberts and co-workers (32-33) have studied the effect of molecular structure close to the diastereomeric nuclei, on the magnitude of the magnetic non-equivalence. These studies were made using 1-phenylethyl benzyl ethers as model compounds. They found that the most important single factor in determining the magnitude of the chemical shift difference was the conformation of the methylene group with respect to the directly bonded phenyl ring. The biggest non-equivalence occurred when the preferred conformation was such that one methylene proton was situated in the plane of the phenyl ring and the second one was appreciably out of this plane. The major contribution to the magnetic non-equivalence then originates in the magnetic anisotropy of the phenyl ring.

The magnitude of the chemical shift difference also depends upon the distance by which the diastereomeric nuclei are removed from the center of asymmetry. The chemical shift difference usually decreases as the distance is increased.

Roberts and co-workers (32) have studied the influence of proximity to the asymmetric center on the non-equivalence with a series of compounds containing an increasing number of bonds between a common asymmetric center and an isopropyl group. The results showed that the non-equivalence decreased as the number of intervening bonds increased. However, a sudden increase in non-equivalence occurred when the methyl groups were five bonds removed from the center of asymmetry. When the number of bonds was increased further, the non-equivalence decreased to zero. This observation would indicate that a six-membered ring conformation of the isopropyl group with respect to the asymmetric center may be populated to a significant extent, in accordance with the Newman "rule of six" (34).

The magnetic non-equivalence is also solvent dependent. Roberts and co-workers (33) have observed an approximate correlation between solvent dielectric constant and the degree of magnetic non-equivalence, in 1-phenylethyl benzyl ether.

They suggest that this variation may reflect changes in the conformation of the benzylic phenyl ring with respect to the methylene group. Variation of the chemical shift difference with solvent can be quite large. For example, the chemical shift difference between the diastereomeric methylene hydrogens in $BrCH_2-CBr(CO_2H)(CH_3)$ varies from 13 c.p.s. in dimethyl formamide to 50 c.p.s. in benzene (30). Variations of the same order of magnitude have also been observed in corresponding olefins (30) where no conformational changes are possible. It would then seem likely that magnetic properties of solvents may produce chemical shift changes which may override those caused by differences in rotational equilibria.

As mentioned previously, variation in temperature also affects the magnitude of the chemical shift between diastereomeric nuclei. The non-equivalence usually decreases with an increase in temperature. This effect has been attributed to the fact that the different conformers tend to become equally populated at higher temperatures (29).

Geminal Coupling Constants in Methylene Groups

Over the last ten years, approximately one thousand geminal coupling constants in methylene groups have been determined. Up until recently, it has been difficult to establish a systematization of this data because of the confusion existing regarding the signs of geminal coupling constants. Early work in this area had predicted a positive value for the coupling constant in methane (J $\doteq \pm$ 12.4 c.p.s.) (35). Subsequent work based on the relative signs of vicinal and geminal coupling constants (36, 37) and geminal and C^{13}-H coupling constants (38) showed that geminal coupling constants are usually negative relative to vicinal and C^{13}-H coupling constants which are very likely to be positive. An added problem is that many geminal coupling constants are close to zero and it is possible to have positive values in certain cases. However, there have been sufficient determinations of signs of geminal coupling constants, particularly relative to C^{13}-H coupling constants to establish certain trends in the variation of J_{Gem}.

The broad trends are reviewed in papers by Pople and Bothner-By (39) and Cookson and co-workers (40). The principal trends are:

(1) In the simplest hydrocarbons, as the hybridization on the carbon atom becomes more s-like, J_{Gem} increases, that is, it becomes more positive.
(Example: CH_4, -12.4 c.p.s.; cyclopropane, -4 c.p.s.; $CH_2=CH_2$, +2.5 c.p.s.)

(2) The substitution of an electronegative atom α to the CH_2 group leads to an increase in J_{Gem}.
(Example: CH_4, -12.4 c.p.s.; CH_3-Cl, -10.8 c.p.s.;
CH_3-I, -9.2 c.p.s.
$CH_2=CH_2$, +2.5 c.p.s.; $CH_2=O$, +40.2 c.p.s.)

(3) The substitution of an electronegative atom β to the CH_2 group leads to a decrease in J_{Gem}.
(Example: CH_4, -12.4 c.p.s.; CH_3-CCl_3, -13.0 c.p.s.;
$CH_2=CH_2$, +2.5 c.p.s.; $CH_2=CHCl$, -1.4 c.p.s.)
The magnitude of the decrease produced by a particular β-substituent, X, depends on the projected angle between the CH_2 group and the C-X bond, and on the C-C-X bond angles and lengths.

(4) The presence of a π-electron system next to the CH_2 group generally leads to a decrease in J_{Gem}. (Example: CH_4, -12.4 c.p.s.; $CH_3-C\equiv N$, -16.9 c.p.s.) For a freely rotating methyl group, an adjacent π bond produces a ΔJ of about -2.0 c.p.s., the effect being additive up to the maximum possible number of four increments. However, ΔJ also varies with the angle between the CH_2 group and the π-system. The maximum ΔJ occurs when the HH axis of the CH_2 group is parallel to the p orbital of the α sp^2 carbon atom (41). The least change in J occurs when the HH axis is parallel with the plane of the double bond.

Pople and Bothner-By (39) have developed a molecular orbital treatment of the electrons in a methylene group. This treatment leads to a theory of the effect of substitution on J_{Gem}. The theory justifies the trends in variation of J_{Gem} outlined above, and more generally, predicts the following trends in geminal hydrogen coupling constants:

(1) An increase in the inductive withdrawal of electrons leads to a positive change in J_{Gem}.

(2) An increase in the hyperconjugative withdrawal of electrons leads to a negative change in J_{Gem}.

(3) The hyperconjugative effect varies with the orientation of the substituent with respect to the methylene hydrogens.

Geminal coupling constants have also been observed to vary with change of solvent. In olefinic methylene groups, J_{Gem} generally decreases as the dielectric constant of the solvent increases (42-46). However, the variation is too weak to permit any definite rationalization of the effect. Smith and Cox (47) have reported a solvent dependence of J_{Gem} in a nondouble bonded system. J_{Gem} in styrene oxide shows a roughly linear variation with dielectric constant of the solvent, going from +6.00 c.p.s. in cyclohexane to +5.31 c.p.s. in dimethylsulfoxide . Variations in concentration (42) and in temperature (45) show no measurable effect on J_{Gem}.

One of the most valuable correlations between the structure of an organic molecule and the parameters derived from its n.m.r. spectrum is the Karplus relation between vicinal H-H coupling constants and ϕ, the dihedral angle between the protons (48).

In contrast, relatively little use has been made of geminal coupling constants to elucidate structural and stereochemical features. In spite of their potential utility, only a few systematic studies of substituent effects on J_{Gem} have been reported. The most notable of these have been made by Bernstein and Sheppard (49) on substituted methanes, and Sheppard and Banwell (50) on ethylene derivatives. This thesis describes an investigation of the effect of substituents on the geminal coupling constant in methylene groups in a series of 2-alkoxytetrahydropyrans. In addition, a unique example of non-equivalent vicinal H-F coupling constants in a CF_3-CH_2 group has been observed. In order to obtain information about the variation in J_{Gem} with structure, we undertook the synthesis of compounds of the type ϕ-CH_2-X in which X contained a center of asymmetry and measured the geminal coupling constant between the benzylic methylene protons in each compound.

EXPERIMENTAL

Benzyl phenyl sulfide

6.0 g of metallic sodium was dissolved in 150 ml of absolute ethanol. 28.5 g of thiophenol was added to the alcoholic solution in a slow but steady stream. 34.4 g of benzyl chloride was added dropwise to the alcoholic solution and the mixture was stirred and refluxed for 2 hrs. The ethanol was distilled off and reaction mixture was poured over cracked ice, filtered, and crystallized from methanol.

Yield = 60%, m.p. = 40-1°; lit. m.p. = 40-1° (78).

Benzyl phenyl sulfoxide

26.0 g of benzyl phenyl sulfide was dissolved in 150 ml of acetone. 20 ml of 30% H_2O_2 was added to the acetone solution. After standing for 3 days, the acetone was evaporated and the sulfoxide product was crystallized from 60% aqueous ethanol.

Yield = 80%, m.p. 124-5°, lit. m.p. = 122-3° (78).

Table 1 Melting points and yields of a few substituted benzyl phenyl sulfoxides.

	M.P.(°C)	Yield (%)
Benzyl phenyl sulfoxide	124-5 lit. 123-4 (78)	75
4-Nitrobenzyl phenyl sulfoxide	162-4 lit. 161-2 (79)	62
4-Chlorobenzyl phenyl sulfoxide	171-3 lit. 173 (80)	80
Benzyl 4-nitrophenyl sulfoxide	167-9 lit. 168-9 (79)	77
Benzyl 2,4,6-trinitrophenyl sulfoxide*	110-12	58

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* Elemental analysis results for this sulfoxide are pending.

The other benzyl phenyl sulfoxides listed in Table 1 were prepared following the procedure given above. The benzyl phenyl sulfides used in these preparations were prepared following the method given for benzyl phenyl sulfide using the appropriately substituted benzyl chlorides, except for 4-nitro and 2,4,6-trinitrophenyl benzyl sulfides which were prepared from benzyl mercaptan and the substituted chlorobenzenes.

Benzyl sec-butyl ether

1.9 g of metallic sodium was dissolved in 100 ml of sec-butyl alcohol. 10.0 g of benzyl chloride was added dropwise to the alcoholic solution, the mixture was stirred and refluxed for 2 hrs., and then poured over cracked ice. The reaction mixture was extracted with ether, and the ether phase was dried over anhydrous sodium sulfate. The drying agent was filtered off and the ether was distilled off. The remaining oil was distilled, and the purest fraction of benzyl sec-butyl ether was collected between 200-3°. Yield, 52%. Lit. b.p.=75-80°/3mm.(32).

Several attempts were made to prepare 4-nitrobenzyl sec-butyl ether using various procedures, but these were unsuccessful.

1-Phenylethyl benzyl ether

A mixture of 12.2 g of sec-phenyl ethanol and 12.7 g of benzyl chloride was refluxed over 21 g of sodium carbonate for 2 days. The inorganic salts were then filtered off and the filtrate was washed with 2N hydrochloric acid and water, and dried over anhydrous sodium sulfate. The drying agent was filtered off and the liquid was distilled at reduced pressure. The purest fraction of 1-phenylethyl benzyl ether was collected between 122-4°/0.3 mm. Yield, 55%. Lit. b.p. = 123-4°/0.3mm.(32).

1-Phenylethyl 4-methoxybenzyl ether

13.8 g of 4-methoxybenzyl alcohol, 36.6 g of 1-phenylethyl alcohol and 2.0 ml of conc. hydrochloric acid in 300 ml of benzene were refluxed for 20 hrs. in a flask equipped with a Stark water trap.

3 ml of water was collected in the trap. The reaction mixture was washed with water, and the organic fraction was dried over anhydrous sodium sulfate. The drying agent was filtered off, and the benzene was distilled off. The remaining oil was distilled at reduced pressure, the purest fraction of 1-phenylethyl 4-methoxybenzyl ether* being collected between 240-3°/10 mm.

Benzyl 2-tetrahydropyranyl ether

A solution of 10.8 g of benzyl alcohol in 20 ml of freshly distilled 3,4-dihydropyran 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 it warmed to room temperature. The reaction mixture was diluted with ether, 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, to remove the ether and the excess dihydropyran.

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* Because of the difficulties encountered in the synthesis of these 1-phenylethyl benzyl ethers, our attention was shifted to the tetrahydropyranyl ethers and, therefore, no effort was made to obtain a sample of 1-phenylethyl 4-methoxy-benzyl ether pure enough for elemental analysis.

The remaining oil was then distilled at reduced pressure. The physical constants and the results of the elemental analysis are given in Table 2.

All the other 2-tetrahydropyranyl ethers listed in Table 2 were prepared following the procedure given for the 2-tetrahydropyranyl ether of benzyl alcohol, except for the ortho-, meta-, and para-aminobenzyl 2-tetrahydropyranyl ethers. The procedure for the preparation of these ethers is given below. All but one of the alcohols used in the preparation of the 2-tetrahydropyranyl ethers were known compounds which were either obtained from commercial manufacturers or prepared from the parent acid, aldehyde or halide by well-known methods. 4-Ethynyl-benzyl alcohol was prepared by Landgrebe & Rynbrandt (51) and a gift sample was obtained from these workers.

4-Aminobenzyl, 2-Tetrahydropyranyl ether

4-aminobenzyl 2-tetrahydropyranyl ether was prepared from 4-nitrobenzyl 2-tetrahydropyranyl ether by hydrogenation with platinum oxide.

40 mg of PtO_2 was placed in the hydrogenation flask and covered with 10 ml of absolute ethanol. The platinum oxide was reduced with hydrogen gas at atmospheric pressure. A solution of 2.37 g of 4-nitrobenzyl 2-tetrahydropyranyl ether in 20 ml of absolute ethanol was added to the hydrogenation flask, and the flask was shaken until 672 cc of H_2 gas was consumed. At this point, the hydrogenation was stopped and the reaction mixture was filtered, and the platinum residue was washed with ether. The ether solution was dried over anhydrous sodium sulfate. The drying agent was filtered off, and after evaporating the ether, the remaining oil was distilled at reduced pressure.

α-Deuteroethanol

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 aluminum deuteride* in 20 ml of anhydrous ether.

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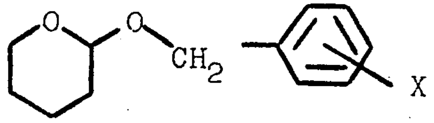
* Purchased from Merck, Sharpe and Dohme, Montreal, Canada.

The mixture was stirred during the addition and for two hours afterwards. Water was then added dropwise to the reaction mixture until a white granular precipitate formed. The precipitate was filtered off, washed with ether and the filtrates were combined and dried over anhydrous sodium sulfate. The ether was distilled off and the remaining liquid distilled at atmospheric pressure. The product was collected at 76-78°. The yield was 2.0 g (43%).

The n.m.r. spectra were measured on a Varian DA-60 spectrometer equipped with external lock. Spectra were measured at temperatures above and below room temperature using a probe assembly which has been described previously (52). All experimental line positions were determined from the average of at least ten spectra. Solute concentration was 20% (w/v) for all measurements, except for those on the 2-tetrahydropyranyl ether of 2,2,2-trifluoroethanol for which the concentration was 40% (w/v). The deuterium spin-decoupling experiment was performed with the aid of an N.m.r. Specialties SD-60 Spin-decoupler.

Table 2 Boiling Points, Yields, and Elemental Analysis Results for a Series of 2-alkoxytetrahydropyrans,



X	b.p.(°C)	Yield %	Elemental Analysis Theory C%	H%	O%	Y%	Found C%	H%	O%	Y%
H	65-6/0.10mm lit.100/2mm(54)	90	74.98	8.39	16.64		75.07	8.24	16.98	
p-NO_2	132-4/0.10mm	80	60.75	6.37	26.98	5.90	60.35	6.97	27.17	5.99
p-CN	132/0.60mm	77	71.86	6.96	14.73	6.45	70.69	7.04		
p-CF_3	74-6/0.13mm	80	59.99	5.81	12.30	21.90	60.25	6.01		21.67
p-CCH	110-15/0.25mm	74						-(a)		
p-Cl	90-2/0.15mm	96	63.61	6.62	14.12	15.65	63.76	6.87	14.49	15.42
p-F	68-70/0.05mm	82	68.54	7.20	15.22	9.04	68.25	7.23		8.92
p-CH_3	85-8/1.1mm	87	75.69	8.80	15.51		75.04	8.71	15.42	
p-OCH_3	96/0.10mm	82	70.24	8.16	21.60		70.29	8.23	21.63	
p-NH_2	126/0.25mm	25						-(a)		

Table 2 (continued)

X	b.p.(°C)	Yield %	Elemental Analysis							
			Theory				Found			
			C%	H%	O%	Y%	C%	H%	O%	Y%
m-NO_2	122-4/0.15mm	70	60.75	6.37	26.98	5.90	60.97	6.63		6.11
m-CN	110-2/1.0mm							- (b)		
m-Cl	82-8/0.10mm	83	63.61	6.62	14.12	15.65	64.28	6.76		14.80
m-F	82-4/0.25mm	82	68.54	7.20	15.22	9.04	68.26	7.48		7.99
m-OCH_3	124-6/0.75mm	87	70.24	8.16	21.60		70.10	8.13		
m-CH_3	100-5/0.25mm	91	75.69	8.80	15.51		75.50	8.71		
m-NH_2	130/0.22mm	25						- (a)		
o-NO_2	140/0.20mm	85	60.75	6.37	26.98	5.90	61.01	6.39		6.00
o-OCH_3	110-2/0.25mm	93	70.24	8.16	21.60		70.19	8.14		
o-CH_3	84-6/0.20mm	90	75.69	8.80	15.51		75.49	8.64		
o-NH_2	118-20/0.30mm	30						- (a)		
o-X'	140-2/0.10mm	82						- (c)		

X' =

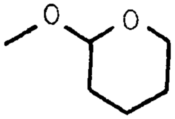


Table 2 (continued)

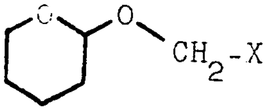
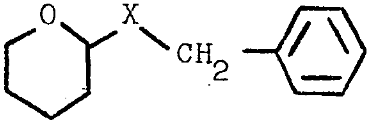
X	b.p. (°C)	Yield %	Elemental Analysis							
			Theory				Found			
			C%	H%	O%	Y%	C%	H%	O%	Y%
										
$C(CH_3)_3$	30/0.2mm lit.76/18mm(53)	50								
CH_3	143-5 lit. 146 (54)	60								
CCl_3	54/0.20mm	86	35.99	4.75	13.72	45.54	36.28	5.57		
CF_3	106	75	45.64	6.02	17.39	30.95	45.45	6.07		30.81
$C(CH_3)=CH_2$	32-4/0.45mm	52	69.19	10.32	20.48		68.99	10.13		
	52/0.13mm lit.124/2.4mm(54)	88								
CCH	29/0.30mm	72	68.54	8.63	22.83		68.39	8.38		

Table 2 (continued)

X	b.p. (°C)	Yield %	Elemental Analysis							
			Theory				Found			
			C%	H%	O%	Y%	C%	H%	O%	Y%
										
S	94-6/0.13mm lit. 86-7/2mm(55)	80								
NH	(b) lit. 114/5mm(56)									

a) It was impossible to obtain a sample pure enough for elemental analysis. The n.m.r. spectra show slight impurities, but it is reasonable to assume that these do not significantly affect the measurement of J_{Gem}.

b) This compound was supplied by Mrs. E. Sano, and although results of elemental analysis are not available, the sample was considered to be fairly pure since its n.m.r. spectrum showed no appreciable impurities.

c) Since this compound is not particularly significant in the interpretation of the results, it was not subjected to elemental analysis.

<u>NOTE:</u> The IR spectrum of each of the compounds listed in Table 2 was measured on a Beckman IR 8 spectrophotometer. These spectra were consistent with the expected structure of the molecules, and revealed no major impurities in the samples.

RESULTS AND DISCUSSION

The first $\emptyset$-CH_2-X compounds which were prepared in order to study the variation of J_{Gem} with structure of the molecule were a series of benzyl phenyl sulfoxides with different substituents on the benzyl phenyl ring and on the phenyl ring directly bonded to the S atom. These substituted benzyl phenyl sulfoxides are listed in Table 3 along with J_{Gem} for the benzylic methylene protons. As we can see from Table 3, there is very little variation of J_{Gem} in the sulfoxides that were studied here. Because of these unpromising results, it was decided to study other series of compounds of the type $\emptyset$-CH_2-X in which X contained a center of asymmetry. Attempts were made to synthesize benzyl sec-butyl ethers and 1-phenylethyl benzyl ethers with substituents on the benzyl phenyl ring, but problems in the synthesis of these compounds led us to abandon the study of these ethers in favor of 2-tetrahydropyranyl ethers which were prepared easily and showed a significant variation of J_{Gem} with the structure of the molecule.

Table 3 J_{Gem} values in a few Benzyl phenyl sulfoxides, Benzyl sec-butyl ether, and two 1-Phenylethyl benzyl ethers

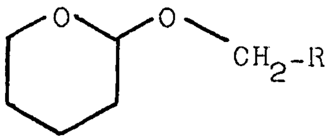
	$-J_{Gem}$(cps)*
Benzyl phenyl sulfoxide ≠	12.64
4-Nitrobenzyl phenyl sulfoxide	12.61
4-Chlorobenzyl phenyl sulfoxide	12.82**
Benzyl 4-Nitrophenyl sulfoxide	12.91**
Benzyl 2,4,6-Trinitrophenyl sulfoxide	12.71
Benzyl sec-butyl ether	12.16
1-Phenylethyl benzyl ether	11.57
1-Phenylethyl 4-Methoxybenzyl ether	11.11

≠ The spectra of the benzyl phenyl sulfoxides were measured in DMSO. In other solvents, the benzylic methylene protons were magnetically equivalent. The spectra of the benzyl sec-butyl ethers and 1-phenylethyl benzyl ethers were measured in deuterochloroform.

* The average deviation in ten measurements was less than 0.1 c.p.s.

**The average deviation in ten measurements was 0.3 c.p.s.

A series of 2-alkoxytetrahydropyrans of general formula I, in which R represents a variety of groups


I

including para-, meta-, and ortho-substituted phenyl and several alkyl substituents, was used to study the effect of various substituents on the geminal coupling constants, J_{Gem}. In all of the 2-alkoxytetrahydropyrans that were studied, the methylene protons in the alkoxy group were magnetically non-equivalent and gave an AB quartet in the n.m.r. spectrum. For example, the n.m.r. spectrum of benzyl 2-tetrahydropyranyl ether, is shown in Figure 6. The other 2-alkoxytetrahydropyrans in the series have basically the same type of spectrum. J_{Gem} was measured directly from the AB quartet which in the spectrum in Figure 6 is centered at τ 5.33.

Figure 6

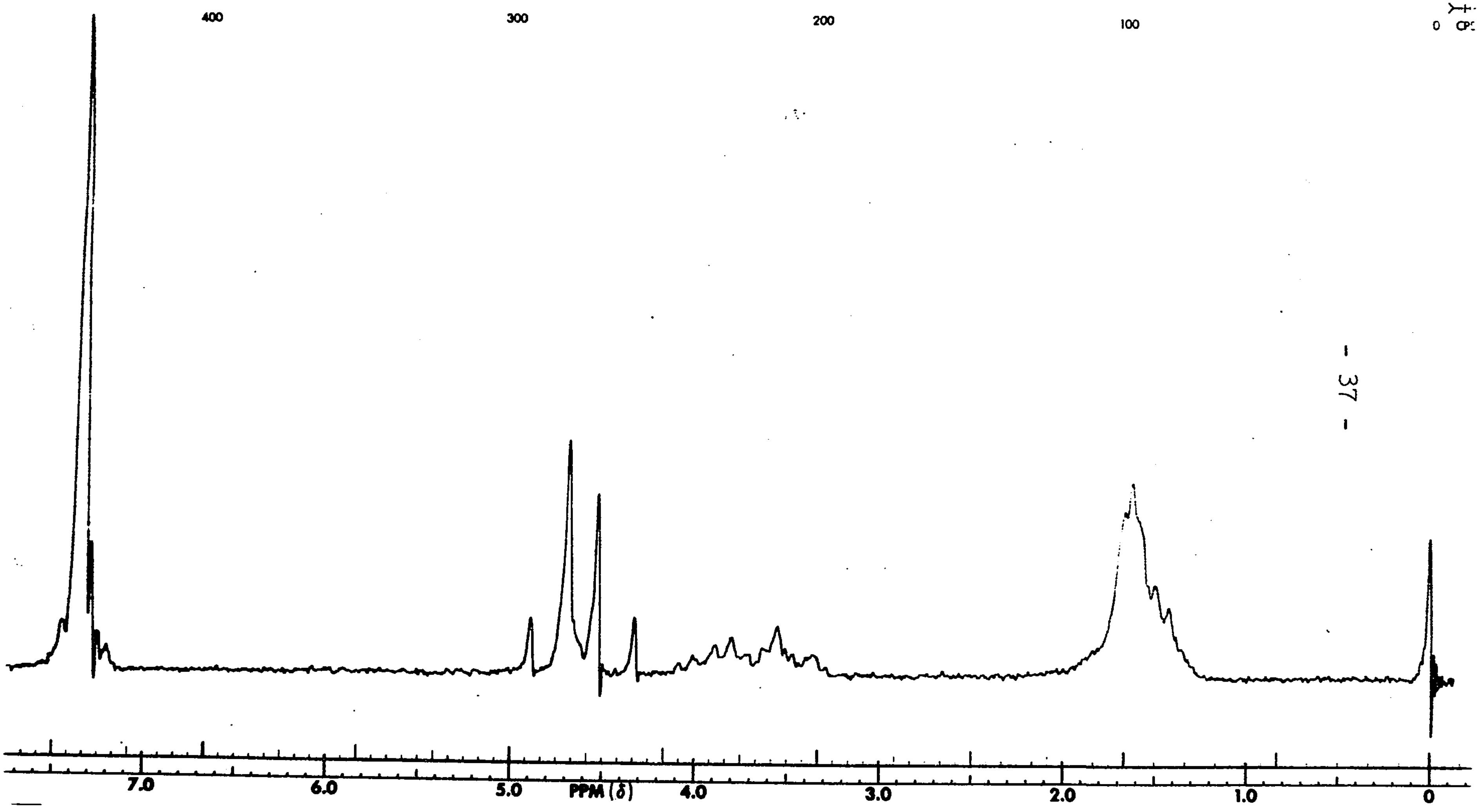


Figure 6 N.M.R. spectrum of benzyl 2-tetrahydropyranyl ether.

In most of the spectra, the signal for the anomeric proton interfered with the low-field half of the AB quartet in such a way that the measurements of J from the low-field half and from the high-field half of the quartet were different. Both the values of J measured from the low-field and high-field halves of the quartet are given in Tables 4 to 10, however, J measured from the high-field half of the quartet was generally used to compare the effect of substituents, since it was felt that this value was more reliable.

In the spectra of the benzyl ethers, each line of the AB quartet was slightly broadened by coupling with the ortho ring protons. This broadening, which has been previously observed by Roberts and co-workers (32, 33) in 1-phenylethyl benzyl ethers, caused a decrease in the accuracy of measurement of J_{Gem}. The standard deviation in ten measurements was generally less than 0.1 c.p.s. Also because of this broadening, a sweep width of 250 c.p.s. rather than a broader one, was generally used to measure the spectra of the benzyl ethers.

The 2-tetrahydropyranyl ether of 2,2,2-trifluoroethanol showed an ABX_3 pattern for the trifluoroethyl group, because of coupling of the methylene protons with the fluorine nuclei. The analysis of the spectrum of this compound will be discussed in detail later.

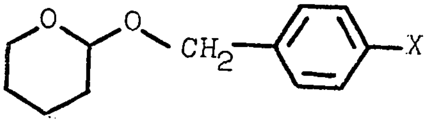
The ether derived from propargyl alcohol showed an ABX pattern for the propargyl group when measured in dimethylsulfoxide. ($J_{AX} = J_{BX} = 2.5$ c.p.s.) This is due to coupling between the methylene protons and the ≡CH proton. In all other solvents, however, the spectrum was of the A_2X type. This indicates that in these solvents the methylene protons are magnetically equivalent as far as can be measured by the NMR instrument. In dimethylsulfoxide the methylene protons have a chemical shift difference large enough to be detected in the n.m.r. spectrum.

All of the geminal coupling constants reported in Tables 3 to 10 are assumed to be negative and the trends in variation of J_{Gem} are established on this basis. This assumption is a very reasonable one when one compares similar examples of sp^3 methylene groups in the literature (39, 40).

Para and Meta Substituents

The n.m.r. parameters derived from the AB quartet in the spectra of each of the para- and meta-substituted benzyl 2-tetrahydropyranyl ethers, are listed in Tables 4 and 5. As we can see from these results, phenyl substituents cause an appreciable change in the magnitude of J_{Gem}. The direction of the effect is in accord with the theoretical predictions of Pople and Bothner-By (39) regarding hyperconjugation. This theory predicts that hyperconjugative withdrawal of electrons makes J_{Gem} more negative, and donation makes J_{Gem} more positive. In this regard, the nitro group presumably enhances the hyperconjugative withdrawing power of the phenyl ring, thus causing a negative shift in J_{Gem}. On the other hand, the amino group enhances the hyperconjugative donating power of the phenyl ring and causes a positive shift in J_{Gem}. Furthermore, the magnitude of the effect exerted by all the para and meta substituents correlates reasonably well with the Hammett substituent constants. This correlation is shown in the plot in Figure 7.

Table 4 N.m.r. Parameters for Para Substituted Benzyl 2-tetrahydropyranyl ethers,



X	$-J_{Gem}$(cps)* (high field)	$-J_{Gem}$(cps)* (low field)	$\Delta\nu_{AB}$ (cps)	τ	σ_p	σ_p^{o}
H	12.00≠	12.10≠	16.9	5.33	0	0
NO_2	13.28	13.71	15.9	5.23	+0.73	-
CN	13.21≠	13.56≠	16.7	5.25	+0.63	-
CF_3	12.78	13.01	16.8	5.39	+0.52	-
CCH	12.54	12.84	16.4	5.38	+0.23	-
Cl	12.04	12.38	16.5	5.40	+0.23	+0.27
F	11.78	12.11	16.4	5.38	+0.06	+0.17
CH_3	11.75≠	11.95≠	17.0	5.36	-0.17	-0.15
OCH_3	11.57≠	11.67≠	16.3	5.40	-0.27	-0.12
NH_2	11.10	11.64	16.1	5.49	-0.66	-0.38

* J_{Gem} values measured from the high field and low field parts of the AB quartet are given in this table, and in tables 5, 7-10. The difference between the two values is due to the anomeric proton signal which usually appears in the area of the low field side of the AB quartet and hinders the measurement of J_{Gem} from this side.

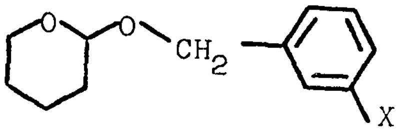
The average deviation in ten measurements was generally less than 0.1 c.p.s.

J_{Gem} was measured at a sweep width of 250 c.p.s. except where noted.

≠ J_{Gem} was measured at a sweep width of 100 c.p.s.

Note: The n.m.r. parameters listed in Tables 4 to 10 were measured in deutero-chloroform.

Table 5 N.m.r. Parameters for Meta Substituted Benzyl 2-tetrahydropyranyl ethers,



X	$-J_{Gem}$(cps)* (high field)	$-J_{Gem}$(cps)* (low field)	$\Delta\nu_{AB}$(cps)	τ	σ_M
H	12.00≠	12.10≠	16.9	5.33	0
NO_2	12.74	13.26	16.6	5.20	+0.71
CN	12.89≠	13.05≠	17.0	5.28	+0.62
Cl	12.47	12.72	17.5	5.36	+0.37
F	12.44	13.12	17.0	5.32	+0.34
OCH_3	12.22	12.64	17.0	5.33	+0.12
CH_3	11.93≠	12.10≠	17.9	5.37	-0.13
NH_2	11.95	12.41	17.2	5.40	-0.16

* The average deviation in ten measurements was generally less than 0.1 c.p.s.

J_{Gem} was measured at a sweep width of 250 c.p.s. except where noted.

≠ J_{Gem} was measured at a sweep width of 100 c.p.s.

Figure 7

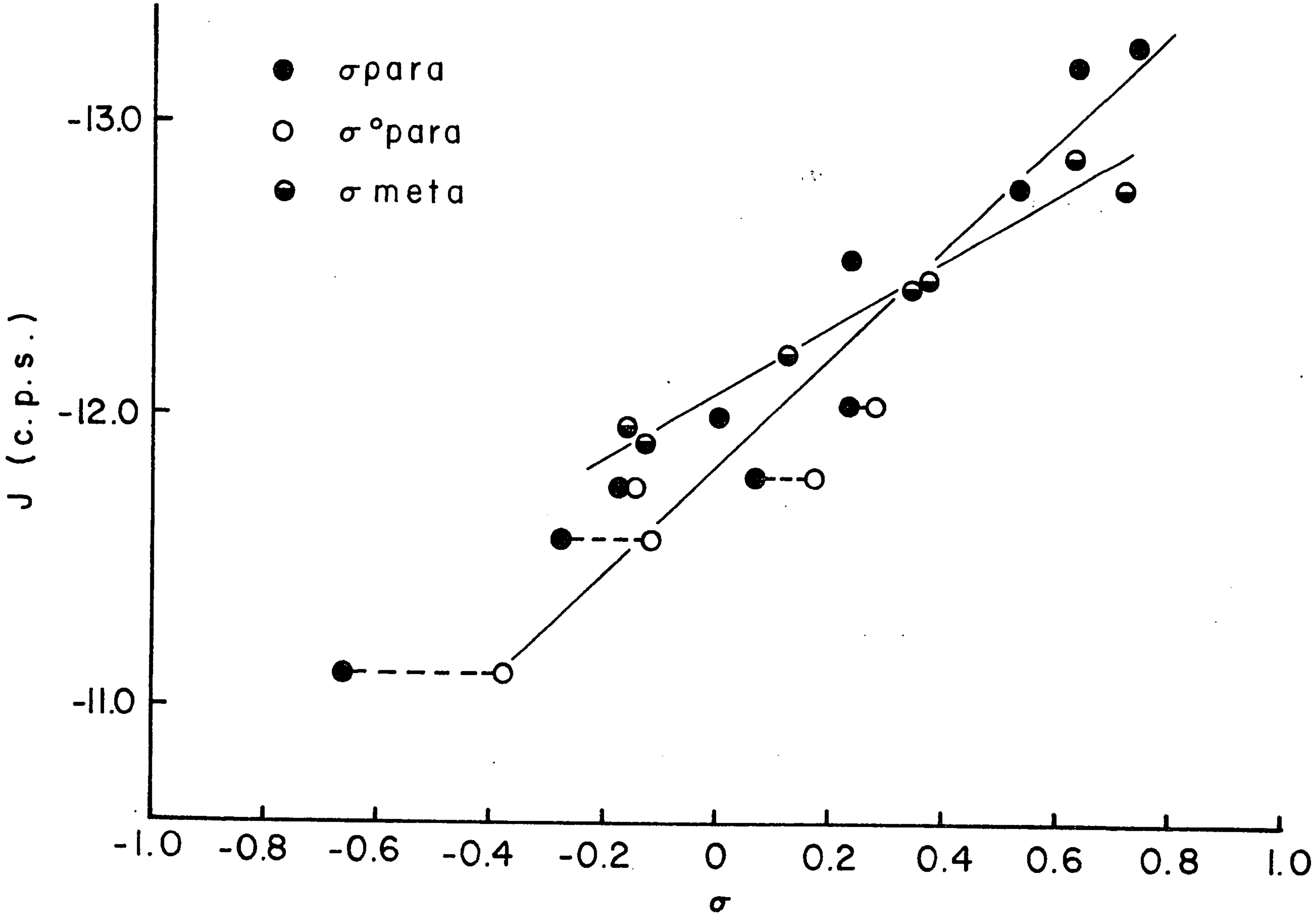
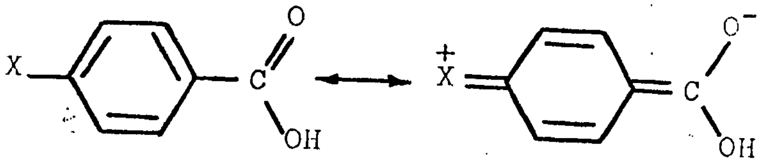


Figure 7 Plot of J_{Gem} in para and meta substituted benzyl 2-tetrahydropyranyl ethers vs. Hammett substituent constants.

The plot of the para substituents shows some curvature. A more linear relationship is obtained when the J_{Gem} is plotted vs. σ^{o} values, calculated by Taft and co-workers (57). The σ^{o} values are calculated from σ_R^{o} values ($\sigma^{o} = \sigma_R^{o} + \sigma_I$). The Hammett σ_R values are enhanced because of the isovalent conjugation effect



which does not occur in the tetrahydropyranyl ethers. This type of conjugation occurs only with substituents which have an electron-donating resonance effect. The new σ_R^{o} values are resonance parameters which have been corrected for this extra contribution to the Hammett σ-values.

The plot of the meta substituents shows a reasonably linear correlation. One interesting feature of the plots in Figure 7 is that the plot of the para substituents shows a larger slope than that for the meta substituents. This indicates that J_{Gem} is more sensitive to the resonance effect than to the inductive effect of a substituent since the predominant effect in para substituents is the resonance effect, and that in meta substituents is the inductive effect.

Taft and co-workers (57) have correlated $\delta_p^F - \delta_m^F$ values for a series of meta- and para-substituted fluorobenzenes, with σ_R^o parameters. They obtained the following correlation $\delta_p^F - \delta_m^F = 2.97\,\sigma_R^o$. Similarly here, $J_{para} - J_{meta}$ values have been plotted vs. σ_R^o values. The plot, shown in Figure 8, shows a fairly good linear relationship.

If we assume that para and meta substituents make equal inductive contributions to J_{para} and J_{meta}, and that the resonance effect of meta substituents is small, $J_{para} - J_{meta}$ is then a measure of the para resonance effect.

The correlation of $J_{para} - J_{meta}$ values with σ_R^o -parameters according to equation 4

$$J_{para} - J_{meta} = -1.77\,\sigma_R^o \quad \text{-----------}(4)$$

is indicated in Table 6 from the comparison between calculated and observed values of $J_{para} - J_{meta}$.

Table 6 Correlation of $J_{para} - J_{meta}$ values with σ_R^o parameters

X	σ_R^o	$J_{para}-J_{meta}$(cps) (experimental)	$J_{para}-J_{meta}$(cps) (calculated)*	Δ(cps)
H	0	0	0	0
CH_3	-0.10	0.18	0.18	0.00
Cl	-0.20	0.43	0.35	0.08
F	-0.35	0.66	0.62	0.04
OCH_3	-0.41	0.65	0.73	0.08
NH_2	-0.48	0.83	0.85	0.02
				Average deviation = 0.04cps

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* Values of $J_{para}-J_{meta}$ calculated from equation $J_{para}-J_{meta} = -1.77\ \sigma_R^o$.

Figure 8

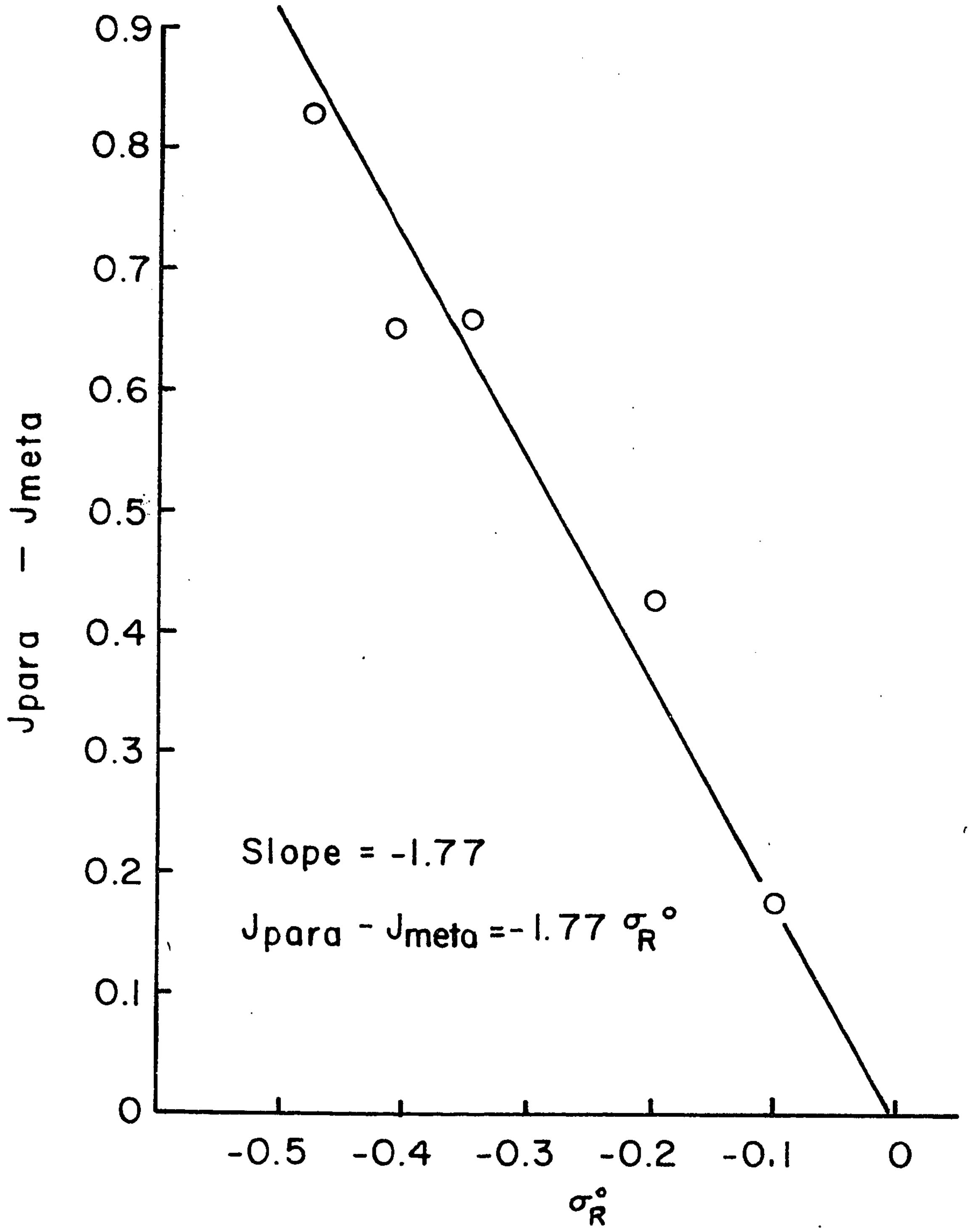


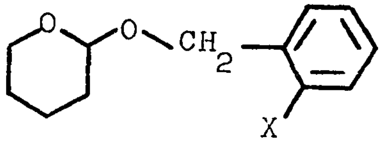
Figure 8 Plot of J_{para}-J_{meta} vs. σ_R°.

The effect of para substituents on J_{Gem} in a few related benzyl derivatives has been reported elsewhere. Oki and Iwamura (58) reported the variation of J_{Gem} in five para-substituted dibenzyl sulfites. The variation in J_{Gem} in these compounds follows the same trends that are reported here, but is about 30% less than in the 2-tetrahydropyranyl ethers. McDonald, Shannon, and Sternhell (59) found no measurable variation of J_{Gem} in the methyl group of several substituted toluenes.

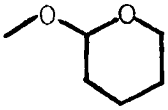
Ortho Substituents

The n.m.r. parameters of the AB non-equivalence quartet for the ortho-substituted benzyl 2-tetrahydropyranyl ethers are listed in Table 7. Ortho substituents can be seen to exert similar effects to that of para and meta substituents. However, these are complicated by steric interaction which will cause rotation about the C-Ar bond and thereby cause a change in J_{Gem}, since J_{Gem} varies with the projected angle between the H-H axis of the CH_2 group and the orientation of the p-orbital of the sp^2 carbon atom.

Table 7 N.m.r. Parameters for Ortho Substituted Benzyl 2-tetrahydropyranyl ethers,



X	$-J_{Gem}$(cps)* (high field)	$-J_{Gem}$(cps)* (low field)	$\Delta\nu_{AB}$(cps)	τ
H	12.00≠	12.10≠	16.9	5.33
NO_2	-**	15.47	20.3	4.99
OCH_3	12.85	13.40	13.4	5.26
CH_3	12.03	12.53	18.6	5.40
NH_2	11.40	11.87	16.3	5.37
X'	12.53	12.83	16.3	5.40

X' = 

* The average deviation in ten measurements was generally less than 0.1 c.p.s.

J_{Gem} was measured at a sweep width of 250 c.p.s. except where noted.

≠ J_{Gem} was measured at a sweep width of 100 c.p.s.

** J_{Gem} could not be measured from the high field side of the AB quartet because of interference from the anomeric proton's signal.

Steric Effects

J_{Gem} has been measured for the benzylic methylene protons in a few para-substituted benzyl phenyl sulfoxides. In contrast to the benzyl 2-tetrahydropyranyl ethers, no change in J_{Gem} with substituents was observed in these sulfoxides. For example, J_{Gem}'s in benzyl phenyl sulfoxide and 4-nitrobenzyl phenyl sulfoxide were 12.64 c.p.s. and 12.61 c.p.s. respectively. As mentioned before, Oki and Iwamura (58) reported a weaker substituent effect on J_{Gem} in para-substituted dibenzyl sulfites, and McDonald, Shannon, and Sternhell (59) found no measurable substituent effect on J_{Gem} in substituted toluenes. The most likely explanation of these contrasting results lies in the orientation of the benzene ring with respect to the methylene hydrogens.

The hyperconjugative effect of an adjacent p-orbital on J_{Gem} has been calculated (41) to be maximal (most negative) when the geometry is as shown in Figure 9(a), and minimal when as in Figure 9 (b).

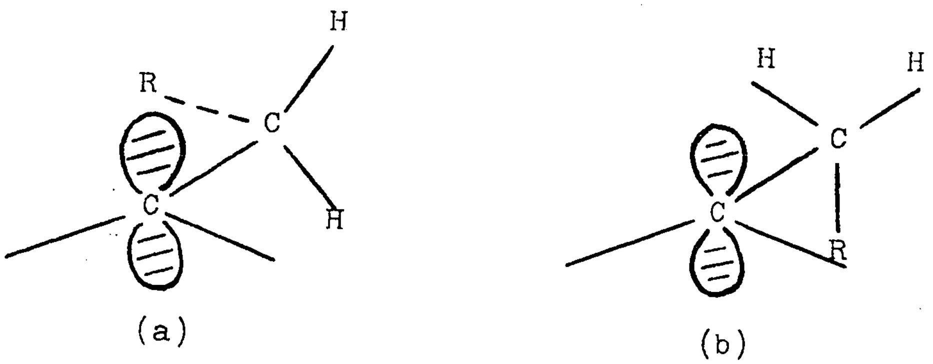
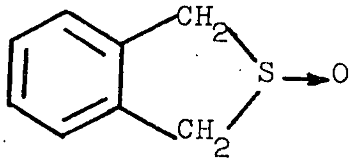


Figure 9. Orientation of the methylene group with respect to an adjacent p orbital.

Cookson and co-workers (37) have reported many examples which support this geometrical relationship.

It would then seem from the above results that variations in J_{Gem} with substituents are more or less pronounced depending upon whether conformation (a) or conformation (b) in Figure 9, predominates. For example, it would seem that conformation (a) predominates in the benzyl 2-tetrahydropyranyl ethers since J_{Gem} in these ethers varies substantially with the substituent, and also in the dibenzyl sulfites, although to a lesser extent.

On the other hand, conformation (b) should predominate in the benzyl phenyl sulfoxides and in the substituted toluenes, since J_{Gem} does not vary with the substituent in these compounds. Support for the proposal that conformation (b) predominates in the benzyl phenyl sulfoxides (J_{Gem} = -12.6 c.p.s.) is provided by the magnitude of J_{Gem} (-16 c.p.s.) (60) in the cyclic sulfoxide,



in which the geometry of the methylene group is fixed as shown in Figure 9(a). Since J_{Gem} has been shown to be most negative when the geometry is as shown in Figure 9(a), the magnitude of J_{Gem} (-12.6 c.p.s.) in the benzyl phenyl sulfoxides would indicate that conformation (b) predominates in these compounds.

The proposal that the variation in J_{Gem} with substituents depends upon the orientation of the methylene group relative to an adjacent p-orbital provides a method of determining the conformation of a methylene group with respect to an adjacent π -bonded carbon atom.

To our knowledge, the only previous work done in this area is Woolfenden and Grant's study (61) of the conformational dependence of the C^{13} chemical shifts in methylbenzenes and the conformational studies of 3-chloro and 3-methoxypropenes made by Bothner-By and co-workers (62).

One of the results of the work of Bothner-By and co-workers (62) is that in 3-methoxypropene the conformation shown in Figure 10(a) is more stable than that shown in Figure 10(b).

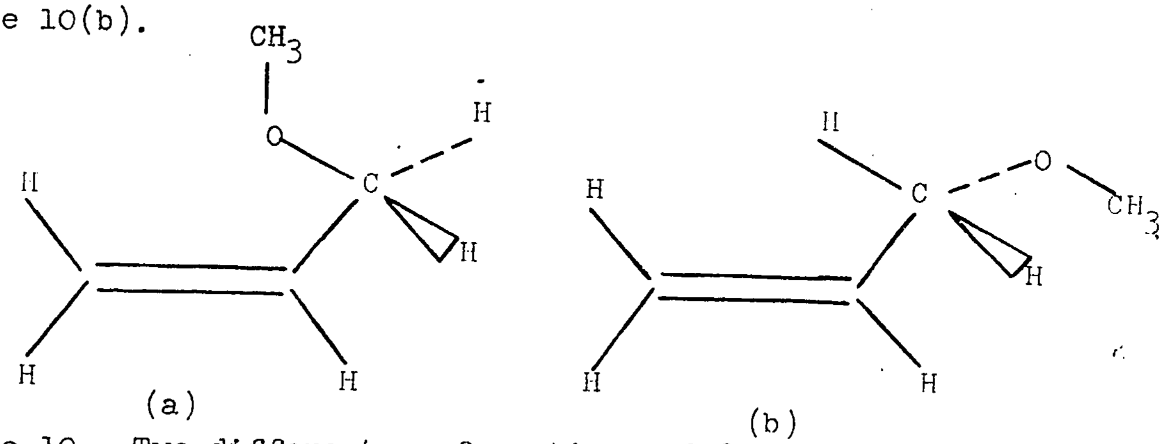


Figure 10. Two different conformations of 3-methoxypropene.

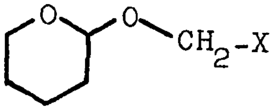
This particular result also supports the proposal made here that the conformation shown in Figure 9(a) where the H-H axis is parallel to the adjacent p-orbital, predominates in the benzyl 2-tetrahydropyranyl ethers.

Other Substituent Effects

The data in Table 8 provide a measure of the β-substituent effect. The results indicate that the groups with increasing inductive withdrawing power cause a negative shift in J_{Gem} in opposition to Pople and Bothner-By's theory (39) which predicts a positive shift in J_{Gem} with increasing inductive withdrawal of electrons. However, Pople and Bothner-By have proposed that for electronegative β-substituents, the resonance effect is dominant. The electron-donating resonance effect of the substituents in Table 8 increases in the order $CH_3 < H < Cl < F$. The results observed here agree with this interpretation.

The data in Table 9 show the hyperconjugative effect of one and two double bonds adjacent to the CH_2 group. It has been shown (40) that for a freely rotating methyl group an adjacent π-bond produces a shift in J_{Gem} of about -2 c.p.s. However, the magnitude of the shift varies with the angle between the CH_2 group and the π-system.

Table 8 N.m.r. Parameters for 2-alkoxytetrahydropyrans,



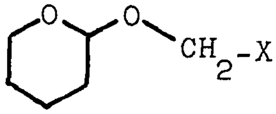
X	$-J_{Gem}$(cps)* (high field)	$-J_{Gem}$(cps)* (low field)	$\Delta\nu_{AB}$(cps)	τ
$C(CH_3)_3$	8.95	9.06	28.1	6.80
CH_3		9.83≠	20.0	6.51
CCl_3	11.56	11.72	11.1	5.82
CF_3		12.53≠	8.8	6.06

* The average deviation in ten measurements was less than 0.1 c.p.s.

J_{Gem} was measured at a sweep width of 100 c.p.s.

≠ J_{Gem} was measured from a 16-line ABX_3 pattern in which J_{Gem} can be measured from 8 different line spacings. J_{Gem} given here is the average of these measurements.

Table 9 N.m.r. Parameters for 2-alkoxytetrahydropyrans,



X	$-J_{Gem}$(cps)* (high field)	$-J_{Gem}$(cps)* (low field)	$\Delta\nu_{AB}$(cps)	τ
$-CH_3$		9.83	20.0	6.51
$-\phi$	12.00	12.10	16.9	5.33
$-C(CH_3)=CH_2$	-	12.86≠	14.1	5.94
	12.77	12.95	10.1	5.45
$-C\equiv CH$**	-	16.70≠	4	5.77

---

* The average deviation in ten measurements was less than 0.1 c.p.s.

J_{Gem} was measured at a sweep width of 100 c.p.s. except where noted.

≠ J_{Gem} was measured at a sweep width of 250 c.p.s.

J_{Gem} could not be measured from the high field side of the AB quartet because of interference from the pyranyl ring C-6 protons' signal.

**Spectra were measured in DMSO.

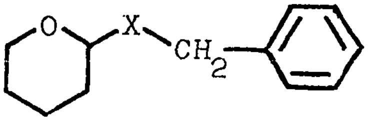
In certain cases, we might expect a shift of -6 c.p.s. for one adjacent π-bond. The values of J_{Gem} listed in Table 9 follow this trend.

The data in Table 10 illustrate the change in J_{Gem} for the substitution $O \rightarrow S \rightarrow NH$. Comparing J_{Gem} for these compounds with J_{Gem} reported (39) for ethylene oxide (+5.5), episulfide (±0.4), and aziridine (±2.0), we see that the shift is much stronger in these cyclic compounds than in the tetrahydropyrans, although presumably in the same direction. This difference must once again be attributed to different conformational populations in the three substituted tetrahydropyrans.

Solvent Dependence of J_{Gem}

As was pointed out in the introduction, J_{Gem} has been shown to vary with the solvent. A study of the dependence of J_{Gem} upon solvent was carried out using the 2-tetrahydropyranyl ether of benzyl alcohol. The geminal coupling constant between the methylene protons of the benzyl group was measured in ten different solvents.

Table 10 N.m.r. Parameters of



X	$-J_{Gem}$(cps)* (high field)	$-J_{Gem}$(cps)* (low field)	$\Delta\nu_{AB}$(cps)	τ
O	12.00	12.10	16.9	5.33
S	12.99	13.46≠	7.7	6.25
NH	13.48	-	13.4	6.03

* The average deviation in ten measurements was less than 0.1 c.p.s.

J_{Gem} was measured at a sweep width of 100 c.p.s. except where noted.

≠ J_{Gem} was measured at a sweep width of 250 c.p.s.

The results are listed in Table 11. J_{Gem} varies from -12.24 c.p.s. in cyclohexane (ϵ = 2.05) to -12.04 c.p.s. in dimethylsulfoxide (ϵ = 42). The results can be divided into two main groups, J_{Gem} measured in solvents of high dielectric constant, and J_{Gem} measured in solvents of low dielectric constant. One exception is J_{Gem} in chloroform where it is unusually low (J_{Gem} = -12.00 c.p.s., ϵ = 5.05). J_{Gem} in solvents of high dielectric constant (ϵ = 12 to 42) has an average value of -12.04 c.p.s., whereas in solvents of low dielectric constant (ϵ =2 to 3) it has an average value of about -12.20 c.p.s. The variation is really quite small, but it would seem to show an opposite trend to that reported by Smith and Cox (47). Their results showed that J_{Gem} decreased as the dielectric constant of the solvent increased. In this case, it would seem that J_{Gem} increases (i.e. becomes less negative) as the dielectric constant of the solvent increases. A similar solvent dependence study was also made on acetaldehyde dibenzyl acetal. The results of this study are also listed in Table 11. The same trend is again observed here. J_{Gem} measured in

Table 11 Solvent Effects on J_{Gem}

Solvent	ϵ (20°)	$-J_{Gem}$ (cps)* (in I)	$-J_{Gem}$ (cps)* (in II)
Cyclohexane	2.0	12.24	12.15
CCl_4	2.2	12.19	12.17
Benzene	2.3	12.22	12.13
CS_2	2.6	12.15	12.10
$CHCl_3$	5.0	12.00	11.85
Pyridine	12.5	12.02	——
DMF	21.0	12.02	11.97
Acetone	21.4	12.08	12.04
DMSO	42	12.04	12.04

* I = benzyl 2-tetrahydropyranyl ether.

II = acetaldehyde dibenzyl acetal.

All data in this table is accurate to within 0.1 c.p.s.

chloroform is also exceptionally low. Great care should then be taken in making any generalizations on the dependence of J_{Gem} with the dielectric constant of the solvent.

2(2,2,2-Trifluoroethoxy)-tetrahydropyran

The tetrahydropyranyl ether of 2,2,2-trifluoroethanol (I) gives rise to a more complex n.m.r. spectrum. Its spectrum, measured in deuterochloroform, is reproduced in Figure 11(a). The complex absorption pattern centered at τ 6.5 represents the methylene protons of the trifluoroethyl group of I. The pattern consists of 16 lines and is the AB part of an ABX_3 pattern. This portion of the spectrum is reproduced on an enlarged scale in Figure 11(b). The signals for the two protons on the 6-carbon atom of the tetrahydropyranyl ring also appear in the same region as the AB pattern, but these signals are very broad and do not interfere significantly with the sharper 16 line pattern. Surprisingly enough, the analysis of the ABX_3 pattern showed that the proton-fluorine coupling constants J_{AX} and J_{BX} had different magnitudes.

The analysis of the sixteen line pattern was carried out according to the method of Waugh and Fessenden (63).

Figure 11(a)

Figure 11(b)

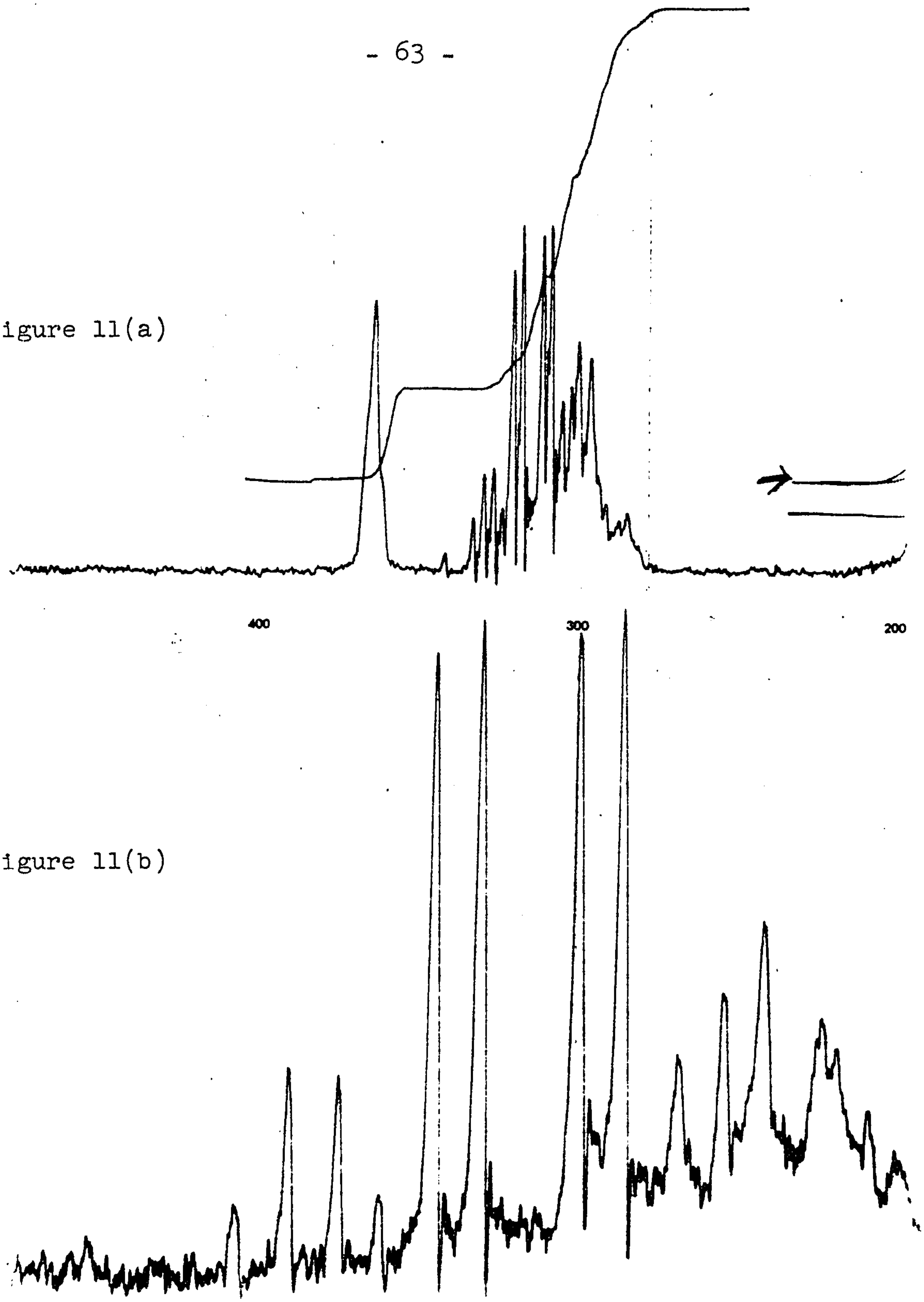


Figure 11(a) N.m.r. spectrum of 2(2,2,2-trifluoroethoxy)-tetrahydropyran.

(b) N.m.r. spectrum of the diastereomeric methylene protons in 2(2,2,2-trifluoroethoxy)-tetrahydropyran.

Figure 12 illustrates the splitting of the signal for protons A and B of the methylene group, caused by coupling of these protons with the fluorines of the trifluoromethyl group. Both the A and B proton signals are split into a quartet by the three fluorine nuclei. The spacings between the lines of quartet A and quartet B are equal to J_{AX} and J_{BX} respectively. The first line of the A quartet and the first line of the B quartet are then split into an AB quartet because of the coupling between the A and B protons. Three other quartets result in the same way from splitting of the second line of the A quartet and the second line of the B quartet, and so on for the third and fourth lines. J_{AX} and J_{BX} can then be calculated from the analysis of the four observed quartets.

Non-equivalence of J_{AX} and J_{BX} is reflected in the observed spectrum by a gradual decrease in the magnitude of the spacing between the two inner lines of each quartet, going in the upfield direction. This decrease can be seen in Figure 11(b).

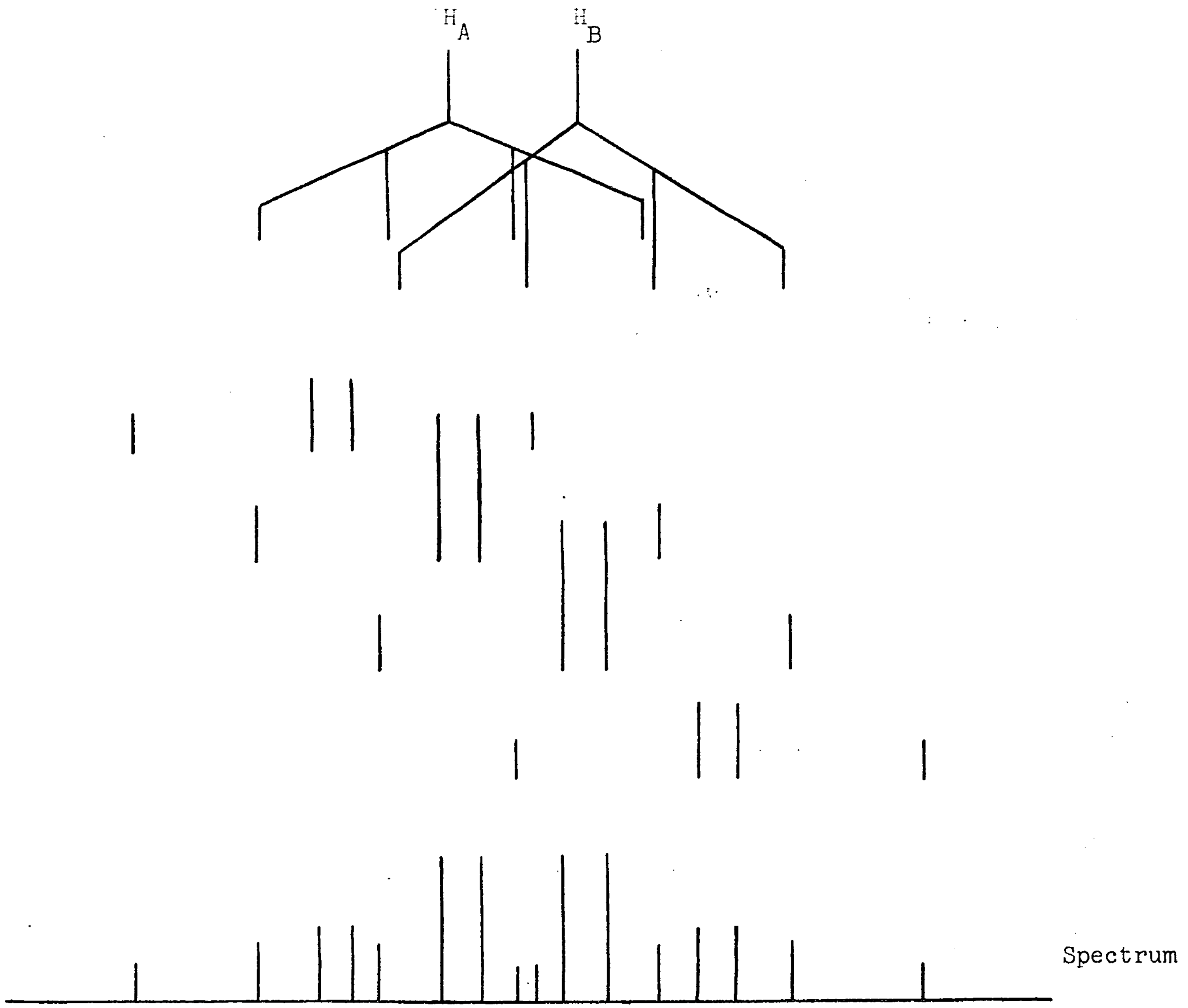


Figure 12 Example of the splitting resulting from coupling of an ABX_3 group.

The parameters obtained from the analysis were as follows: J_{AX} = 9.13 c.p.s.; J_{BX} = 8.77 c.p.s.; J_{AB} = -12.53 c.p.s.; $\Delta\nu_{AB}$ = 8.84 c.p.s. The ABX_3 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 similar examples in the literature (64-67). The parameters quoted above were then used to calculate a theoretical pattern of the ABX_3 splitting. The result is shown in Figure 13(b). It is compared with the experimental spectrum in Figure 13(a). The theoretical line positions agreed to within 0.1 c.p.s. with the corresponding experimental ones. The proton magnetic resonance spectrum of I was also measured on a 100 mC instrument, to verify the previous results. The same non-equivalence of vicinal H-F coupling constants was again observed.

The spectrum of I was also measured in several other solvents and at several temperatures. The parameters obtained from each ABX_3 analysis are listed in Table 12. In all cases $J_{AX} \neq J_{BX}$.

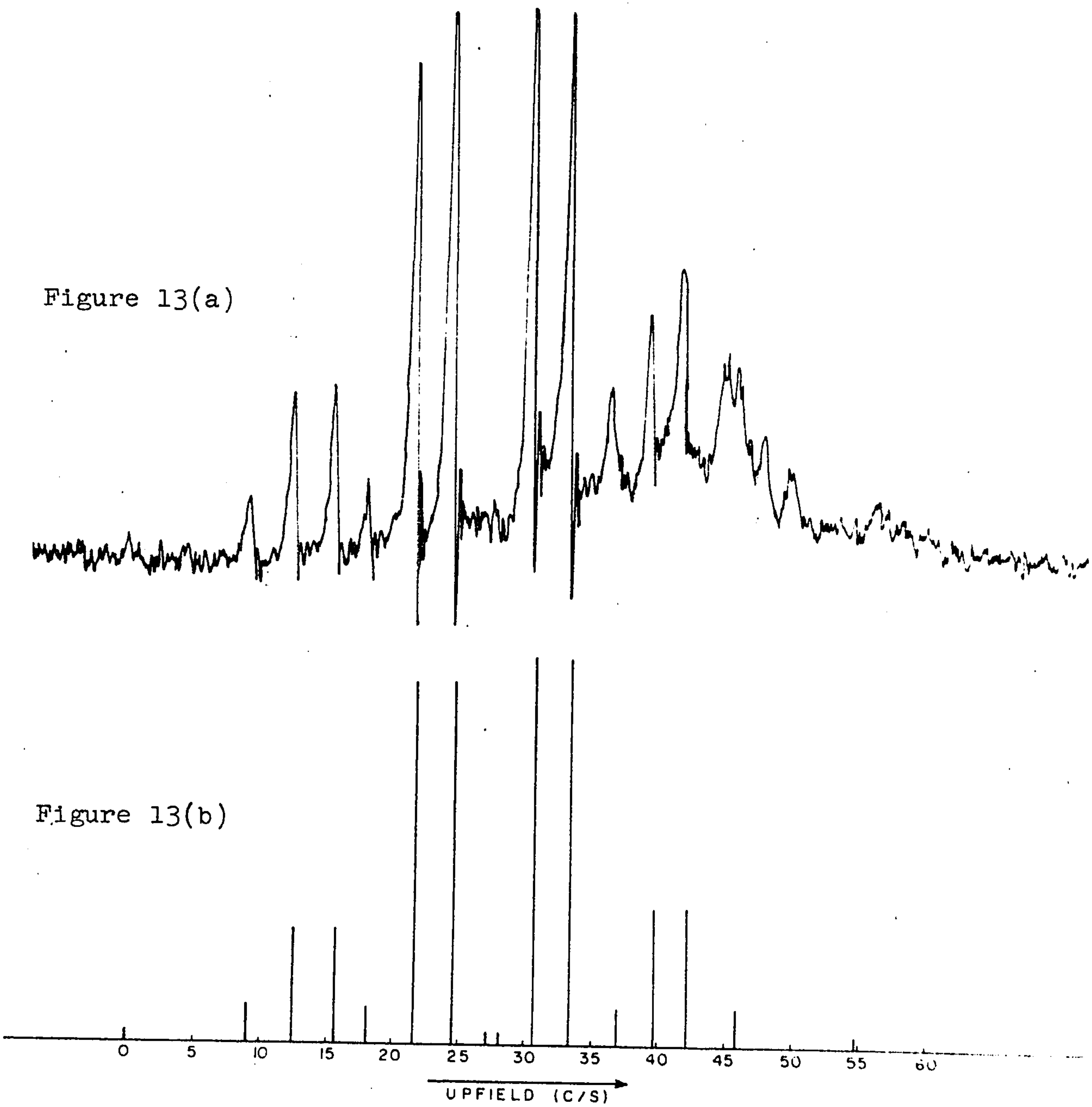


Figure 13(a) Experimental n.m.r. spectrum of the diastereomeric methylene protons in 2(2,2,2-trifluoroethoxy)-tetrahydropyran.

(b) Calculated n.m.r. spectrum of the diastereomeric methylene protons in 2(2,2,2-trifluoroethoxy)-tetrahydropyran.

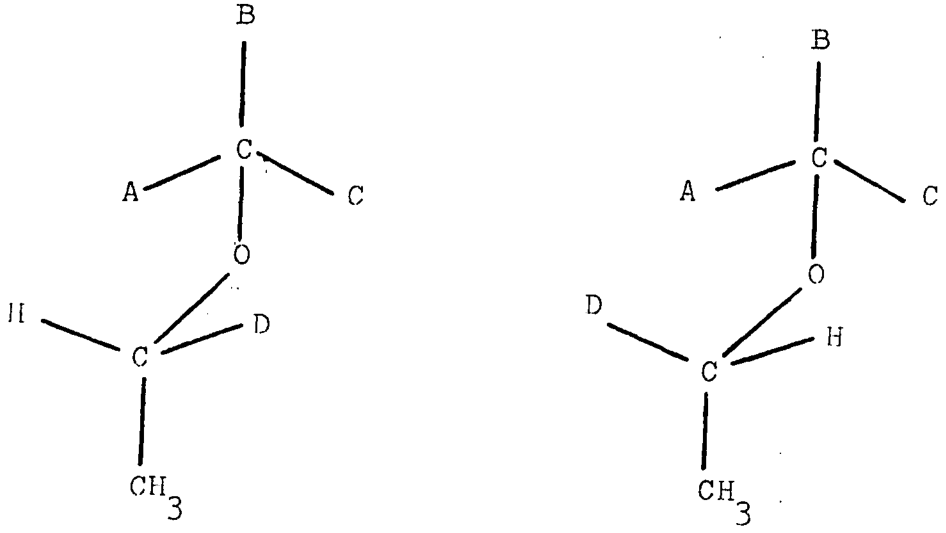
Table 12 N.M.R. Parameters of 2(2,2,2-trifluoroethoxy)-tetrahydropyran

Solvent	T(^oC)	J_{H_A-F}(cps)	J_{H_B-F}(cps)	ΔJ(cps)*	$\Delta\nu_{AB}$(cps)
$CDCl_3$	-38	9.07	8.77	0.30	9.8
	28	9.13	8.77	0.36	8.8
CH_2Cl_2	-43	9.35	8.63	0.72	10.1
	-28	9.21	8.87	0.34	10.1
	28	9.14	8.89	0.25	9.1
	60	9.01	8.77	0.24	9.0
	98	9.12	8.76	0.36	8.5
Benzene	28	9.15	8.92	0.23	15.0
Acetone	28	9.33	9.12	0.21	6.6

* All data in this table is accurate to within 0.1 c.p.s. except for the spectral measurements at -43° in CH_2Cl_2, where the accuracy is only 0.3 c.p.s. due to line broadening.

The variation in coupling constants with changes of solvent or temperature is quite small, and in fact of the order of the possible error in the values of the coupling constants. It is, therefore, not possible to deduce any trends of the variation of the coupling constants with changes of solvent or temperature from the available information.

The NMR spectrum of the tetrahydropyranyl ether of ethanol (II) was also examined to see if the vicinal proton-proton coupling constants exhibited the same non-equivalence as the vicinal proton-fluorine coupling constants in I. Here, the ethyl group gives rise to a 16 line ABC_3 pattern also, but unfortunately the analysis of such a pattern is too complex to allow detection of non-equivalence of the order of magnitude of that observed in I. The two vicinal proton-proton coupling constants were determined by another method. A racemic mixture of α-deuteroethanol, prepared from the reduction of acetaldehyde by lithium aluminum deuteride, was converted by reaction with 2,3-dihydropyran to the diastereomeric mixture of tetrahydropyranyl ethers (III).



III

The n.m.r. spectrum of this mixture measured in deutorochloroform during simultaneous irradiation of the deuterium nuclei is shown in Figure 14. Each of the two components of the racemic mixture gives rise to an AB_3 pattern in the n.m.r. spectrum. The A portions of these two AB_3 patterns were analysed according to Corio's method (4) and J_{CH_3-CH} was calculated for each of the two components of the mixture. The values found were 7.18 c.p.s. and 7.19 c.p.s.

The non-equivalence of the vicinal coupling constants evident in the trifluoroethyl group of I cannot be detected in the case of an ethyl group.

Figure 14

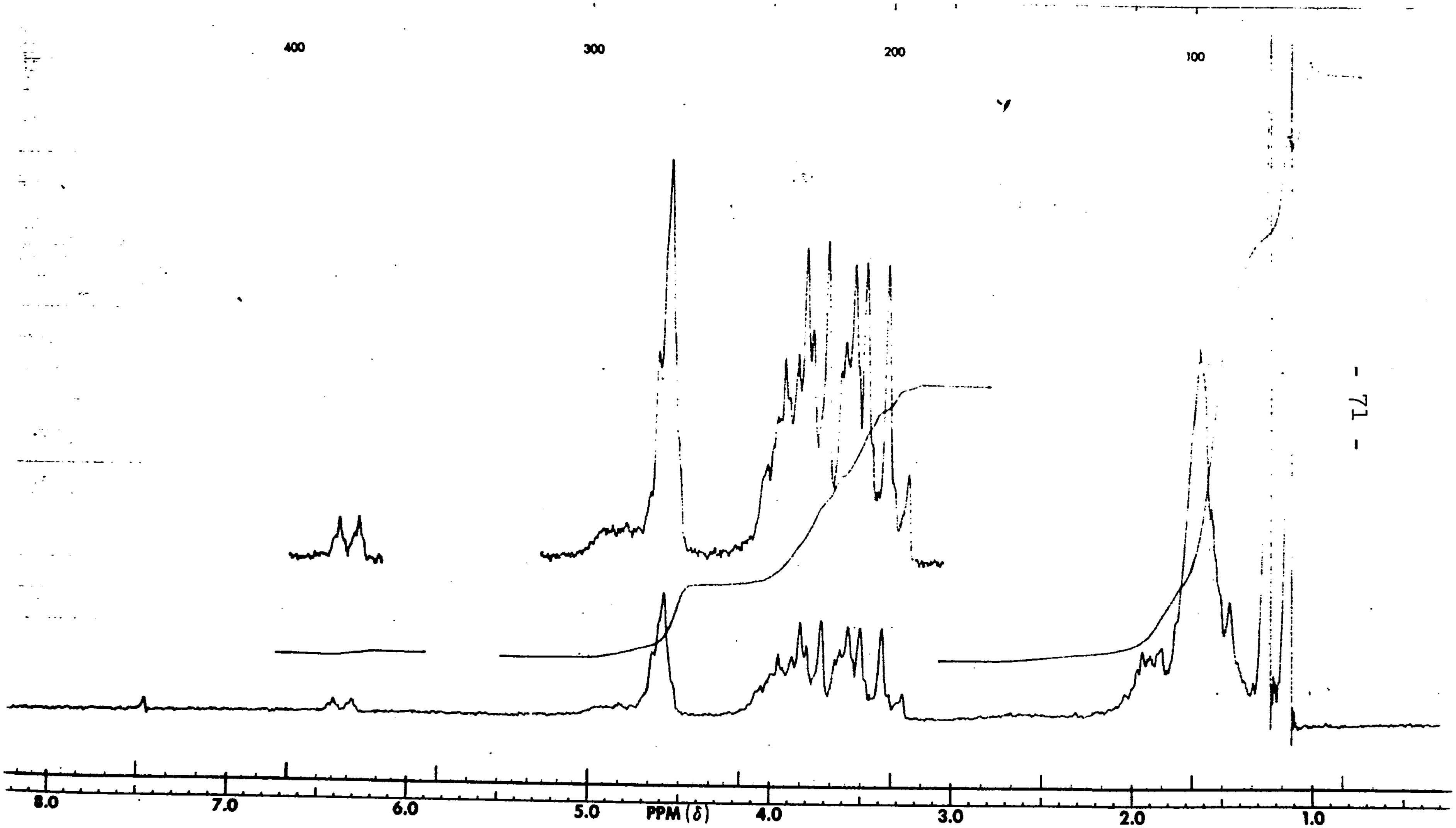
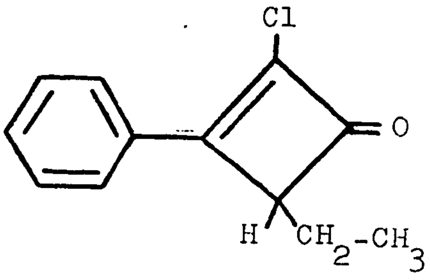


Figure 14 N.m.r. spectrum of a diastereomeric mixture of 2(1-deuteroethoxy)-tetrahydropyrans.

It would then seem that vicinal H-F coupling constants are more sensitive than vicinal H-H coupling constants to variations in bonding. There is some evidence in the literature (68-71) which shows the greater sensitivity of fluorine n.m.r. spectral parameters to small structural differences. It may also be that the greater electronegativity of the CF_3 group is responsible in some way for the appearance of non-equivalent vicinal coupling constants in the trifluoroethyl group only.

As was mentioned in the introduction, magnetic non-equivalence may be defined in terms of chemical shifts and coupling constants. Magnetic non-equivalence in the chemical shift sense only, occurs when the chemical shifts of the nuclei are different, but the nuclei are coupled equally to every other nucleus in the molecule. Many examples of this type of non-equivalence have been reported in the literature (7). Magnetic non-equivalence in the spin coupling sense only, occurs when the nuclei have identical chemical shifts, but are coupled differently to one or more other nuclei in the molecule. This is the case for the methylene protons in 1,1-difluoroethylene (8) and 1-chloro-2-bromoethane (72). The non-equivalence here is readily understood since the two nuclei in question have different geometrical relationships to the neighbouring nuclei. It is also possible to have magnetically non-equivalent nuclei which have both different chemical shifts and unequal couplings. In cyclohexanol the protons on the 2-carbon atom have different chemical shifts and are coupled unequally to the single proton on the 1-carbon atom (9). The methylene protons in the ethyl group in A have different chemical



(A)

shifts and are coupled unequally to the adjacent methine proton (28). The differences in vicinal coupling constants in these examples, however, are readily explained and indeed expected when one considers the well-known Karplus relationship (48) between vicinal proton-proton coupling constants and the dihedral angle, ϕ.

The magnetic non-equivalence observed in I is of this latter type where both chemical shifts and coupling constants are involved. However, the non-equivalence of the vicinal H-F coupling constants observed in I cannot be explained as readily as in the previous examples since there is no rigid structure which could account for different dihedral angles between each of the methylene protons and the fluorines. This type of non-equivalence is without precedent. There is an erroneous report of such a case in the literature. Finegold (15) reported that the vicinal coupling constants in diethyl sulfite were unequal. However, Kaplan and Roberts (37) later showed this report to be wrong because of the use of a positive sign for the geminal coupling constant in the analysis of the ABC_3 spectrum of diethyl sulfite by Finegold. The use of a negative sign for the geminal coupling constant gave much better agreement with the experimental spectrum and resulted in equal vicinal coupling constants.

Since the non-equivalence of the vicinal H-F coupling constants in I cannot be explained on the basis of the simple Karplus relationship for the reasons given already, some other explanation must be sought. First of all, coupling between nuclei occurs primarily through the bonding electrons (48). There is some evidence that coupling between protons and fluorine nuclei sometimes occurs through space (73), but this seems to be limited to a few examples where there are five bonds between the H and F nuclei It is then possible for the H and F nuclei to lie close to one another by way of a six-membered ring. Vicinal H-F coupling constants have also been shown to be strongly dependent upon the dihedral angle, ϕ (71, 74, 75). The fluorines in I, however, are chemically equivalent, that is, they have the same chemical shift. This is obvious, since an ABXYZ spectrum instead of an ABX_3 spectrum would be observed if the fluorines had different chemical shifts. This means that the CF_3 group must be rotating fast enough so that on the n.m.r. time scale the environment around all three fluorines is averaged out, and thus the same for all three nuclei. It is possible that the non-equivalent coupling could be a result of different dihedral angles between H_A and the three fluorines compared with H_B and the three fluorines, as shown in Figure 15. Since the fluorines are chemically equivalent, however, only a difference in the C-H_A and C-H_B bonds can account for the non-equivalent couplings. The difference between the C-H_A and C-H_B bonds may be a difference in bond length, H-C-C bond angle, or bond hybridization, all of which affect J (76).

The most favorable conformation for I is shown in Figure 16. The CF_3CH_2O group is in the axial position because of the anomeric effect (77). The narrow half-band width of the signal for the anomeric proton at τ5.2 is direct evidence for the axial CF_3CH_2O group. The remaining bonds in this group are assumed to occupy the staggered conformation in which the bulkiest substituents are trans to one another. In this conformation one of the methylene protons is quite close to the oxygen atom of the ring. It may be that there is some O - - - H_A interaction which leads to a change in the C-H_A bond,

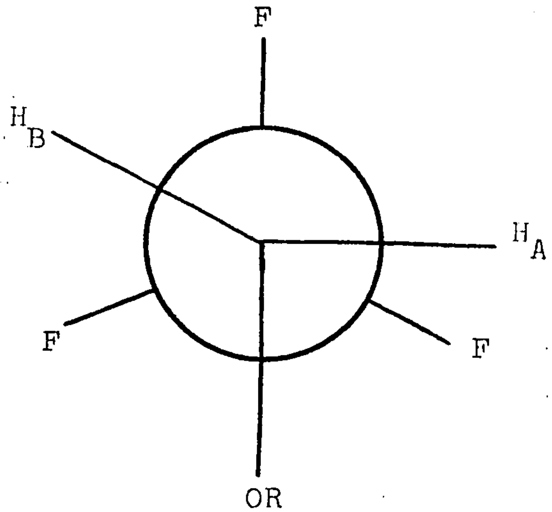


Figure 15. Dihedral angles in a trifluoroethyl group.

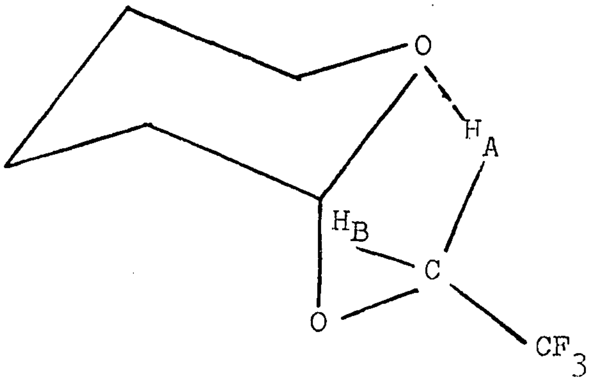


Figure 16. The most favorable conformation of 2(2,2,2-trifluoroethoxy)-tetrahydropyran.

thus making the C-H_A and C-H_B bonds non-equivalent.

Throughout the discussion we have referred to a "non-equivalence" of vicinal H-F coupling constant. It is interesting to compare non-equivalence in the chemical shift sense, and in the coupling constant sense. As mentioned before, non-equivalence of chemical shift is due both to conformational preferences and "intrinsic asymmetry". The observation of intrinsic asymmetry is either evidence for electronic differences in the two C-H bonds (or C-F bonds, as the case may be) or evidence for differences in magnetic environment due to bond distortions elsewhere in the molecule. In contrast, non-equivalence in vicinal couplings is evidence specifically for electronic differences in the C-H bonds.

CONCLUSIONS

The relationship established between the geminal coupling constant and the Hammett substituent parameters, and the marked dependence of substituent effects on the angle between the H-H axis of the methylene protons and the orientation of an adjacent p-orbital, indicate that such correlations between the structure of the molecule and the geminal coupling constant may be extremely useful to elucidate structural and stereochemical features in a molecule, just as the Karplus relation between vicinal H-H coupling constants and ϕ, the dihedral angle, has proven to be.

In contrast to the observation of intrinsic asymmetry non-equivalence which is either evidence for electronic differences in bonding or for differences in magnetic environment, the observation of non-equivalence in vicinal coupling constants observed here is evidence specifically for electronic differences in bonding.

CLAIMS FOR ORIGINAL WORK

1. Twenty-four new 2-alkoxytetrahydropyrans were prepared.
2. A linear correlation has been established in a series of para and meta substituted benzyl 2-tetrahydropyranyl ethers between J_{Gem} of the benzylic methylene protons and σ_p^o and σ_m , the Hammett substituent parameters.
3. A linear relationship has been established in a series of para and meta substituted benzyl 2-tetrahydropyranyl ethers between $J_{para} - J_{meta}$, the difference between the geminal coupling constants of the benzylic methylene protons in the para and meta substituted benzyl ethers, and σ_R^o , the corrected Hammett resonance parameters for para substituents. This relationship follows the equation

$$J_{para} - J_{meta} = -1.77 \sigma_R^o .$$

4. A method of determining the conformation of a methylene group with respect to an adjacent π-bonded carbon atom has been suggested. This method is based on the proposal made here that the substituent effect on J_{Gem} depends upon the orientation of the methylene group relative to the adjacent p orbital.

5. The unique and surprising non-equivalence of vicinal H-F coupling constants in a CF_3-CH_2 group has been measured in various solvents and at different temperatures. The non-equivalence $J_{AX} \neq J_{BX}$ has been interpreted as evidence that the C-H_A and C-H_B bonds of the trifluoroethyl group differ electronically.

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