CARBON-13 MAGNETIC RESONANCE SPECTROSCOPY

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Abstract

High-resolution, natural-abundance ^{13}C spectra have been obtained from a wide variety of organic compounds; ^{13}C chemical shifts and coupling constants have been correlated with other molecular properties.

Geminal and vicinal, carbon-proton couplings in benzene and the five- and six-membered aromatic heterocycles have been related to the corresponding proton-proton couplings in substituted ethylenes. The carbon-proton coupling constants in benzene are $J_{CCH} = +1.0$, $J_{CCCH} = +7.4$ and $J_{CCCCH} = -1.1$ Hz. Extended Hückel wavefunctions are uniformly poor in explaining the long-range, carbon-proton couplings in aromatic systems.

Couplings between carbon and elements other than hydrogen have been observed in proton decoupled ^{13}C spectra. All of the carbons in fluorobenzene and 1-fluoronaphthalene, but only six of the carbons in 2-fluoronaphthalene are coupled to the fluorine. One-bond, carbon-phosphorus coupling in trialkylphosphines is negative, while one-bond, carbon-phosphorus coupling in tetra-alkylphosphonium ions is positive. Atoms which do not use hybrid orbitals to form bonds to carbon (F, P(III), Se, Te) may have negative, one-bond coupling constants because of the failure of the average energy approximation. One-bond couplings between carbon and carbon, silicon, tin, lead and mercury appear to be explainable in terms of an effective nuclear charge and the s-bond order of the metal. Couplings between carbon and nitrogen and phosphorus(IV) have significant negative contributions to the Fermi contact coupling expression, though, within one series, correlations with s-bond order may be valid. Carbon-carbon coupling in cyclopropane derivatives (10-15 Hz) is consistent with a high degree of p character in the interior orbitals. Some two- and three-bond carbon-carbon coupling constants have also been observed.

Substituent effects of hydroxyl groups on the ^{13}C chemical shifts of continuous-chain alkanes depend both on steric and electronic factors. The hydroxyl substituent effects in the long-chain, primary alcohols are $\alpha = -48.3$, $\beta = -10.2$, and $\gamma = +6.0$ ppm. The upfield γ effect is attributed to steric crowding in the *gauche* conformations. Additivity of the hydroxyl and carbonyl and alkyl substituent effects in alkyl-substituted cyclohexanols and cyclohexanones has been demonstrated.

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I. Introduction

The practical use of ^{13}C nuclear magnetic resonance has been hindered by low natural abundance of this nucleus (1.1%), low inherent sensitivity to nmr detection (1.6% relative to protons at constant field) and long relaxation times (1, 2). Various methods have been used to overcome these difficulties.

Isotopic enrichment increases the number of ^{13}C nuclei in the active sample volume. Furthermore, specific introduction of ^{13}C allows unambiguous assignments of the carbon resonances to be made. The main disadvantage of this technique is the expense of preparing the labelled materials. The possibility of using ^{13}C as a non-degradative tracer in labelling studies has received only limited attention because of the experimental difficulties in observing ^{13}C resonances (3).

The INDOR technique developed by Baker (4) allows the ^{13}C resonances to be detected with the sensitivity of proton nmr. For observation of ^{13}C resonances by INDOR the field of the spectrometer is adjusted so that a ^{13}C satellite resonance in the proton spectrum is on resonance. A weak rf field is then swept through the ^{13}C spectrum. When a transition in the ^{13}C spectrum is irradiated which has an energy level in common with the proton line, a perturbation of the proton resonance is seen. This technique demands excellent spectrometer stability and the clear observation of the ^{13}C satellites of the proton spectrum. Because of the complexity of the proton spectrum of large molecules, the technique is limited to simple structures, and so far has been mainly used for the magnetically equivalent protons of methyl groups.

In order to exploit the maximum signal-to-noise ratio from the direct observation of a given sample, high rf fields are used and to lessen difficulties with saturation, the field is swept rapidly and the spectra are observed in the dispersion mode. By adjusting the rf field so that the trailing halves of the dispersion peaks are saturated and thus not seen, the spectrum resembles an ordinary absorption-mode spectrum. Trailing peaks in spin-spin multiplets are partly saturated because of magnetization transfer effects (which might better be termed cross-relaxation). Linewidths of true singlets are on the order of 10 Hz because of broadening associated with the rapid sweep rate. Small chemical shifts and long-range coupling cannot be resolved, but the resolution is adequate for some studies. Most ^{13}C studies have been carried out in this manner.

A major advance in the field of natural abundance ^{13}C nmr was the application of complete proton decoupling during conventional field-sweep experiments. Grant and Paul (5) found that the signal-to-noise ratio was improved both by the collapse of the proton induced multiplet structure and a positive nuclear Overhauser effect. Because the sensitivity was increased, slower passage conditions could be used resulting in higher resolution. Precision of measurement was also improved because the ratio of the decoupling and the observing frequencies could be measured an order of magnitude more accurately than the peak separations in rapid-passage spectra. The spectra were easier to interpret because only singlets are seen for each unique type of carbon. With linewidths on the order of 1 Hz long-range effects on the ^{13}C chemical shifts could be studied for the first time. Although the spectra obtained using this technique are very useful in the study of chemical shifts, they suffer from the fact that all proton spin-spin coupling information is lost. The sensitivity is quite good when the proton decoupling frequency is optimized, but the frequency range over which the signal-to-noise improvement is seen is only a few Hz.

Two instrumental advances have made direct observation of ^{13}C nmr more practical. Field-frequency stabilization, either from an internal reference signal or by means of an auxiliary control sample, allows long-term stability to be maintained. Time-averaging of weak signals using a small digital computer allows weak signals to be observed if the spectrometer is sufficiently stable and if the experimenter is willing to wait long enough.

Recently it has proved possible to lock a conventional HA-100 to the ^{13}C resonance of an enriched sample of methyl iodide contained in a capillary tube inside a 5-mm nmr tube (6). Although the lock signal borders on the "invisible", it is sufficient to keep the field from drifting and to actuate the Autoshim* circuitry making time-averaging possible.

Two state-of-the-art nmr spectrometers incorporating field-frequency stabilization and time-averaging have been built by Varian Associates: the AFS-60 delivered to D.M. Grant at the University of Utah and the DFS-60 used in this work. The unique features of the DFS-60 will be described in some detail.

The DSF-60 (Digital Frequency Sweep) is a state-of-the-art nmr spectrometer specially designed and built for J. D. Roberts by F. Nelson and V. Burger of Varian Associates, Palo Alto, California. Basically the instrument is an HA-60 spectrometer with modifications in the locking and sweep circuitry. In contrast to the frequency-sweep systems of conventional spectrometers which are derived by sweeping an audio-frequency sideband, the DFS-60 utilizes a centerband sweep. Because the sideband frequency is constant, phase shifts are eliminated. A Varian 4355 digital programmer electronically changes the output frequency of a Hewlett-Packard 5100-5110A frequency synthesizer. The programmer can advance the frequency of the synthesizer by increments as small as 0.01 Hz in either direction. Total sweep widths range from 1 Hz to 5 KHz and sweep times from 25 to 500 seconds. In order to achieve slow-passage spectra, it has been found to be more convenient to narrow the sweep width at a given sweep time than to increase the sweep time. Because the sweep is not mechanically controlled the flyback is a nominal 0.2 sec which allows more scans to be collected in a particular range of interest in a given period of time.

The synthesizer has two major outputs: the frequency-swept 15 MHz signal which is used to excite the ^{13}C transitions and a very stable 30 MHz signal which is used for field-frequency control. The frequency of the latter signal is doubled to 60 MHz and is used to excite proton transitions for locking purposes. A modulation frequency of 6 KHz is used in order to avoid overlapping sidebands and centerbands in the ^{13}C spectrum. The field-frequency control may be actuated either by a resonance in the sample as with the HA-60-IL systems, or alternatively the field may be locked to a water sample contained in a "piggy-back" probe which is located close to the sample, as in the HA-60-EL or A-60 systems. If the external lock is used, the positions of the resonances are measured with respect to an internal standard and the Autoshim* unit which maintains the optimum Y gradient when the DFS-60 is operated in internal-lock mode is inoperative. All proton decoupling is currently done in the external lock mode, because the proton decoupling signal must enter on the same circuitry used to excite the transitions for the internal lock.

The proton decoupler consists of a second Hewlett-Packard 5100-5110A frequency synthesizer. The synthesizer is nominally tuned to 30 MHz and the second harmonic detected and amplified by a Boonton 230 A power amplifier. A Daven rf attenuation network was used for applications where less than the maximum power was required. The amount of decoupling power which can be applied to the probe is at present limited by the heat dissipation. During decoupling experiments, the samples become distinctly warm.

Although the DFS-60 is considerably more stable than previous ^{13}C spectrometers, it is no more sensitive. The signal-to-noise ratio for a single pass through the resonance of natural abundance, neat, benzene, under optimum proton decoupling conditions and with rf and sweep rate adjusted for time-averaging is 100:1.

Operation in internal lock mode requires only time. No operator intervention is needed except to verify that the field-frequency lock is maintained. At present, adjusting the proton decoupling frequency is the limiting feature in obtaining proton decoupled ^{13}C spectra. The decoupling frequency must be within 4 Hz of the proton chemical shifts of directly bonded protons for optimum results. Generally about 20 minutes is required to find the optimum proton decoupling frequency for each carbon of a typical sample. Noise decoupling may in the future alleviate this difficulty (7). Fourier transform spectroscopy (8) will probably not be useful in ^{13}C studies because of the long relaxation times of ^{13}C.

Review of Recent Work

The field of ^{13}C nmr has been reviewed previously (9, 10) and the earlier work will not be discussed here in detail. Studies of ^{13}C nuclear magnetic resonance may be conveniently divided into four classifications: 1) chemical shifts, 2) one-bond, carbon-proton coupling constants, 3) long-range, carbon-proton coupling constants, and 4) couplings of carbon and other nuclei.

Most studies of ^{13}C chemical shifts have used rapid-passage, dispersion-mode techniques, and thus would have to be classified as low-resolution by present-day standards. Because of the small chemical shifts associated with distant effects in aliphatic and alicyclic compounds, most carbons are not resolved by the rapid-passage techniques. Therefore, aromatic and olefinic compounds, carbonyl carbons and the substituted carbons in aliphatic systems have been the most studied.

The carbonyl group has been a favorite object of study because its ^{13}C resonance occurs in an otherwise unoccupied region of the spectrum and it has no directly bonded protons and appears as a "singlet." Solvent effects (11) and deuterium isotope effects (6) on the carbonyl resonance of acetone have been studied. Stothers has correlated the carbonyl resonance of substituted acetophenones (12) with the angle between the carbonyl group and the plane of the aromatic ring. Similar studies have been made for the exocyclic carbons in substituted styrenes (13), methyl benzoates (14), and anisoles (15). Savitsky (16) correlated the chemical shifts of carbonyl carbons in various alicyclic compounds with $n \rightarrow \pi^*$ ultraviolet transitions. The unusual chemical shift of the carbonyl group in five-membered rings was explained in terms of the average excitation energy. The carbonyl resonances in cyclic ketones have also been studied by Lauterbur and Stothers (17). Lauterbur has determined the ^{13}C chemical shifts of the cycloalkanes (18).

Mathias has measured the carbonyl chemical shifts of substituted benzaldehydes by INDOR techniques (19). The ^{13}C chemical shifts of acids, their anions and the various protonated species in concentrated sulfuric acid and antimony pentafluoride have been the subjects of several investigations (20,21).

The unsaturated carbons in alkenes (22) and alkynes (23) have been studied by Maciel. Stothers obtained the ^{13}C chemical shifts of the sp^2 carbons in some α-β unsaturated ketones (24). Savitsky studied the chemical shifts of some cis- and trans-substituted ethylenes (25). An additivity relationship was derived which predicted chemical shifts to within 2 ppm based only on the substituents directly bonded to the carbon of interest (26). Maciel has observed the α carbons in saturated heterocycles (27), amines (28), and nitriles (29). Malinowski has measured the chemical shifts of some substituted cyclopropanes (30). Savitsky (31) and Maciel (32) have studied the additivity of substituent effects on the chemical shifts of the aromatic carbons in disubstituted benzenes. Retcofsky has studied the chemical shifts in substituted pyridines and finds that substituent effects are the same as those in benzenes (33). Lauterbur has observed the carbonyl resonances in some metal carbonyl complexes and the aromatic carbons in some cyclopentadienide complexes (34). Retcofsky studied the conformation of butadiene iron-tricarbonyl by observing the ^{13}C chemical shifts and carbon-proton coupling constants (35). Mathias and Gil have observed the chemical shifts of the diazines and some of their protonated species by double resonance techniques (36).

Grant, using the proton decoupling technique (5), has measured the ^{13}C chemical shifts in a wide variety of compounds. Because of the better resolution more distant effects on the chemical shift can be seen. The study of the continuous-chain and branched alkanes provided the basis for other studies in the aliphatic series. A series of additive substituent parameters were derived from which the chemical shifts of all the carbons could be predicted (5). The same idea of additive substituent parameters was applied to the study of the cyclohexane carbons in the methylcyclohexanes (37). Pairwise substituent effects were needed to adequately explain the chemical shifts in the polyhalomethanes (38). Both molecular-orbital and valence-bond calculations were used to explain the chemical shifts observed in the aromatic five-membered heterocycles (39), purine (40), and some alternate and non-alternate aromatic hydrocarbons (41). The methyl resonances in methylbenzenes were correlated with the possible conformations of the methyl groups (42). The effect of protonation of the six-membered nitrogen heterocycles was investigated (43). Substituent effects in primary, continuous-chain compounds have been obtained (44). Retcofsky's observation that only nearest neighbor interactions need be considered results from the cancellation of the substituent effects from the β and γ positions. Additivity of substituent effects on disubstituted ethanes was also investigated (44).

Stothers has used proton decoupled spectra to determine the conformational preference of a hydroxyl group in hydroxycyclohexanes (45, 46). Studies of substituent effects in substituted norbornanes are being carried out by several groups.

One-bond, carbon-proton couplings are generally observed in proton spectra. Carbon-proton couplings of all simple compounds in which the satellites are easily seen are now routinely reported. In the organometallic field a wealth of data has been gathered on compounds of the type $(CH_3)_nMX_{4-n}$ (47-51), where M is silicon or tin and X is either halogen or methoxy. Carbon-proton couplings in the methoxy group have also been reported. Within the average energy approximation, the carbon-proton coupling constant is dependent on the carbon orbital hybridization, the effective nuclear charge appearing in the radial function of the carbon 2s orbital and the average excitation energy. The practice of attributing the large changes in the carbon-proton coupling in highly substituted methanes to hybridization changes has been discredited (52, 53). Both nuclear charge (52) and excitation energy (54) effects have been put forward as alternative explanations. No one parameter is sufficient to explain the changes, and probably all of them must be considered simultaneously.

Goldstein has measured several one-bond, carbon-proton coupling constants in the quest of proton-proton couplings from the satellite spectra (55-60). He has found several correlations between this type of coupling and the electronegativity of the attached groups. Hammaker has studied carbon-proton couplings in aldehydes (61) and Simonnin (62) has studied the couplings in substituted acetylenes. Olah has studied the effects of charge and hybridization on carbon-proton coupling in some carbonium ions (63) and carbanions (64). The original report of the coupling constant in the isopropyl carbonium ion was incorrect, and the revised value of 168 Hz is in agreement with the hybridization criteria generally applied to hydrocarbon coupling constants. Tori and Nakagawa (65) have obtained the carbon-proton couplings in a number of heterocycles and their methyl derivatives. Laszlo (66) has also studied these coupling constants and Laszlo and Schleyer (67) and Tori (68) have studied the carbon-proton coupling constants of a number of cyclic and bicyclic systems.

Tanabe (69) has used carbon-proton coupling with ^{13}C enrichment in a study of the biosynthesis of griseofulvin.

The only systematic study of long-range, carbon-proton coupling constants remains that of Karabatsos and his co-workers using enriched compounds and observing the coupling in proton spectra (70-72). McLauchlan and McFarlane have used INDOR techniques to observe coupling between carbon and other nuclei and have found some long-range, carbon-proton coupling constants (and have missed others).

Dreeskamp (73-75) has used homonuclear tickling techniques to determine the magnitudes and signs of some carbon-proton coupling constants in acetylenes, ethylenes, aldehydes and substituted ethanes. Simonnin (62) has been able to observe the inner satellites of the proton spectrum of some acetylenes. Govil (76) has used homonuclear tickling to determine some carbon-proton coupling constants in aromatic systems. Freeman (77) has used heteronuclear tickling and other fancy double resonance techniques (78) to investigate the signs and magnitudes of long-range, carbon-proton coupling, always observing the proton spectrum. Olah (21) has observed long-range coupling in the proton spectrum of some ^{13}C enriched carbonium ions.

The standard work in the field of carbon-fluorine coupling remains that of Muller and Carr (79). Mohanty (80) observed carbon-fluorine coupling in the satellites of the fluorine spectrum of substituted fluorobenzenes, but no decoupling was used and the results are likely to be of low accuracy. Reuben and Demiel (81) observed one- and two-bond, carbon-fluorine coupling in some fluorinated ethylenes.

McLauchlan and McFarlane (82-93) have studied the coupling of carbon and other elements by heteronuclear tickling techniques. Coupling has been observed with silicon, tin, lead, nitrogen, phosphorus, mercury, selenium, and tellurium. Relative signs have also been determined. Dreeskamp (75) has used similar techniques with the tetramethyl derivatives of group IV with samples enriched with ^{13}C. McLauchlan (88) determined the sign of the carbon-carbon coupling constant in acetonitrile by heteronuclear tickling. Grant (94) has observed carbon-carbon coupling in singly labelled acetic acid and determined the sign by heteronuclear decoupling. Both workers show that one-bond, carbon-carbon coupling has the same sign as one-bond, carbon-proton coupling. Grant (95) has also investigated polar effects on carbon-carbon coupling in *t*-butyl derivatives using natural abundance ^{13}C. Carbon-nitrogen couplings have been observed in the ^{15}N spectra of doubly labelled compounds (96).

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II. Carbon-Proton Coupling in Aromatic Compounds

Although the one-bond, carbon-proton coupling constants in the aromatic heterocycles are well characterized (1,2) there have been no systematic studies of the long-range, carbon-proton coupling constants in these systems. Direct observation of the inner satellites of the proton spectrum is hampered by the strong resonances arising from molecules with no ^{13}C. If the proton spectrum is particularly simple, these inner satellites can be observed (3) but they can not be assigned to a particular carbon without further information. The analysis of the outer satellites of the proton spectrum is dependent on the differences between the long-range, carbon-proton coupling constants, but the magnitudes cannot be determined (4, 5). Homonuclear tickling of the inner satellites while observing the outer satellites allows all of the proton transitions to be found and a complete iterative analysis is then possible (6). The preparation of ^{13}C-enriched compounds alleviates all the spectroscopic problems, but the synthetic obstacles may be just as forbidding. If all of the proton-proton coupling constants are known, the fine structure in the ^{13}C spectrum is sufficient to determine all of the long-range, carbon-proton coupling constants.

Previously reported ^{13}C spectra of benzene were obtained either under rapid-passage conditions and showed only a broad doublet due to the one-bond, C-H coupling (7, 8), or with proton decoupling (9) and gave only a single line. Bernstein (10) has recently studied the proton spectrum of 3,4,5,6-tetradeuterio-1,2-$^{13}C_2$-benzene and has determined the four coupling constants in this AA'XX' system. The especially interesting result is the two-bond coupling J_{CCH} which was found to be +1.0 Hz.

Lauterbur (2) has determined the ^{13}C chemical shifts of the six-membered nitrogen heterocycles and some of their methyl derivatives, but the spectra were taken under rapid-passage dispersion-mode conditions and the line broadening associated with the rapid sweep rate precluded observation of the long-range coupling. A high-resolution spectrum of pyridine has been published but no detailed interpretation was given (11).

Page, Alger, and Grant (12) have measured the ^{13}C-chemical shifts and one-bond, carbon-proton coupling constants in some heterocycles by a combination of complete proton decoupling techniques for determination of the carbon-chemical shifts and rapid-passage, dispersion-mode conditions for determination of the one-bond, carbon-proton coupling constants in the ^{13}C spectrum. Neither technique allows the observation of the long-range, carbon-proton coupling constants.

Results

The ^{13}C chemical shift of benzene relative to internal carbon disulfide in the sample used in this work was 968.0 ± 0.3 Hz., or

64.1 ppm at 15.1 MHz. One half of the experimental spectrum of benzene is shown in Figure 2.1. Because of the complexity of this spectrum , it was found helpful to study some deuterated benzenes to aid in the interpretation. The ^{13}C spectrum of 1,2,3,5-tetradeuteriobenzene, which was the most useful in this respect is shown in Figure 2.2. The carbons attached to deuterium appear as a broad triplet, in contrast to the previous observation (13) that such carbons cannot be observed at all because of extremely short relaxation times. The carbons directly attached to a proton show the effect of long-range coupling to the other proton in the molecule. Since all proton-proton, proton-deuterium, and carbon-deuterium couplings in this particular case are small compared to the carbon-proton couplings, the three-bond coupling constant J_{CCCH} was determined to be ± 7.4 Hz from a first-order analysis of the spectrum. The magnitude of this coupling is confirmed by the observation of a doublet of triplets for the carbons attached to protons in 1,3,5-trideuteriobenzene, with the small coupling constant again being 7.4 Hz.

The ^{13}C spectrum was calculated using the proton-proton coupling constants determined from observation of the ^{13}C satellites in the proton spectrum (4) or interpolation of the observed variation of proton-proton coupling constants of substituted benzenes with electronegativity (14), two long-range coupling constants determined from deuterated benzenes, and a value for the four-bond coupling

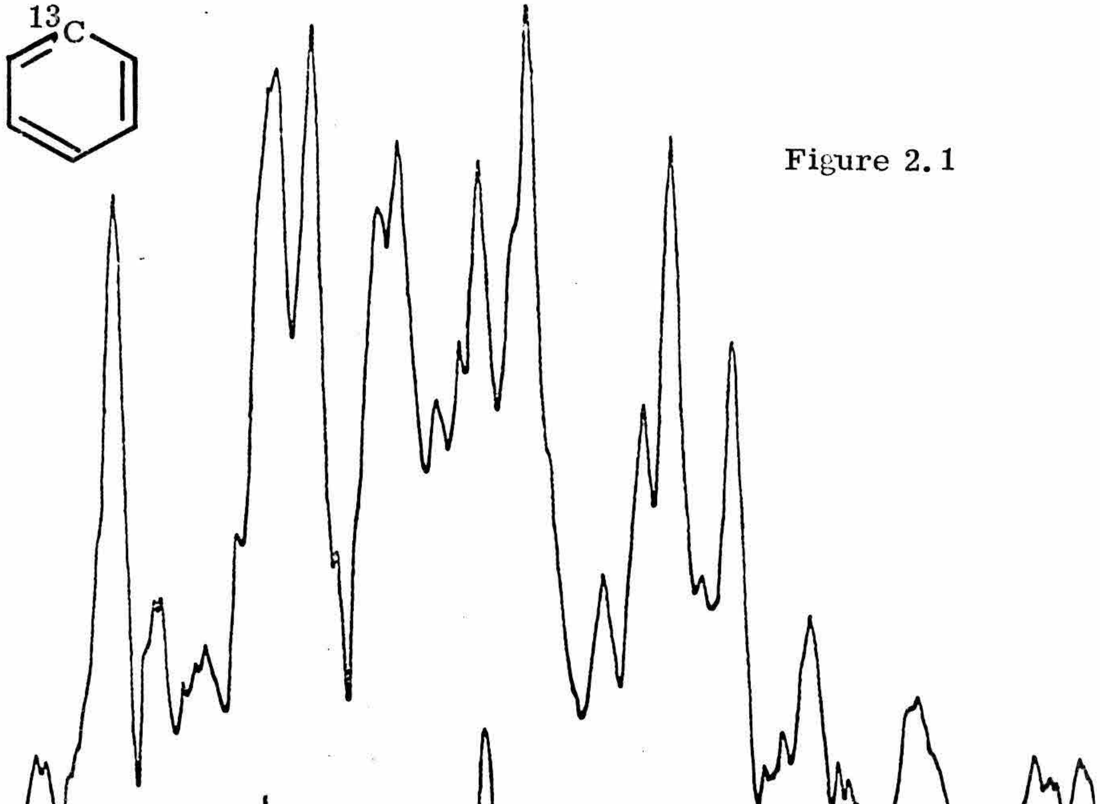


Figure 2.1

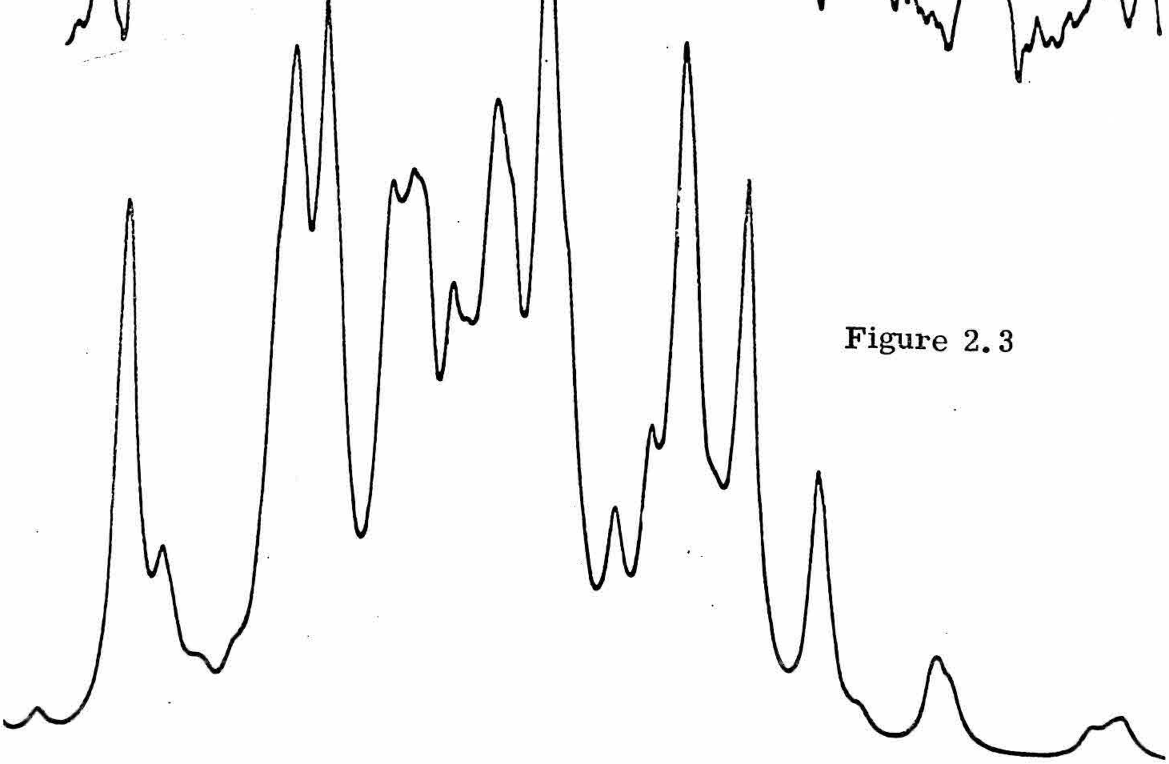


Figure 2.3

Figure 2.1. Natural abundance ^{13}C spectrum of benzene showing the high-frequency half, taken with a sweep rate of 0.25 Hz/sec. for 67 scans using TMS as internal reference at 60,0006,000 Hz. The left edge of this spectrum is at 15,090,550 Hz and right edge is at 15,090,525 Hz.

Figure 2.3. Calculated ^{13}C spectrum for benzene obtained with the parameters in Table 2.4.

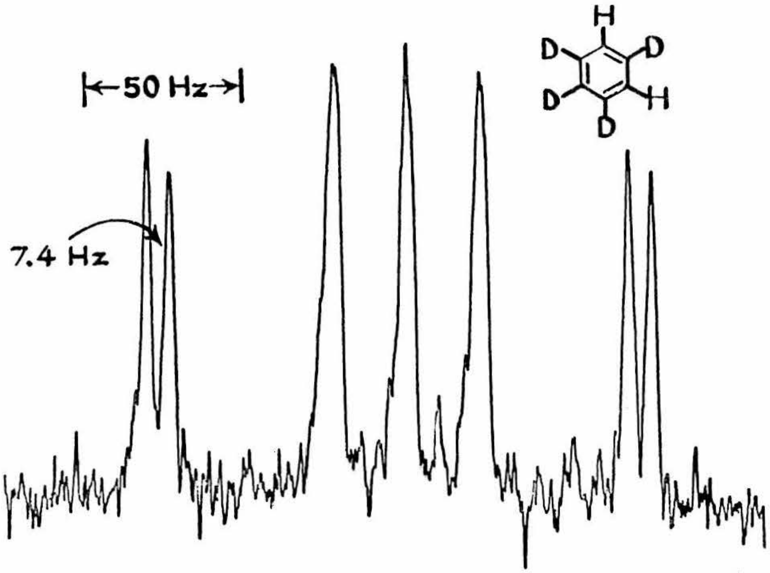


Figure 2.2. Natural abundance spectrum of 1,2,3,5-tetradeuteriobenzene after 217 scans. The outer four lines arise from ^{13}C(-H) while the middle three lines arise from ^{13}C(-D).

constant calculated from the difference between J_{CCCCH} and J_{CCH} and the known value of J_{CCH}. The calculated spectrum is shown in Figure 2.3. The agreement is excellent.

The ^{13}C chemical shifts and couplings for the five-membered nitrogen heterocycles are summarized in Table 2.1. The carbon-proton coupling constants for pyrrole, furan, thiophene, and selenophene are given in Table 2.2 and Table 2.3 presents the long-range, carbon-proton coupling constants which have been observed for the methyl-substituted heterocycles with partial decoupling of the methyl protons. These parameters were obtained from first-order considerations (Tables 2.1 and 2.3) and trial-and-error calculations (Table 2.2). The iterative portions of the LAOCOON program could not be used because too few transitions could be assigned. The long-range carbon-proton coupling constants are judged to be accurate to within ± 0.1 Hz.

The ^{13}C spectra of the poly-aza compounds are all first order, and consequently no information was obtained about the relative signs of the coupling constants nor of the correct assignment of an observed splitting to its proper proton. There are, however, only two ambiguities in the assignments of the long-range coupling constants. The larger of the two coupling constants involving C-4 in imidazole is assigned to H-5 by analogy with the corresponding coupling constants in 1,2,3-triazole. The two coupling constants involving C-3 in pyrazole remained unassigned, even after 3-methylpyrazole was studied.

Table 2.1

^{13}C Chemical Shifts and Coupling Constants of the Five-Membered Nitrogen Heterocycles

Compound	Carbon	Chemical Shift[a]	$\underline{J}^{b}_{CH-2}$	$\underline{J}^{b}_{CH-3}$	$\underline{J}^{b}_{CH-4}$	$\underline{J}^{b}_{CH-5}$
Pyrrole	2	74.1	182	c	c	c
	3	85.1	7.8	170	4.6	7.8
Pyrazole	3	59.5	-	190	(6.5, 7.5)	
	4	88.1	-	9.5	178	9.5
Imidazole	2	57.1	208	-	9.4	9.4
	4	71.0	7.3	-	199	13.0
1, 2, 3-Triazole		62.4	-	-	205	13.4
1, 2, 4-Triazole		45.2	-	208	-	9.4
Tetrazole		48.8	-	-	-	216

a) Chemical shifts are in ppm upfield from carbon disulfide.

b) In Hz.

c) The average of these values is 7.6 Hz.

Table 2.2

Long-Range, Carbon-Proton Coupling Constants in the Monosubstituted Five-Membered Heterocycles

Compound	Position	$\underline{J}^a$ CH-2	$\underline{J}^a$ CH-3	$\underline{J}^a$ CH-4	$\underline{J}^a$ CH-5
Pyrrole	2	-	b	b	b
	3	7.8	-	4.6	7.8
Furan	2	-	7.0	10.8	7.0
	3	14.0	-	4.0	5.8
Thiophene	2	-	7.35	10.0	5.15
	3	4.7	-	5.9	9.5
Selenophene	2	-	7.0	10.0	3.5
	3	4.5	-	6.0	10.4

a) In Hz.

b) The average of these values is 7.6 Hz.

Table 2.3

Long-Range, Carbon-Proton Coupling Constants in Some Methyl-Substituted Heterocycles

Compound	Position	$\underline{J}^{a}_{CH-2}$	$\underline{J}^{a}_{CH-3}$	$\underline{J}^{a}_{CH-4}$	$\underline{J}^{a}_{CH-5}$
2-Methylfuran	2	-	6.8	9.95	6.8
	3	-	-	4.0	5.5
	4	-	4.2	-	13.1
	5	-	10.4	7.2	-
2-Methylthiophene	3	-	-	5.8	8.2
	4	-	5.55	-	3.8
	5	-	6.8	9.8	-
3-Methylthiophene	2	-	-	8.95	4.3
	4	7.2	-	-	5.5
	5	4.3	-	8.95	-
2, 5-Dimethylpyrrole	2[b]	-	7.3	7.3	-
	3[c]	-	-	4.6	-
3-Methylpyrazole	3	-	-	d	d
	4	-	-	171.4	9.65
	5	-	-	7.5	183.2

a) In Hz.

b) $\underline{J}_{CNH} = 3.3$ Hz.

c) $\underline{J}_{CCNH} = 7.1$ Hz.

d) The average of these two coupling constants is 6.7 Hz.

The spectra of compounds with only one heteroatom are much more difficult to interpret. Pyrrole itself gives only a broad one-bond, carbon-proton doublet for the α carbon because of line broadening associated with quadrupole relaxation involving the ^{14}N and a non-zero ^{13}C-^{14}N coupling. This carbon was the only one in the series of nitrogen heterocycles which showed an effect from the ^{14}N quadrupole. In the other compounds, the relaxation was complete. The β carbon of pyrrole appears as a quartet (J = 7.8 Hz) of doublets (J = 3.0 Hz). If a trace of sodium hydroxide is added to catalyze the exchange of the proton attached to nitrogen, one of the 7.8 Hz coupling constants disappears leaving a triplet of doublets, conclusively showing that $\underline{J}_{CCNH}$ = 7.8 Hz. As a bonus, either the effect of the ^{14}N-^{13}C coupling or the ^{13}C-N-H coupling (or both) on the α ^{13}C line width is reduced sufficiently so that the α carbon resonance begins to show fine structure. The resulting broad quartet ($\underline{J}$ = 7.6 Hz) indicates that either all three long-range carbon-proton coupling constants are equal or that the spectrum is deceptively simple. The width of each line of the multiplet is 3 Hz, which shows that the carbon-nitrogen coupling is still not completely washed out by the quadrupolar interaction and relaxation. The β carbon of 2,5-dimethylpyrrole with decoupling of the methyl protons showed a doublet ($\underline{J}$ = 7.1 Hz) of doublets ($\underline{J}$ = 4.6 Hz). Since the large coupling constant has already been assigned to the proton bound to nitrogen, the smaller one must be due to the geminal interaction with the "other" β proton. The two unassigned coupling constants in pyrrole itself must then be due to coupling with the α protons. The α carbon of 2, 5-dimethylpyrrole is a triplet (J = 7.3 Hz) of doublets (J = 3.3 Hz). Since there was no sign of a small coupling in the pyrrole when the proton on nitrogen is exchanging rapidly, the 3.3 Hz coupling in 2, 5-dimethylpyrrole is assigned to the geminal ^{13}C-N-H interaction. The two remaining couplings must arise from geminal and vicinal interactions with the β protons. With 2, 5-dimethylpyrrole the ^{13}C-^{14}N couplings are apparently completely averaged to zero by quadrupolar relaxation because there is no broadening of the α carbon resonances.

Whenever fewer lines are seen in a spectrum than are theoretically expected, there is the possibility that either two coupling constants are accidentally equivalent or that the spectral parameters are such that a deceptively simple spectrum is observed. Although the spectrum observed for pyrrole has here been interpreted in terms of accidental equivalence, there is a distinct possibility that the spectrum is actually deceptively simple, and the observed identical spacings are only averages of the true coupling constants. The possible range of the carbon-proton coupling constants in pyrrole which might produce a first-order style spectrum was investigated and it was concluded that the spectrum of the β carbon is not deceptively simple, while the line width of the α carbon is such as to make any assignment ambiguous.

The ^{13}C spectra of furan, thiophene and selenophene all show some second-order features which assist in assignment of the couplings to the proper protons. One-half of the spectrum of each carbon in these molecules is shown in Figures 2.4-2.9. While the two halves of the spectra of the two furan carbons are mirror images of each other, this is not quite true for thiophene and selenophene. However, the differences are minor, and the two halves of the α and β carbons of these compounds which are not shown overlap quite badly (12). As a result it was not possible to assign the individual transitions to their proper carbon until the spectrum had been completely analysed using the resolved halves. The spectra calculated using the parameters given in Table 2.2 agree quite well with the observed spectra.

The assignments of the long-range coupling constants in Table 2.2 which were used to match the ^{13}C spectra of these heterocycles are not unique; several permutations of the coupling constants and their assignments match the spectra to within experimental error and further information was needed to unambiguously assign the coupling constants to their respective protons.

Some of the weak calculated transitions would have been helpful, but could not be observed because of the low signal-to-noise level of the ^{13}C spectra. Part of the required information was provided by the work of Goldstein (5) on the differences between some of the long-range, carbon-proton coupling constants as obtained by analysis of the ^{13}C satellites of the proton spectra of the parent

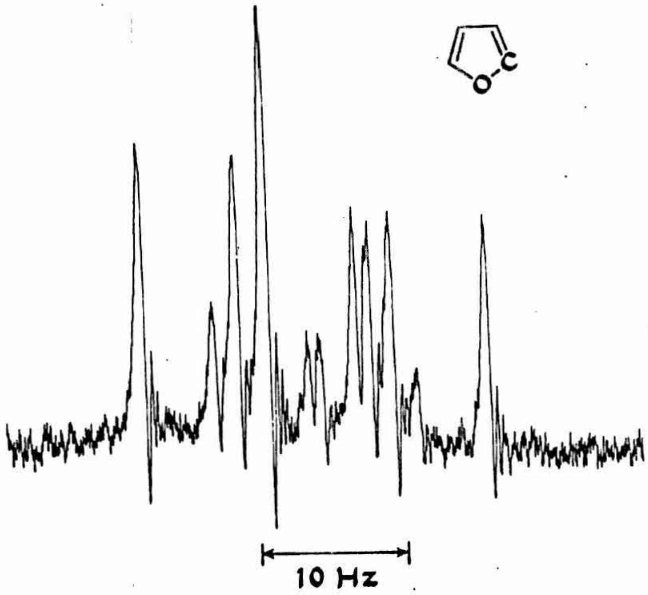


Figure 2.4. Natural abundance ^{13}C spectrum of the α carbon of furan showing the downfield half, time averaged for 400 scans.

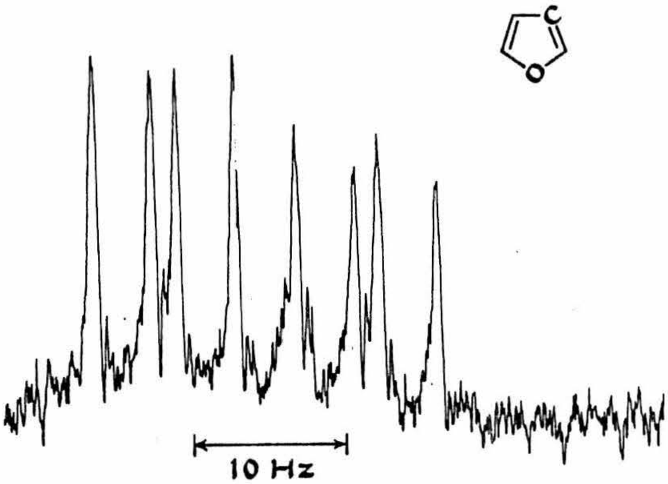


Figure 2.5. Natural abundance ^{13}C spectrum of the β carbon of furan showing the downfield half, time averaged for 400 scans. The upfield portions of the ^{13}C spectra of the α and β carbons of furan are mirror images of the downfield halves and are not shown.

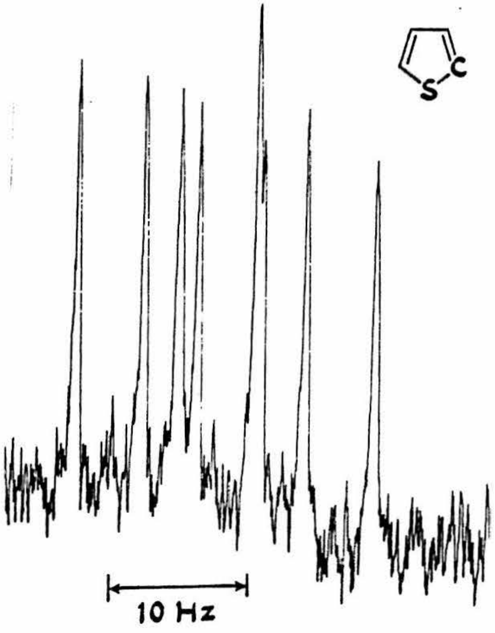


Figure 2.6. Natural abundance ^{13}C spectrum of the α carbon of thiophene showing the upfield half, time averaged for 150 scans.

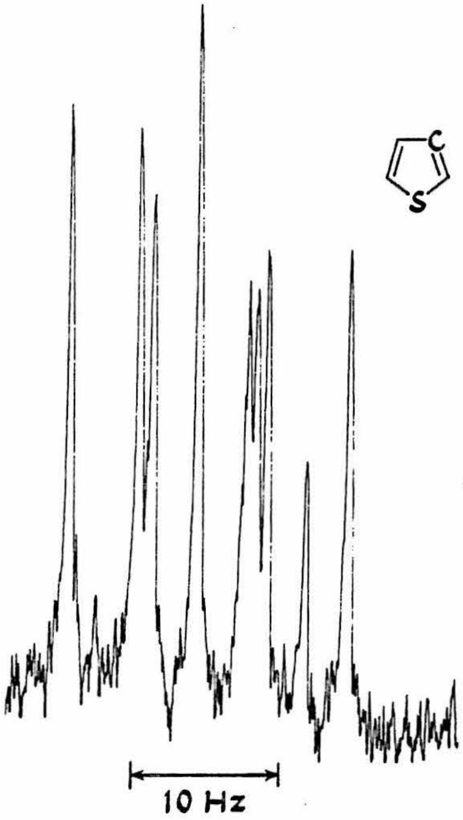


Figure 2.7. Natural abundance ^{13}C spectrum of the β carbon of thiophene showing the upfield half, time averaged for 150 scans. The downfield portions of the ^{13}C spectra of the α and β carbons of thiophene are badly overlapped and are not shown.

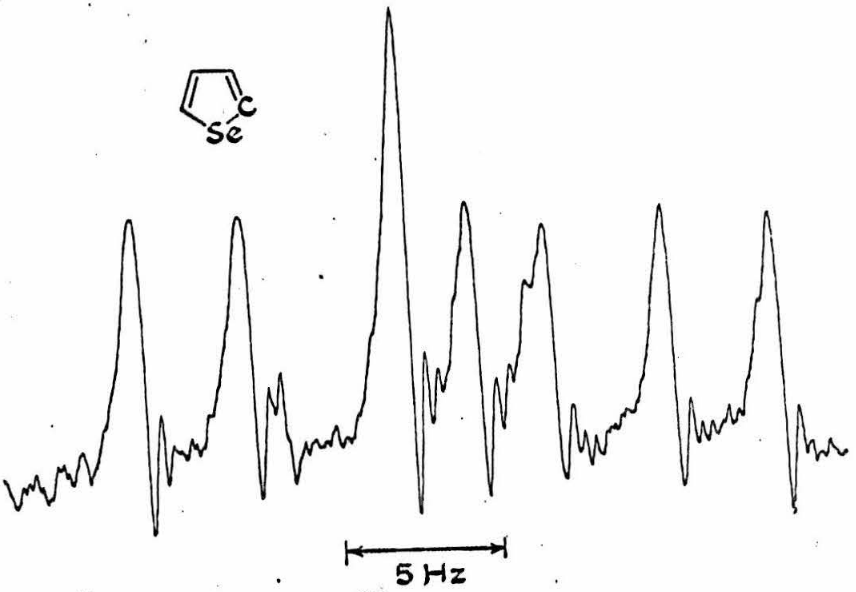


Figure 2.8. Natural abundance ^{13}C spectrum of the α carbon of selenophene showing the downfield half, time averaged for 400 scans.

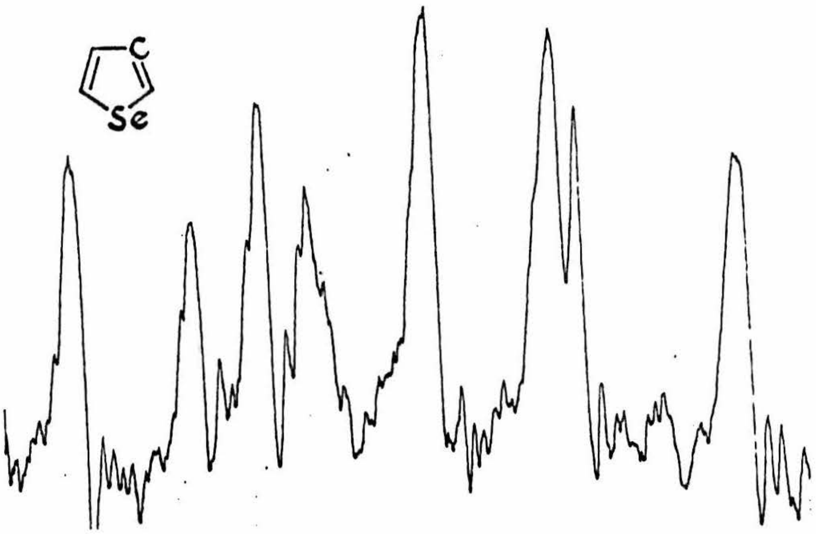


Figure 2.9. Natural abundance ^{13}C spectrum of the β carbon of selenophene showing the downfield half, time averaged for 400 scans. The upfield portions of the ^{13}C spectra of the α and β carbons of selenophene are badly overlapped and are not shown.

compounds. Other evidence was provided by spectra of methyl-substituted derivatives.

The resonances of the three proton-substituted carbon atoms of the monomethylthiophenes are first order. Goldstein (5) has reported differences between the carbon-proton coupling constants involving the β carbon of thiophene itself as follows:

$$\underline{J}_{C\text{-}3,H\text{-}4} - \underline{J}_{C\text{-}3,H\text{-}2} \approx 1 \text{ Hz}$$

$$\underline{J}_{C\text{-}3,H\text{-}5} - \underline{J}_{C\text{-}3,H\text{-}4} \approx 4 \text{ Hz}$$

For C-3 of 2-methylthiophene, there are two possible assignments of the long-range carbon-proton coupling constants,

$$\underline{J}_{C\text{-}3,H\text{-}5} = 8.2 \text{ Hz and } \underline{J}_{C\text{-}3,H\text{-}4} = 5.8 \text{ Hz} \qquad \text{or}$$

$$\underline{J}_{C\text{-}3,H\text{-}4} = 8.2 \text{ Hz and } \underline{J}_{C\text{-}3,H\text{-}5} = 5.8 \text{ Hz}$$

Of these only the first leads to the correct value for the difference as observed by Goldstein. For C-4 of 2-methylthiophene, the numbering system must be reflected about the C_2 axis, exchanging the subscripts 2 and 5, and 3 and 4 for a comparison with Goldstein's data. Of the two possible assignments

$$\underline{J}_{C\text{-}4,H\text{-}3} = 5.55 \text{ Hz and } \underline{J}_{C\text{-}4,H\text{-}5} = 3.8 \text{ Hz}$$

or

$$\underline{J}_{C\text{-}4,H\text{-}3} = 3.8 \text{ Hz and } \underline{J}_{C\text{-}4,H\text{-}5} = 5.55 \text{ Hz}$$

only the first again is consistent with the difference data. Govil (6) has recently determined some long-range, carbon-proton coupling constants in 2-bromothiophene by homonuclear tickling techniques. The magnitude of the reported couplings are in good agreement with those in the parent compound (Table 2.2) when the expected substituent effects are taken into account.

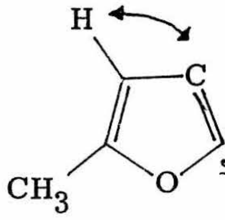
The above analysis is based on the assumption that methyl substitution does not change the sign of the difference between the carbon-proton coupling constants. That even the magnitudes are relatively insensitive to methyl substitution is seen by comparing the coupling constants for the methyl-substituted compounds with those finally derived for the unsubstituted compounds. A further consistency in the assignments is the geminal carbon-proton coupling between either β carbon and the "other" β proton which is about 5.5 Hz. From Table 2.2 it can be seen that the long-range, carbon-proton coupling constants involving C-2 also fit Goldstein's difference data.

$$\underline{J}_{C\text{-}2,H\text{-}4} - \underline{J}_{C\text{-}2,H\text{-}3} \approx 3.0 \text{ Hz}$$

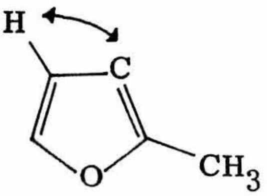
$$\underline{J}_{C\text{-}2,H\text{-}4} - \underline{J}_{C\text{-}2,H\text{-}5} \approx 6.0 \text{ Hz}$$

The spectrum of the β carbon of furan is strictly first order and any permutation of the long-range coupling constants leads to the same ^{13}C spectrum. The correct assignments can be made by observing the two β carbons in 2-methylfuran. Here C-3 shows two coupling constants of 5.5 and 4.0 Hz, while C-4 shows couplings of 13.1 and 4.2 Hz. The two coupling constants of 4 Hz are most reasonably the geminal carbon-proton constants to the "other" β

proton. The coupling constants involving the α carbon which is

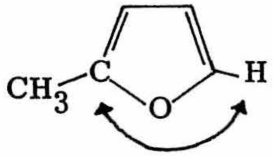


$\underline{J}_{CCH} = 4.2$ Hz



$\underline{J}_{CCH} = 4.0$ Hz

found for C-2 but not C-5 of 2-methylfuran must arise from the cross-oxygen, vicinal, carbon-proton interaction.



$\underline{J}_{COCH} = 6.8$ Hz

The coupling constants in selenophene were assigned so as to lead to the smallest difference between thiophene and selenophene.

The ^{13}C spectra of pyridine, pyridazine and pyrazine are shown in Figures 2.10-2.15. The ^{13}C spectra of pyrimidine and s-triazine are first order and are not shown. Only the low field half of the pyrazine spectrum is shown because the high field half is its mirror image. The carbon-proton coupling constants which have been determined for the parent heterocycles are given in Table 2.4. Long-range coupling constants are believed to be accurate to ± 0.2 Hz.

Because of the complexity of the spectra of some of the parent

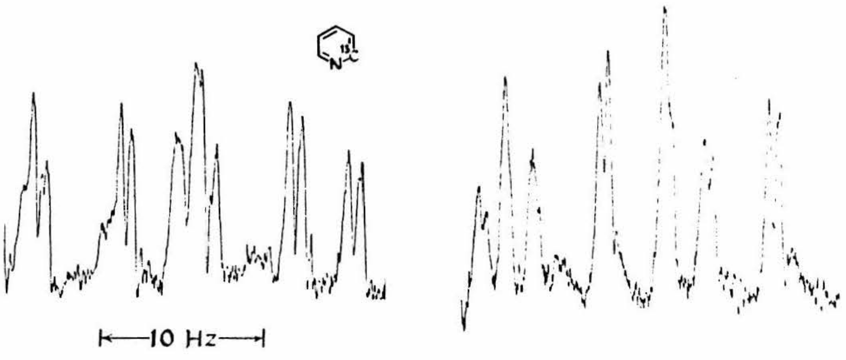


Figure 2.10. Natural abundance ^{13}C spectrum of C-α of pyridine.

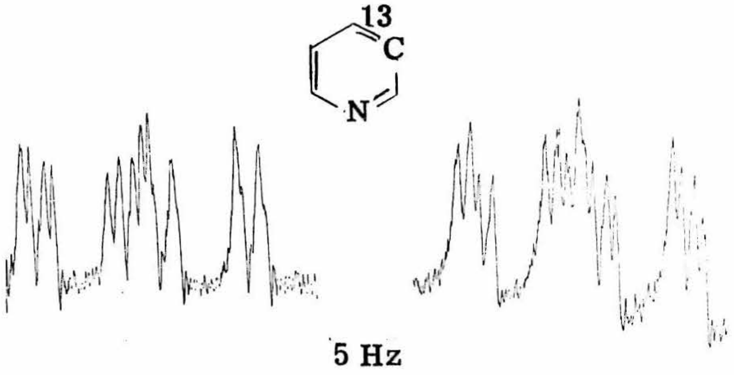


Figure 2.11. Natural abundance ^{13}C spectrum of C-β of pyridine.

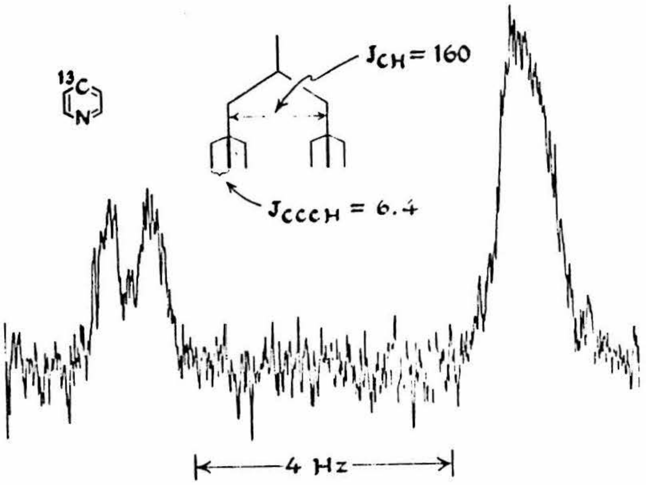


Figure 2.12. Partial ^{13}C spectrum of C-γ of pyridine, taken with a sweep rate of 0.02 Hz/sec for 100 scans.

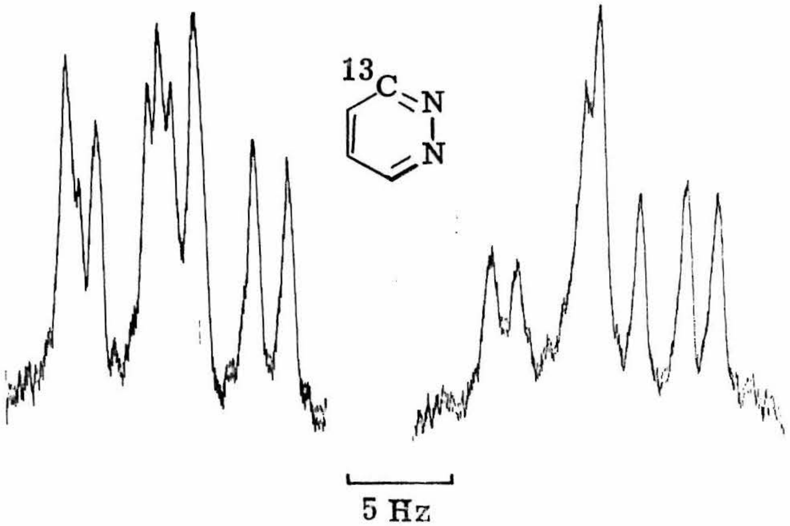


Figure 2.13. Natural abundance ^{13}C spectrum of C-α of pyridazine.

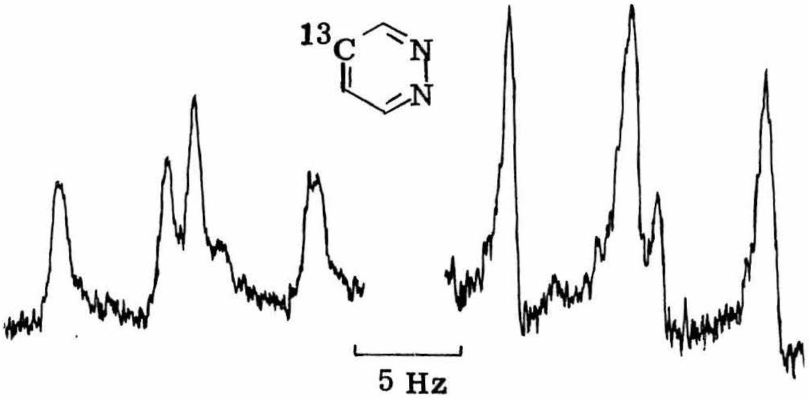


Figure 2.14. Natural abundance ^{13}C spectrum of C-β of pyridazine.

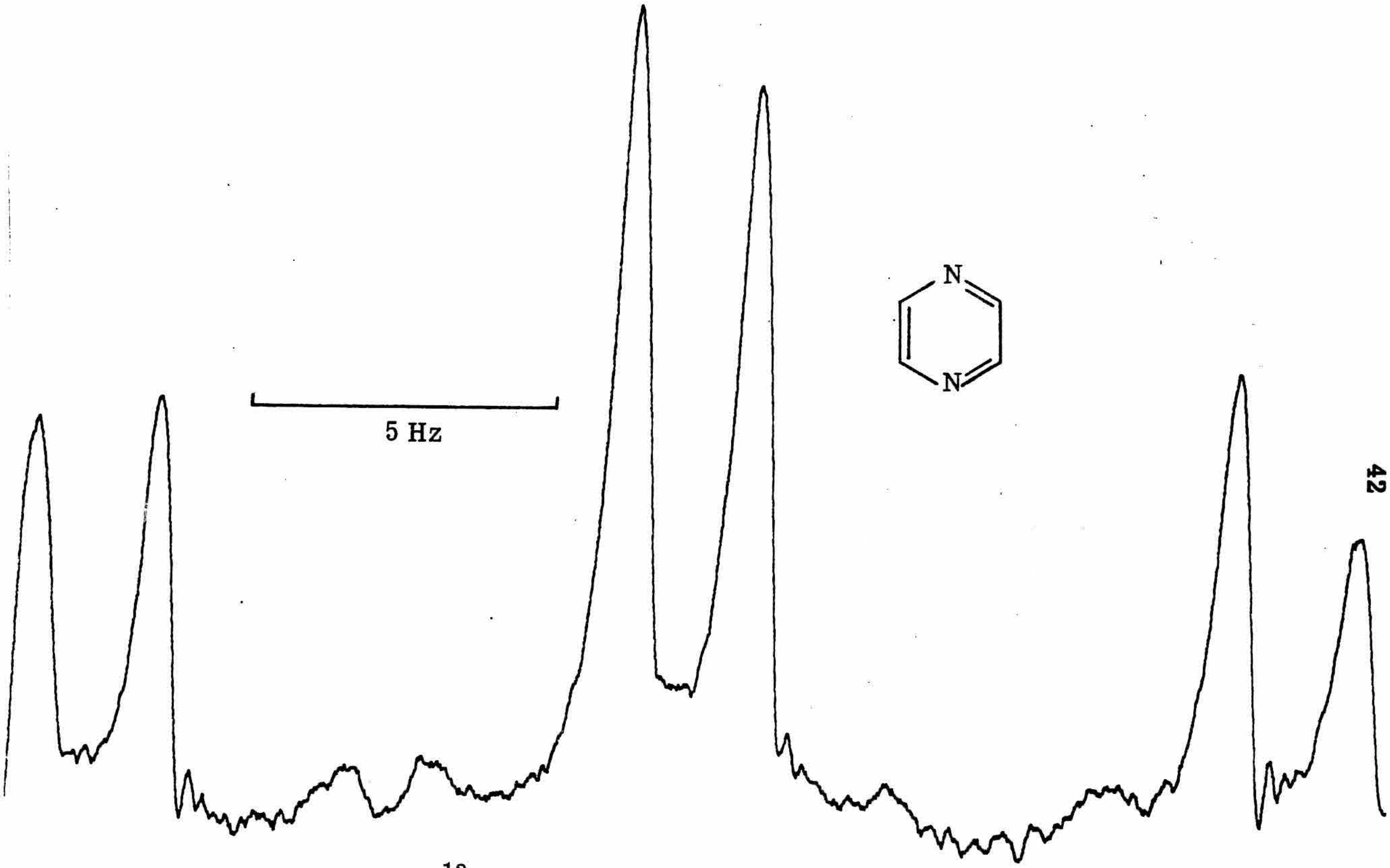


Figure 2.15. Natural abundance ^{13}C spectrum of pyrazine showing upfield half.

compounds, various methyl derivatives were examined and the carbon-proton coupling constants found in these simpler systems were then applied to the analysis of the parent compounds. Selective decoupling of the methyl protons was necessary to observe the long-range coupling to the aromatic protons. The decoupling power was quite critical; too much and the coupling to the aromatic protons was perturbed, too little and the coupling from the methyl protons was not completely eliminated. The carbon-proton coupling constants determined by this technique are best taken as lower limits to the true values. The long-range carbon-proton coupling constants in the methyl substituted heterocycles are given in Table 2.5

Two slightly different sets of proton-proton coupling constants have been reported for pyridine (15, 16). Both give good agreement with a 100 MHz spectrum of pyridine and both can be used equally well to match the ^{13}C spectrum. To a first order approximation the spectrum of the γ carbon is a doublet (H-4) of triplets (H-2, H-6). However with the extremely slow passage conditions used to obtain Figure 2.12 an additional splitting is seen. The second-order splitting is only consistent with a value of 0.0 ± 0.1 Hz for the geminal coupling with H-3 and H-5.

Gil (17) calculated the proton-proton coupling constants in pyridazine from the ^{13}C satellites of the proton spectrum. He also derived values for the long-range, carbon-proton coupling constants assuming that the carbon-proton coupling across three bonds would

Table 2.4

Coupling Constants in Six-Membered Aromatic Compounds[a]

Compound	Carbon	H-2	H-3	H-4	H-5	H-6
Benzene		+1.0	+7.4	-1.1		
Pyridine	2	175.3	+3.3	+6.4	±1.6	+10.9
	3	+8.7	162.5	+1.0	+6.4	±1.6
	4	+6.4	0.0	169.2	0.0	+6.4
Pyridazine[b]	3	-	181.5	-	-	-
	4	-	+6.7	169.9	0.0	+5.2
Pyrimidine	2	202.7	-	10.3	0.0	10.3
	4	9.1	-	182.8	1.9	5.3
	5	1.9	-	9.5	166.2	9.5
Pyrazine		182.7	10.4	-	-1.5	9.8
<u>s</u>-Triazine		207.5	-	7.95	-	7.95

a) In Hz.

b) This spectrum has not been successfully analyzed.

Table 2.5

Long-Range, Carbon-Proton Coupling in Methyl-Substituted Six-Membered Heterocycles

Compound	Carbon	H-2	H-3	H-4	H-5	H-6
2-Methylpyridine	2	-	2.4	6.7	0.0	11.2
	3	-		0.0	6.5	1.5
	4	-	0.0		0.0	6.3
	5	-	6.3	0.0		8.7
	6	-	0.0	6.5	3.8	
3-Methylpyridine	2		-	5.25	0.0	10.95
	3	6.7	-	0.0	6.7	0.0
	5	1.45	-	0.0		10.2
	6	10.6	-	6.4	2.1	
4-Methylpyridine	2		4.2	-	-0.7	10.6
	3	8.7		-	5.6	1.6
	4	6.35	0.0	-	0.0	6.35
3,5-Dimethylpyridine	2		-	5.8	-	11.2
	3	7.7	-	0.0	-	1.6
	4	5.3	-		-	5.3
2,6-Dimethylpyridine	2	-	2.5	6.4	-0.7	-
	3	-		0.0	5.1	-
	4	-	<0.3	-	<0.3	-
2,4-Dimethylpyridine	2	-	11.3	-	1.6	11.3
	4	-	0.0	-	0.0	6.7
	5	-	5.5	-		8.6

Compound	Carbon	H-2	H-3	H-4	H-5	H-6
	6	-	0.0	-	4.0	
2, 4, 6-Trimethyl-pyridine	3	-		-	5.1	-
3-Methylpyridazine	4	-	-	-	0.0	5.5
	5	-	-	0.0		7.45
	6	-	-	b	b	
5-Methylpyrimidine	2		-	10.6	-	10.6
	4	9.1	-	-	-	4.35
2, 5-Dimethylpyrazine	2	-	9.4	-	-	9.4
	3	-		-	-	1.4
2, 6-Dimethylpyrazine	2	-	9.95	-	1.25	-
	3	-		-	9.7	-
Mesitylene[c]	1	0.0	-	0.0	-	0.0
	2			6.4	-	6.4

a) In Hz.

b) The average of these two coupling constants is 4.7 Hz.

c) J_{CCH} (methyl) 6.0

J_{CCCH} (methyl) 4.25.

be nearly zero. In general, three-bond coupling in these systems is larger than two-bond coupling.

The proton-proton coupling constants in pyrazine were assumed to be the same as those of the mono-methyl derivative (18). The proton-proton coupling constants of pyrimidine and s-triazine do not affect the ^{13}C spectrum.

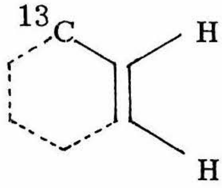
The 25 MHz ^{13}C spectrum of C-1 of mesitylene has been reported (19). The 1:3:3:1 quartet was attributed to coupling with the methyl protons. Coupling with the geminal ring protons was zero. The undecoupled ^{13}C spectrum of C-2 is a broad doublet (J ≐ 160 Hz) with no obvious fine structure. On decoupling the methyl protons a triplet (J = 6.4 Hz) is seen which arises from coupling with the vicinal ring protons. On weak irradiation of the ring protons each half of the doublet appears as a septet (J = 4.25 Hz) arising from the vicinal coupling with the two adjacent methyl groups.

Discussion

Laszlo (20) has shown that for selected compounds the increment in the one-bond coupling J_{C-H} associated with replacing an α-C by α-N is +23 Hz. This relationship works reasonably well for a number of the poly-aza compounds, but fails by a factor of two for the difference between J_{C-H} for 1,2,3-triazole and tetrazole and the difference between J_{C-H} of C-4 of imidazole and 1,2,4-triazole. Obviously more distant nitrogens also have an effect because the carbons of the nitrogen heterocycles with a single α nitrogen have one-bond, carbon-proton coupling constants which differ by 23 Hz. Neither a two-parameter equation including additive α and β effects nor a four-parameter equation including nitrogen-nitrogen pairwise interactions could be found giving a satisfactory correlation for the observed variation in these couplings. As a result, it would seem hazardous to make structural assignments based on direct additivity of substituent effects for one-bond, carbon-proton coupling constants in compounds of these types.

Since the available data for proton-proton couplings are much more extensive than for carbon-proton coupling, it would be particularly desirable to be able to relate couplings involving ^{13}C and protons to those involving only protons. A theoretical basis for this has already been described (21), but the treatment has only been applied to aliphatic systems, and with limited success. Assuming that the carbon in question is in the same steric and electronic environment as a certain proton and that the Fermi contact term is the dominant coupling mechanism, the two coupling constants such as J_{CCCH} and J_{HCCH} can be related by a single parameter which depends only on the hybridization of the carbon in question. Assuming a specific form for the carbon 2s orbital (a Slater orbital with exponent 3.25 was used), the constant relating the two couplings was determined as 0.40 for an sp$_2$ carbon giving the relationship $J_{CCH} = 0.4\ J_{HCH}$.

Previously, this relationship has only been applied to intramolecular cases, but with the correct choice of model compounds there seems to be no reason why it should not be extended to intermolecular comparisons. Several compounds (II-IV) are proposed as models for benzene (I). The relevant coupling constants for these compounds and the predicted benzene coupling constants based on them are given in Table 2.6.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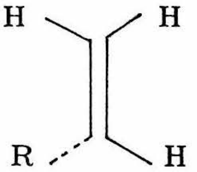
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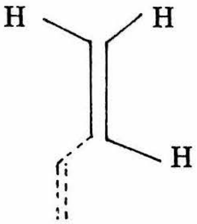
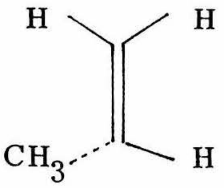

III


IV

The choice of a correct model compound for the four-bond coupling is difficult. Although the analogy is imperfect, a negative sign has been predicted for the four-bond proton-proton coupling constant in allene (22) which is 7.1 Hz (23). There are two equivalent paths possible for transmission of the spin information in allene and they are expected to give an additive effect. On this basis a single path with three intervening $\underline{sp}_2$ hybridized carbon atoms should lead to a proton-proton coupling constant of -3.5 Hz which with Karabatsos' formulation leads to prediction of -1.4 Hz for the four-bond coupling constant J_{CCCCH} in benzene.

Table 2.6

A Comparison of Carbon-Proton Coupling in Benzene with Proton-Proton Coupling in Ethylenes

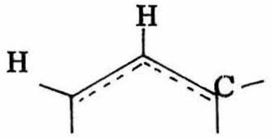
	J_{CCH}	J_{CCCH}
Benzene (observed)	+1.0	+7.4
Calculated from J_{HH} in:		
ethylene[a]	+1.0	+7.6
butadiene[b]	+0.7	+6.8
propene[c]	+0.8	+6.8

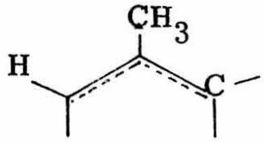
a) Reference 26.

b) R. T. Hobgood and J. H. Goldstein, *J. Mol. Spec.*, **12**, 76 (1964).

c) P. C. Lauterbur and R. J. Kurland, *J. Am. Chem. Soc.*, **84**, 3405 (1962).

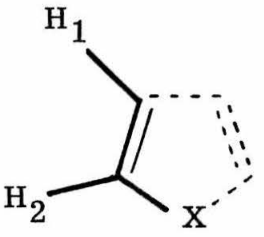
Vicinal, carbon-proton coupling across a methyl group is approximately 0.9 times the corresponding coupling in an unmethylated compound. The ratio is the same as that of the *trans*,

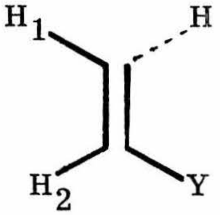




proton-proton coupling in ethylene (19.1 Hz) (24) and propene (16.8 Hz) (25). The relative signs of the long-range, carbon-proton coupling constants in the monosubstituted heterocycles were determined to be the same by spectral analysis techniques. Since the poly-aza compounds all exhibit first-order spectra, other techniques are required to determine the signs of the coupling constants. Unfortunately, double resonance gave ambiguous results because of the small proton-proton coupling constants and the slight broadening of the proton resonances by coupling with ^{14}N. In the six-membered nitrogen heterocycles, the geminal and vicinal carbon-proton coupling constants are all positive. The carbon-proton coupling constants of the nitrogen heterocycles are probably all positive, on the basis of the following argument.

The monosubstituted heterocycles may be considered as substituted ethylenes as shown in Figure 2.16. This model neglects the in-plane angular distortions which are produced when the two-carbon fragment is incorporated into a five-membered ring and also the





X	J_{CCH_1}[a]	J_{CCH_2}[a]
N	7.6	7.8
O	7.0	14.0
S	7.35	4.7
Se	7.0	4.5

Y	J_{CCH_1}[a]	J_{CCH_2}[a]
Br[b]	+7.5	+5.8
OAc	7.5	9.4

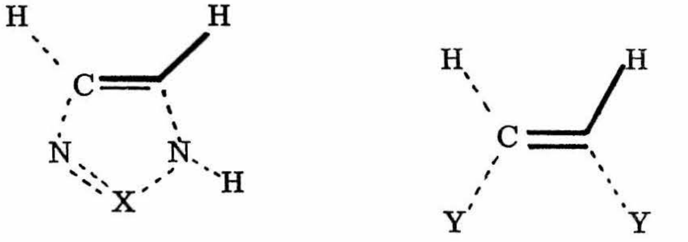
a) In Hz.

b) Reference 24.

Figure 2.16. A comparison of the geminal carbon-proton coupling constants in the five-membered nitrogen heterocycles and monosubstituted ethylenes.

substituent effects of the other ring atoms. The ideal model compounds would be monosubstituted ethylenes in which the substituents are identical to the heteroatom in the five-membered ring. Since the geminal, carbon-proton coupling constants for compounds of this type are not available, a poorer model must be used. The only monosubstituted ethylene for which the relative signs of all the carbon-proton coupling constants are known, and whose substituent has an electronegativity close to that of oxygen or nitrogen, is vinyl bromide (24). Compared with the geminal, carbon-proton coupling constant of -2.4 Hz for ethylene (26) the observed geminal, carbon-proton coupling constants in vinyl bromide provide evidence for a positive sign for geminal, carbon-proton coupling constants when only one nitrogen is attached to the two-carbon fragment. The larger geminal, carbon-proton coupling in vinyl acetate is similar in magnitude to that observed for the corresponding coupling in furan.

For the heterocycles where both carbons of the two-carbon fragments are attached to nitrogens, cis-disubstituted ethylenes are the proper model compounds. The geminal, carbon-proton coupling constant of cis-dichloroethylene is large and positive (6) and of similar magnitude to the corresponding couplings in imidazole and 1, 2, 3-triazole. Thus, it seems that the signs and magnitudes of the geminal, carbon-proton coupling constants of the five-membered



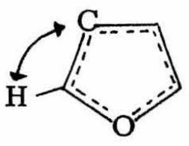
X	J_{CCH}[a]	Y	J_{CCH}[a]
CH	13.0	Cl	+15
N	13.4	Br	+14.7

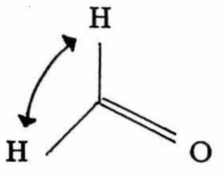
a) In Hz.

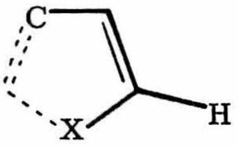
Figure 2.17. A comparison of the geminal proton-proton coupling constants in the five-membered nitrogen heterocycles with disubstituted ethylenes.

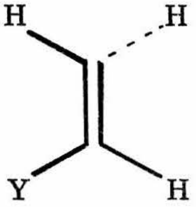
nitrogen heterocycles can be explained with reference to substituent effects in substituted ethylenes, and in-plane distortion of the bond angles may only have a small effect.

The vicinal carbon-proton coupling constants show considerably less variation in these compounds. Thus, while the two coupling constants whose magnitudes are larger than all others have both carbons flanked by nitrogens, the variation is small. The magnitudes of the carbon-proton coupling constants are quite adequately explained with reference to the trans proton-proton couplings in substituted ethylenes and the Karabatsos relationship for sp^2 carbons, $\underline{J}_{CH} = 0.4\ \underline{J}_{HH}$ (21). The coupling constants $\underline{J}_{C\text{-}2,\,H\text{-}3}$ and $\underline{J}_{C\text{-}2,\,H\text{-}4}$ in monosubstituted heterocycles seem to be independent of the nature of the heteroatom. The coupling constants $\underline{J}_{C\text{-}3,\,H\text{-}2}$ show the same variation to substituent as the corresponding carbon-proton couplings in monosubstituted ethylenes. The magnitude of $\underline{J}_{C\text{-}3,\,H\text{-}2}$ in furan is possibly reminiscent of the large geminal proton-proton coupling in formaldehyde (27). The vicinal coupling $\underline{J}_{C\text{-}3,\,H\text{-}5}$ follows the electronegativity trends of the trans, proton-proton coupling constants in substituted ethylenes as shown in Figure 2.18. The same models explain many of the trends seen in the six-membered









X	J_{CCCH} [a]	Y	J_{HCCH} obs. [a, b]	J_{CCCH} calcd. [a, c]
N	7.8	N	16	6.4
O	5.8	O	14	5.6
S	9.5	S	16	6.4
Se	10.4	Sn	20	

a) In Hz.

b) W. Brügel, Th. Ankel, and F. Krückeburg, Z., Electrochem., 64, 1121 (1960).

c) Reference 21.

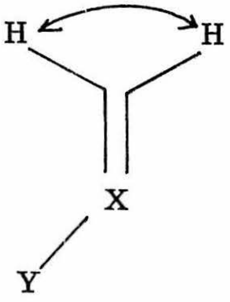
Figure 2.18. A comparison of the vicinal carbon-proton coupling constants to vicinal proton-proton coupling constants in substituted ethylenes.

heterocycles also. Some of the models and the predicted and observed coupling constants are given in Table 2.7. While the magnitudes are not precisely predicted by the Karabatsos relationship, the trend toward more positive values of the coupling constant with less electronegative substituents seems clear. The variations of $\underline{J}_{C-2, H-5}$ with substituent groups seem to depend on the size of the intervening heteroatom, as do the vicinal carbon-proton coupling across the metal atom in the tetramethyl derivatives of group IV (28). Although the quantitative agreement with the predictions of the Karabatsos theory is best for benzene, the qualitative trends are correctly predicted throughout the heterocyclic series.

Extended Hückel wavefunctions (29) have been used to calculate the Fermi contact contribution to the carbon-proton coupling constants by the Pople-Santry formalism (30). The valence-state ionization potentials for the various orbitals were taken as: C(2s) -21.4 eV;C(2p) - 11.4 eV; N(2s) - 26.0 eV; N(2p) - 13.4 eV. The Slater orbital exponents were H, 1.15; C, 1.625, and N, 1.95 (31). The idealized geometries approximated the five-membered ring system as regular pentagons with ring bond lengths taken as 1.35 Å and all nitrogen and carbon-to-proton bond lengths as 1.07 Å. Six-membered rings were approximated as regular hexagons with carbon-carbon or carbon-nitrogen bond lengths of 1.39 Å. The results of these calculations are given in Table 2.8.

Table 2. 7

A Comparison of Proton-Proton Coupling in Substituted Ethylenes with Carbon-Proton Coupling in Six-Membered Aromatic Heterocycles



X	Y	J_{CCH} pred.[a]	Ref.	Compound	J_{CCH} obs.[a]
C	H_2	+1.0	b	Benzene	+1.0
C	CH_3	+0.8	c	Mesitylene	0.0
N	C	+6.4	d	Pyridine-C-3	+8.7
N	N	+4.4	d	Pyridazine-C-4	6.4
C	NH_2, H	0.0	e	Pyridine-C-4	0.0
		6.4	e, f		6.4

a) In Hz.

b) Reference 24.

c) Reference 25.

d) B. L. Shapiro, S. L. Ebersole, G. J. Karabatsos, F. M. Vane and S. L. Manatt, J. Am. Chem. Soc., **85**, 4041 (1963). These coupling constants are solvent dependent.

e) W. Brügel, Th. Ankel and F. Krückeberg, Z. Electrochem., **64**, 1121 (1960).

f) J_{CCCH} vs. J_{HCCH} (trans).

Table 2.8

Carbon-Proton Coupling Constants in Aromatic Compounds Calculated from Extended Hückel Wavefunctions[a]

Compound	Carbon	H-1	H-2	H-3	H-4	H-5	H-6
Benzene	1	98	-5.9	1.4	0.1	-	-
Pyridine	2	-	114	-5.8	1.6	0.8	0.8
	3	-	-6.8	99	-6.0	1.5	0
	4	-	1.1	-5.9	98	-	-
Pyrrole	2	-5.2	118	-4.9	2.0	1.6	
	3	1.7	-6.3	99	-5.3	1.5	
Pyrazole	3	-	-	118	-5.3	1.3	
	4	-	-	-6.3	100	-	
Imidazole	2	-	141	-	1.6	-	
	4	-	1.1	-	118	-6.3	
1, 2,4 -Triazole		-	-	141	-	1.1	
1, 2, 3-Triazole		-	-	-	118	-6.6	

a) In Hz.

The geminal carbon-proton coupling constants in all the nitrogen heterocycles were calculated to fall between -4.9 and -6.6 Hz, although the experimental values are all positive and show considerable variation. The systematic trends evident in the data of Table 2.1 are not reflected in the calculated values. Also, the calculated vicinal carbon-proton coupling constants fall irregularly between +1.1 and +2.0 Hz.

The extended Hückel theory appears to generally predict one-bond, carbon-proton coupling constants which are considerably below the experimental values; however, trends in aliphatic systems are more-or-less faithfully reproduced (32). The calculated values of the one-bond, carbon-proton coupling constants in nitrogen heterocycles were 99, 118, or 141 Hz depending on whether there were no, one, or two adjacent nitrogens. The variation is in the right direction but the experimental trend toward higher values of $\underline{J}_{CH}$ with the accumulation of nitrogen in the molecules was not reproduced. The predicted proton-proton coupling constants are in equally poor agreement with the experimental results. The trends for the long-range coupling constants seem to suggest that the wavefunctions have the character of an sp^2 carbon attached to a saturated system. The couplings would be correct for aliphatic compounds of the type

$$\overset{13}{=C}-\overset{\overset{H}{|}}{C}-\overset{\overset{H}{|}}{C}-$$

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III. Coupling of Carbon and Nuclei Other than Protons

Three methods have been used to observe coupling between carbon and elements other than hydrogen. Direct observation of the ^{13}C satellites of the fluorine spectrum is generally used to observe carbon-fluorine coupling (1, 2). Observation of the inner satellites is difficult and only has been done in a few simple cases (3, 4). Even if the inner satellites can be seen, assigning them to specific carbons is not possible. When the one-bond coupling constants are small, the satellites are hidden by the resonances of molecules with no ^{13}C.

Heteronuclear tickling while observing the outer satellites in the proton spectrum has been used, but the proton spectrum must be quite simple and the technique has been mainly limited to the carbon of methyl groups (5).

If enriched compounds are prepared several spectroscopic techniques can be used. The ^{13}C satellites may be visible in the spectrum of the other nucleus (6), or the high resolution ^{13}C spectrum may be observable (7). If carbon-carbon coupling is being studied and the two labelled carbons are chemically but not magnetically equivalent, then the carbon-carbon coupling may influence the proton spectrum. This technique was used to determine the carbon-carbon coupling in ethane, ethylene, and acetylene (8, 9) and benzene (10).

The undecoupled and proton-decoupled ^{13}C spectra of fluorobenzene are shown in Figure 3. 1. The undecoupled spectrum required

700 scans and on closer inspection has all the complexity of the X part of an ABB'CC'MX spin system. The decoupled spectrum required 30 scans and the only remaining fine structure unambiguously arises from carbon-fluorine coupling. Most of the coupling constants were obtained from proton-decoupled ^{13}C spectra.

Fluorine: The carbon-fluorine coupling constants obtained for a series of ortho, meta and para substituted fluorobenzenes are given in Tables 3.1, 3.2, and 3.3. The carbon bonded to the fluorine was shifted considerably downfield (11, 12) showed a large carbon-fluorine coupling constant (1, 12) and was insensitive to the proton decoupler frequency. The carbon bearing the substituent was also insensitive to the decoupling frequency except for substituents with protons which could couple with the ring carbons. With benzaldehydes, the optimum decoupling frequency was at the aldehyde resonance. Additivity of substituent effects on the ^{13}C chemical shifts (13) was invoked to assign the remaining ^{13}C resonances. The carbons ortho to the fluorine generally appeared upfield and had *ca.* 20 Hz carbon-fluorine coupling constants. If two assignments were ambiguous on the basis of the chemical shifts, the proton chemical shifts (from the decoupling frequency) or the carbon-fluorine coupling constants were considered in making the assignments.

As part of the general study of substituent effects on

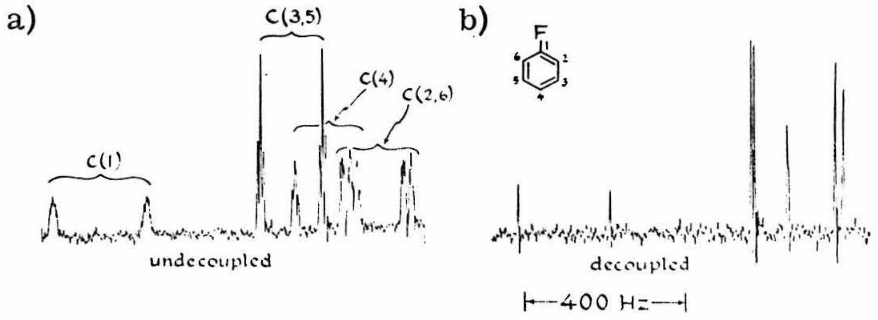


Figure 3.1. ^{13}C spectrum of fluorobenzene: a) undecoupled 700 scans; b) proton decoupled 30 scans.

Table 3.1

Carbon-Fluorine Coupling in Ortho Substituted Fluorobenzenes

Substituent	$J_{C\text{-}1,F}$	$J_{C\text{-}2,F}$	$J_{C\text{-}3,F}$	$J_{C\text{-}4,F}$	$J_{C\text{-}5,F}$	$J_{C\text{-}6,F}$		
H	245.3	21.0	7.7	3.3	7.7	21.0		
F	248.8	14.1	-3.0	b	b	20.5		
Cl	248.7	17.5	0	4.05	7.2	20.8		
Br	247.0	20.7	0	3.35	7.1	21.95		
I	245.6	25.2	1.46	3.5	7.2	23.4		
NO_2	264.4	-	4.25	2.8	8.7	20.6		
NH_2	237.5	12.7	+3.8	3.6	6.7	18.4		
NH_3^+	248.6	13.8	0	3.9	7.5	18.4		
OH	238.8	13.7	1.94	3.78	6.6	18.0		
O^-	235.8	12.15	3.4	3.3	7.0	19.0		
CH_3	243.9	17.0	+4.8	3.7	7.9	22.1	CH_3	3.8
CHO	257.7	8.2	1.86	3.75	9.1	20.45	CHO	6.4
$COCH_3$	254.2	12.8	2.54	3.4	9.0	23.7	CO CH_3	3.2 <0.4
2-Fluoro-pyridine	236.7	-	14.7	4.2	7.75	37.4		

a) In Hz. b) The average of these two coupling constants is 5.2 Hz.

Table 3.2

Carbon-Fluorine Coupling in Meta Substituted Fluorobenzenes

Substituent	$J_{C-1,F}$	$J_{C-2,F}$	$J_{C-3,F}$	$J_{C-4,F}$	$J_{C-5,F}$	$J_{C-6,F}$		
H	245.3	21.0	7.7	3.3	7.7	21.0		
F	245.4	25.3	12.1	3.6	9.8	21.2		
Cl	249.5	24.6	10.0	3.4	8.9	21.3		
Br	250.4	24.5	9.3	3.4	8.4	21.1		
I	249.0	23.2	7.8	3.3	8.1	20.8		
NO_2	250.9	26.5	8.3	3.3	8.2	21.5		
NH_2	241.4	24.6	11.0	2.3	10.2	21.3		
NH_3^+	247.5	25.6	9.8	3.4	8.9	21.2		
OH	244.5	24.8	11.3	3.0	10.2	21.2		
O^-	241.4	21.5	11.4	2.4	11.0	21.4		
CH_3	243.6	21.1	7.2	2.2	8.5	21.2	CH_3	1.75
CHO	248.2	21.7	6.3	2.9	7.8	21.8	CHO	2.4
$COCH_3$	246.3	22.2	5.9	2.9	7.75	21.6	CO CH_3	1.9 0.68

Table 3.3

Carbon-Fluorine Coupling in Para Substituted Fluorobenzenes

Substituent	$J_{C-1,F}$	$J_{C-2,F}$	$J_{C-3,F}$	$J_{C-4,F}$		
H	(-)245.3	21.0	7.7	3.3		
F	242.0	24.3	8.5	3.8		
Cl	245.5	23.1	8.2	3.1		
Br	246.7	23.7	8.0	3.3		
I	247.4	22.2	7.6	3.4		
NO_2	256.6	24.0	10.2	(b)		
NH_2	233.2	22.4	7.5	1.86		
NH_3^+	246.8	23.7	9.1	3.2		
OH	237.4	23.0	7.9	2.14		
O^-	236.1	22.7	8.0	1.6		
CH_3	243.5	21.1	7.75	2.9	CH_3	O
CHO	255.0	22.4	9.7	2.6	CHO	O

a) In Hz.

b) Resonance is broadened due to partial relaxation of the coupling due to the nitrogen quadrupole.

carbon-fluorine coupling in fluorobenzenes, the difluorobenzenes were examined. Because the carbon-fluorine coupling constants were not easily determined in these three compounds, the method used will be discussed in some detail.

There are nine structurally different carbons in the three difluorobenzenes. One resonance in each compound is insensitive to the proton decoupling frequency, is shifted to low field and is a doublet of doublets with the larger coupling being *ca.* 250 Hz. This resonance is assigned to the carbon bearing the fluorine. There is only one other type of carbon in para-difluorobenzene. The two 1:2:1 triplets in the meta isomer are assigned to C-2 and C-5, and of these two, C-2 is shifted upfield by the ortho fluorines and has the larger of the two coupling constants. The remaining resonance is assigned to C-4. Of the two resonances in the ortho isomer, the downfield signal is assigned to C-4 which is not adjacent to a fluorine. The resonance multiplet is a 1:2:1 triplet which indicates that either the three- and four-bond coupling constants are equal or that the spectrum is deceptively simple.

The proton decoupled ^{13}C spectra of C-3 of 1,2-difluorobenzene, C-4 of 1,3-difluorobenzene and C-2 of 1,4-difluorobenzene are shown in Figures 3.2, 3.3, and 3.4. Each spectrum shows the six lines characteristic of the X part of an ABX spin system (14).

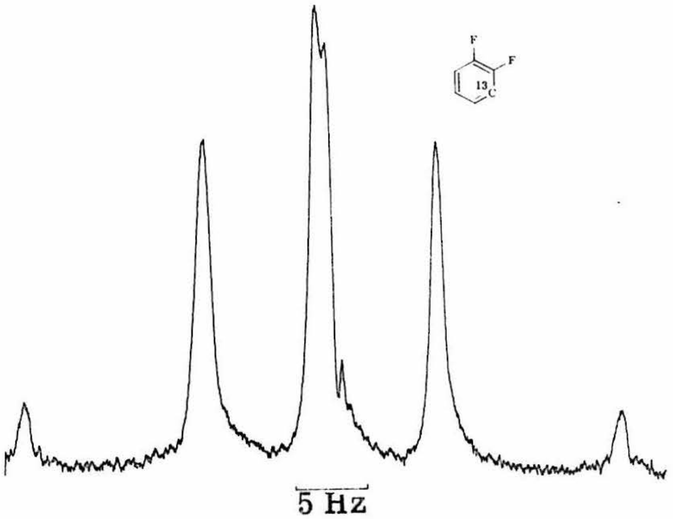


Figure 3.2. ^{13}C spectrum of C-3 of 1,2-difluorobenzene.

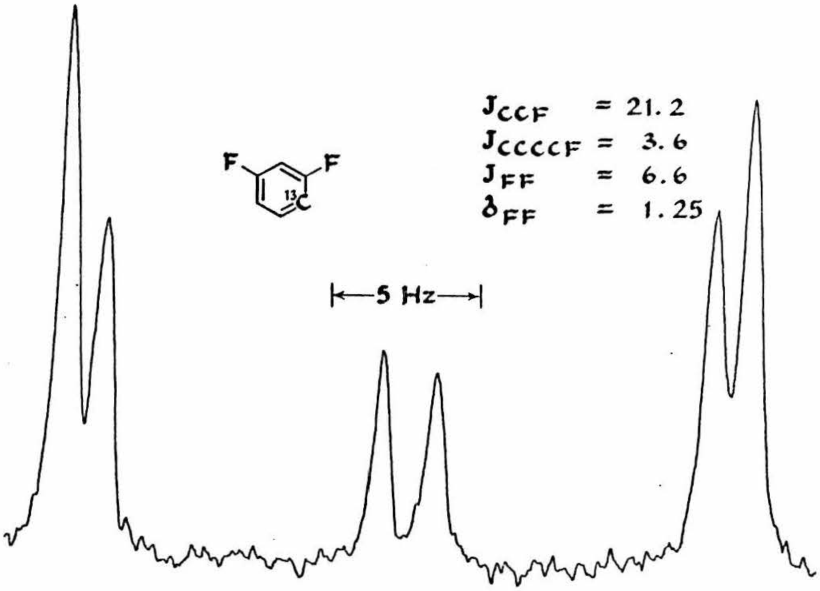


Figure 3.3. ^{13}C spectrum of C-4 of 1,3-difluorobenzene.

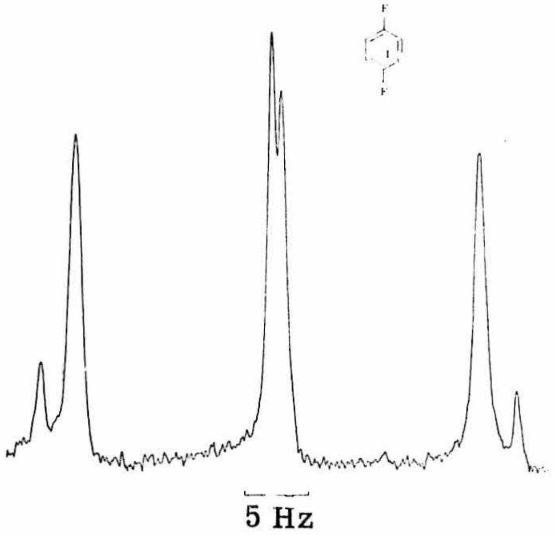


Figure 3.4. ^{13}C spectrum of C-2 of 1,4-difluorobenzene.

The ABX spectrum is a function of four variables, the chemical shift between the A and B nuclei and the three coupling constants J_{AB}, J_{AX} and J_{BX}. If sufficient lines are seen, all the parameters can be extracted directly from the resonance frequencies, however, the resonance frequencies in the X part of the spectrum contain only three pieces of information, in the notation of Roberts (14), $(D_+ + D_-)$,$(D_+ - D_-)$ and $(J_{AX} + J_{BX})$. Without additional information the four spectral parameters cannot be obtained from these three frequencies. However, given any one of the four parameters from another source, the resonance frequencies in the X part of the spectrum are sufficient to determine the other three parameters.

From a complete analysis of the proton and fluorine spectra of 1, 3-difluorobenzene, Mohanty (15) and McDonald (16) obtained values for the fluorine-fluorine coupling constant. Unfortunately, the values obtained by these two workers differed quite significantly, although both workers claimed that their parameters matched the experimental proton and fluorine spectra.

Although an infinite number of parameter sets match the observed frequencies of the X part of an ABX spectrum, only one set, the correct solution, will match the observed intensities. Because the intensities of the ^{13}C spectra are notoriously sensitive to saturation, magnetization transfer and Overhauser effects from decoupling (17) the intensity information is not as reliable as would be desired, but in the absence of accurate values for one of the parameters, a method of analysis based on intensities will have to suffice. A value for one of the parameters, usually the chemical shift between the two fluorines, was guessed and the ABX equations solved for the other three parameters and the intensities in the X part of the spectrum. The sensitivity of this calculation is shown in Figure 3.5 where the variation of the three dependent variables is plotted versus the assumed chemical shift difference for para-difluorobenzene. The region which gives the best agreement with the observed intensities is also indicated. The ^{13}C spectrum is about five times as sensitive to changes in the fluorine-fluorine chemical shift as it is to changes in any one of the coupling constants. Thus if the chemical shift is known to within ±0.04 Hz, the coupling constants are known to ±0.2 Hz. The values for the three fluorine-fluorine coupling constants are in reasonable agreement with the corresponding coupling constants found by Evans in some substituted derivatives (18). The fluorine-fluorine coupling constant in 1,3-difluorobenzene agrees with the value found by McDonald (16). Given the value for the fluorine-fluorine coupling constant in 1,2-difluorobenzene from the analysis of the spectrum of C-3, the ^{13}C spectrum of C-4 can be calculated using various sets of carbon-fluorine coupling constants in order to determine if the spectrum is deceptively simple. Indeed, the 1:2:1 triplet persists over a wide range of three- and four-bond, carbon-fluorine coupling

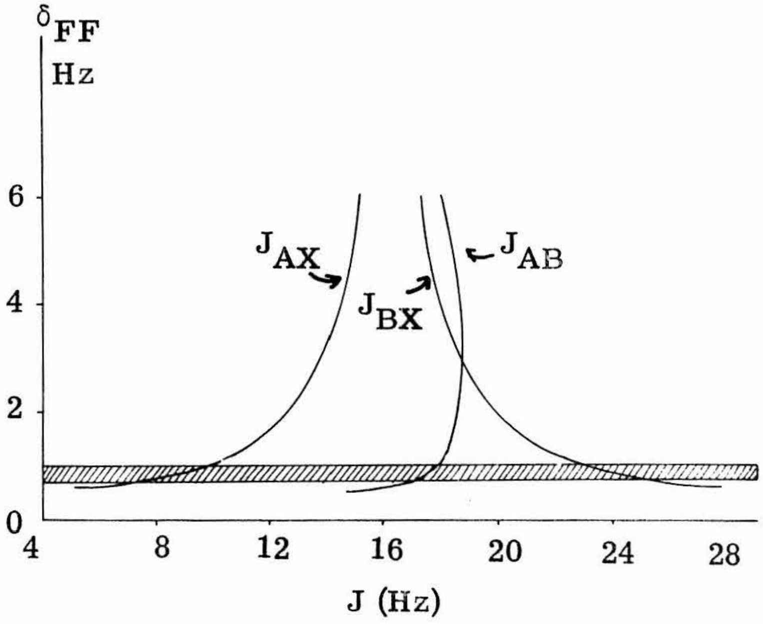


Figure 3.5. Sensitivity of the coupling constants in the ABX spectrum of C-2 of 1,4-difluorobenzene to the magnitude of δ_{AB}. Region of best agreement with the observed spectrum is indicated.

constants including the probable value of about 3 Hz for the four-bond coupling. The two carbon-fluorine coupling constants are probably not equal in this case.

In each of the three difluorobenzenes the carbon giving the second-order spectra is ortho to one of the fluorines. In 1, 3-difluorobenzene, the second fluorine is para to the carbon, while in the 1, 2- and 1, 4-difluorobenzenes the second fluorine is meta to the carbon. In both the latter cases, the chemical shift between the two fluorines is ca. 0. 5 Hz smaller than in the former case which may be indicative of the difference between the three-bond and four-bond ^{13}C isotope effect on the fluorine chemical shift (1). The parameters found for the difluorobenzenes are summarized in Table 3.4.

Because of the large vicinal, proton-fluorine coupling constants in the fluorobenzenes, both halves of the carbon-fluorine doublet arising from an ortho carbon could not be sharpened at the same proton decoupling frequency. In all cases irradiation at the higher proton frequency sharpened the high frequency half of the ^{13}C spectrum and vice versa. The geminal, carbon-fluorine coupling constant thus has the same sign as the vicinal, proton-fluorine coupling constant. Snyder (19) has shown that the signs of all the proton-proton and proton-fluorine coupling constants in fluorobenzenes are positive by a complete analysis of the spectrum in a liquid crystal. Analysis of the ^{13}C spectra of 1, 3- and 1, 4-

Table 3.4

Chemical Shifts and Coupling Constants Obtained from the Analysis of the Proton Decoupled ^{13}C Spectra of the Difluorobenzenes

Fluorine and Carbon Positions	J_{CF} Hz	J_{CCF} Hz	J_{CCCF} Hz	J_{CCCCF} Hz	F-F Chemical Shift, Hz, at 56.4 MHz	J_{FF} Hz
1,2-F_2						
C-1	248.8	14.1				
C-3		+20.5	-3.0		0.63	19.0
C-4			a	a		
1,3-F_2						
C-1	245.4		12.1			
C-2		25.3				
C-4		+21.2		+3.6	1.25	6.6
C-5			9.8			
1,4-F_2						
C-1	242.0			3.8		
C-2		+24.3	+8.5		0.85	17.5

a) The average of these two coupling constants is 5.2 Hz.

difluorobenzene has shown that the two-, three- and four-bond carbon-fluorine coupling constants in fluorobenzene have the same sign, and are all positive. The one-bond coupling is probably negative (3).

The proton decoupled ^{13}C spectrum of benzotrifluoride shows four quartets and one singlet, the latter best assigned to the para carbon. The one-bond and two-bond coupling constants of 279.5 and 32.5 Hz are unexceptional. The couplings of 3.9 Hz and 1.56 Hz to the ortho and meta carbons can not be assigned at the present time.

The generality and additivity of the fluorine substituent effects on carbon-fluorine coupling was investigated by studying some polyfluorobenzenes. The proton decoupled ^{13}C spectra of the three tetrafluorobenzenes and pentafluorobenzene were obtained. The spectra of all the carbons in 1,2,4,5-tetrafluorobenzene and 1,2,3,4-tetrafluorobenzene had second-order features and the analyses were not pursued further. The fluorine-substituted carbons of 1,2,3,5-tetrafluorobenzene gave first-order spectra, while the spectrum of C-4 again showed second-order features. The only resonance with three different long-range, carbon-fluorine coupling constants is assigned to C-1. The remaining two carbons are both on the same symmetry axis and have similar coupling patterns, but they can be distinguished because C-2 is shifted upfield by the two adjacent fluorines. Assignment of the doublet is to the para fluorine in both cases and the triplet to the ortho or meta fluorines. Assignment of the carbon-fluorine couplings to C-1 can not be made from symmetry considerations alone.

The coupling constants of the two carbons on the symmetry axis of pentafluorobenzene can be assigned by first-order considerations. The unique carbon-fluorine coupling (J = 3.7 Hz) involving C-6 is assigned to the para fluorine and the triplet (J = 23.4 Hz) to the ortho fluorines. From the line width only an upper limit of 2 Hz could be placed on the coupling to the meta fluorines. The larger of the two triplets (J = 13.2 Hz) involving C-3 is assigned to the ortho fluorines and the smaller coupling (J = 5.2 Hz) to the meta fluorines. The four-bond, carbon-proton coupling is ±1.7 Hz. The carbon-fluorine coupling constants in the polyfluorobenzenes are summarized in Table 3.5. In general, the fluorine substituent effects as derived from the difluorobenzenes can not be used to predict the carbon-fluorine coupling constants in the more highly substituted fluorobenzenes.

The ^{13}C chemical shifts and carbon-fluorine coupling constants which could be obtained from a first-order analysis of the spectrum of pentafluoroiodobenzene are given in Table 3.6. The carbon para to the iodine is assigned by its intensity and the fact that the basic carbon-fluorine doublet (J = 255 Hz) is further split into a triplet (J = 13.5 Hz) of triplets (J = 4.6 Hz). Correspondingly, the carbon bonded to the iodine has no large one-bond, carbon-fluorine coupling and appears as a doublet (J = 4.8 Hz to F - 4) of triplets

Table 3.5

Carbon-Fluorine Coupling in Polyfluorobenzenes

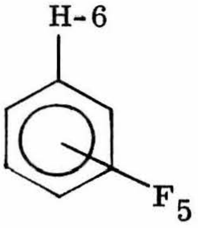
Compound	Carbon	Coupling Constants Hz
1, 2, 3, 5-Tetrafluorobenzene	1	5.4, 11.1, 14.9
	2	15.2(2F), 5.8
	5	13.0(2F), 3.8
Pentafluorobenzene	2	4.0, 7.8, 11.7, 15.5
	3	5.2(2F), 13.2(2F)
	6	23.4(2F), 3.7(1F)

Table 3.6

Carbon-Fluorine Coupling in Pentafluoroiodobenzene.

Carbon	Chemical shift[a]	J_{CF}	J_{CCF}	J_{CCCF}	J_{CCCCF}
1	127.5	-	28.4	1.3	4.8
2	45.0	254	(12.1, 6.1, 4.5, 3.4)[b]		
3	55.5	257	(second-order spectrum)		
4	50.9	255	13.5	4.6	-

a) In ppm upfield from carbon disulfide, benzene is at 64.1 ppm.

b) The coupling constants cannot be assigned to their proper fluorines.

(J = 28.4 Hz) of triplets (J = 1.3 Hz). The remaining carbons are assigned on the basis of their relative bandwidths and chemical shifts. The carbon ortho to the iodine would be expected to be downfield relative to the meta carbon because there is one less ortho fluorine, and for the same reason the sum of the carbon-fluorine coupling constants as reflected in the bandwidths would be expected to be smaller. The relative signs of the coupling constants can not be determined from the first order analysis, nor can they be assigned to their proper fluorines. Other pentafluoro-derivatives which have been studied include the aniline, phenol, chloride and bromide. Unfortunately the multiplets of most of the carbons overlap to such an extent that the carbon-fluorine coupling constants could not be determined.

Both the ^{13}C satellites of the fluorine spectrum and the ^{13}C spectrum of hexafluorobenzene have been obtained. At present there is not enough information available about substituent effects on carbon-fluorine and fluorine-fluorine coupling constants to complete the analysis of the spectrum. Although the detailed analysis remains to be done, some qualitative conclusions may be drawn. The one-bond, carbon-fluorine coupling constant is close to 250 Hz rather than the 360 stated by Van Der Kelen (20). None of the four parts of the pseudo AX spectrum is symmetrical about its center of gravity, nor are the two halves of the A part or the X parts mirror images of each other. Because of ^{13}C isotope effects on the fluorine chemical shifts the seven-spin system is best described as ABB'CC'DX. Even assuming that the coupling constants are not affected by the isotopic substitution, there are three relative chemical shifts, three fluorine-fluorine coupling constants, and four carbon-fluorine coupling constants to be determined. The liquid-crystal results for the fluorine-fluorine coupling constants can only be taken as order of magnitude estimates and do not provide a good enough starting point for an iterative analysis (21).

The ^{13}C chemical shifts, the fluorine substituent effects on the chemical shifts and the carbon-fluorine coupling constants of 1- and 2-fluoronaphthalene are given in Table 3.7. The proton on C-8 of 1-fluoronaphthalene is shifted downfield by the peri interaction with the fluorine. The carbon resonance which sharpens on irradiation of the low field proton resonance is assigned to C-8. The carbon directly bonded to the fluorine is found at low field, is insensitive to the proton decoupling frequency and is a doublet of 250 Hz. The carbons ortho to the fluorine have large, positive substituent effects on the carbon chemical shift and have relatively large, carbon-fluorine coupling constants. The doublet which is sensitive to the decoupling frequency is assigned to C-2, and the one which is not to C-9. The resonance at lower field which is also insensitive to the decoupler frequency is assigned to C-10.

Table 3.7

Carbon-Fluorine Coupling in 1- and 2-Fluoronaphthalene

Compound	Carbon	Chemical Shift[a]	Substituent Effect[b]	J_{CF}(Hz)
1-Fluoronaphthalene	1	-33.1	-33.5	251.1
	2	+16.9	+14.3	19.9
	3	+ 0.4	- 2.2	8.2
	4	+ 2.1	+ 1.7	4.0
	5	0.0	- 0.4	1.7
	6	- 0.9	- 3.5	0.8
	7	- 1.7	- 4.3	3.2
	8	+ 5.5	+ 5.1	5.1
	9	+ 1.9	+ 7.1	16.4
	10	- 9.2	- 4.0	4.8
2-Fluoronaphthalene	1	+11.1	+10.7	25.2
	2	-33.2	-35.8	248
	3	+16.3	+13.7	20.4
	4	- 3.1	- 3.5	8.8
	5	- 0.7	unassigned	0
	6	- 0.2		0
	7	+ 0.1		0
	8	+ 0.4		0
	9	- 7.0	- 1.8	9.2
	10	+ 2.1	+ 7.3	2.5

a) In ppm upfield from benzene.

b) In ppm upfield from the corresponding position in naphthalene (22).

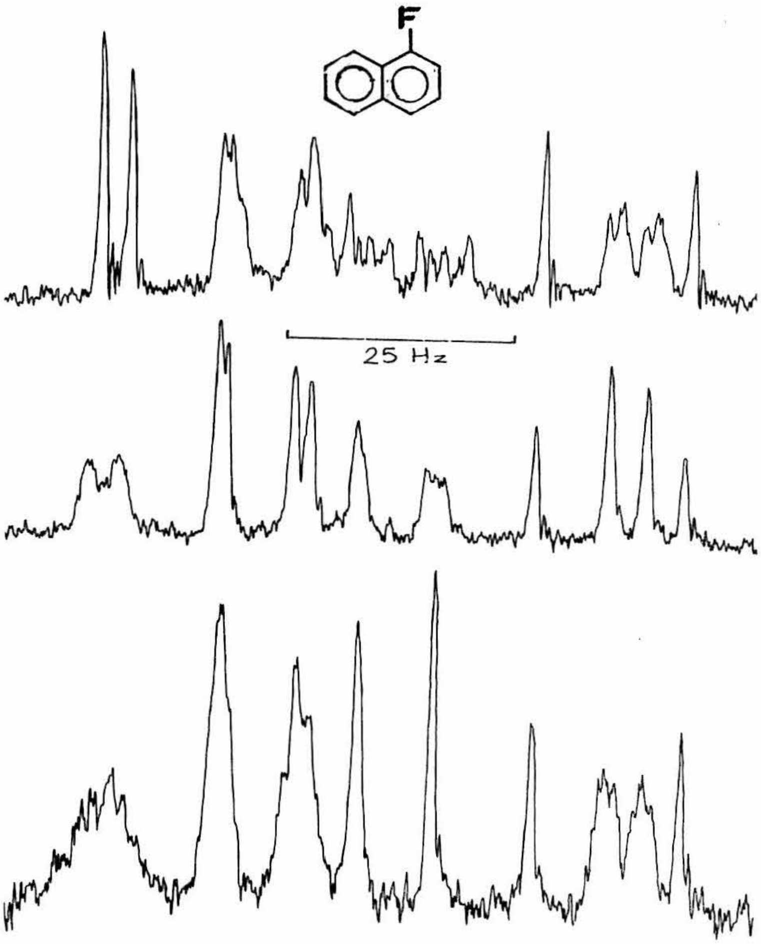


Figure 3.6. Partial ^{13}C spectrum of 1-fluoronaphthalene with different settings of the proton decoupler. Bottom 0; middle offset 12.0 Hz; top offset 31.4 Hz.

Figure 3.6 shows a region of the ^{13}C spectrum of 1-fluoronaphthalene under different decoupling conditions. Three separate settings of the decoupler are required to sharpen all six resonances in this region. The one doublet which is insensitive to the decoupler frequency has been assigned to C-9. The meta and para carbons are assigned on the basis of the expected fluorine substituent effects on the chemical shifts, leaving only C-5, C-6 and C-7 unassigned. There is little to be said for any one particular assignment because all of the carbon-fluorine coupling constants are small and the chemical shift differences are within 2 ppm of each other. The assignment presented in Table 3.7 is based on a possible (but not proven) correlation of the long-range, carbon-fluorine coupling with the distance between the two nuclei involved. The magnitude of the coupling constants assigned to the carbons in the same ring as the fluorine are very similar to the corresponding coupling constants in fluorobenzene. The signs of the cross-ring coupling constants cannot be assigned at this time.

The ^{13}C spectrum of 2-fluoronaphthalene, with each signal optimally decoupled, consisted of six doublets and four singlets. The doublets are assigned to the carbons in the same ring as the fluorine. The directly bonded carbon is shifted downfield, is insensitive to the decoupling frequency and is a doublet of _ca._ 250 Hz. The two ortho carbons are shifted upfield and have carbon-fluorine coupling constants of ca. 20 Hz. The α-carbon, C-1, is assigned to the downfield resonance and the β-carbon C-3 to the upfield resonance by analogy with naphthalene (22). The two bridge carbons are insensitive to the proton decoupler frequency and are distinguished by their carbon-fluorine coupling constants and the upfield shift of C-10 which is para to the fluorine. The remaining carbon which is coupled to the fluorine is assigned to C-4. At present, there is no way of distinguishing between possible assignments of the four carbons in the other ring. If, as was suggested earlier, the distance between the carbon and the fluorine is the relevant factor in the cross-ring couplings, no cross-ring coupling would be expected in 2-fluoronaphthalene because all the carbons in this ring are farther from the fluorine than any of the carbons in 1-fluoronaphthalene.

In order to determine the signs of some of the long-range, carbon-fluorine coupling constants a difluoronaphthalene was prepared in which the two fluorines, by symmetry, have the same chemical shift except for possible ^{13}C isotope effects. Since the cross-ring couplings were of prime interest, both fluorines should be at α-positions, and preferably in different rings so that one coupling constant could always be definitely assigned to the fluorine in that particular ring. To minimize fluorine-fluorine interactions which might distort the electronic structure of the molecule 1,5-difluoronaphthalene was initially chosen for study. A composite proton decoupled ^{13}C spectrum is shown in Figure 3.7. In this spectrum the protons have been sequentially decoupled. The ^{13}C spectra of the five types of carbon can be analyzed as one AMX system (C-1), one AA'X system (C-3), two ABX systems (C-2 and C-9) and one deceptively simple A_2X (C-4).

The four line AMX pattern is easily assigned to C-1. The extreme downfield chemical shift and 250 Hz. coupling constant as well as insensitivity to the decoupling frequency are all characteristic of a carbon with a directly bonded fluorine. The smaller coupling constant is then assigned to C-1, F-5. The bridge carbons are also easily identified as one of the ABX patterns. This resonance is also insensitive to the decoupling frequency, and compared to the pattern for C-3 which is immediately downfield from it, is seen to be of considerably lower intensity. The differential intensity arises from the nuclear Overhauser effect which attends the complete decoupling of directly bonded protons. The magnitudes of the coupling constants are also consistent with the ortho-meta relationship to the two fluorines, and the two coupling constants have the same sign. The other ABX pattern, which closely approaches an AMX because the two carbon-fluorine coupling constants differ considerably in magnitude is assigned to C-2 on the basis of the upfield chemical shift of this carbon arising from its ortho relationship to the fluorine and also to the one large carbon-fluorine coupling constant which is characteristic of the geminal relationship.

As was the case with the difluorobenzenes, the value of the fluorine-fluorine coupling in 1, 5-difluoronaphthalene was not known at the start of this investigation. The same approach to the analysis of the ABX spectra in the difluoronaphthalene was used as with the difluorobenzenes. A value of the chemical shift between the two fluorines was guessed and the ABX equations solved using the three frequency separations in the ^{13}C spectrum. The values for the three coupling constants thus obtained were then used to calculate the ^{13}C spectrum and the observed intensities compared with the experimental spectrum. As with the difluorobenzenes the ^{13}C spectrum is much more sensitive to the chemical-shift difference between the two fluorines than it is to any of the coupling constants. The two ABX systems were solved completely independently and it was quite gratifying to find that the values of $\underline{J}_{FF}$ which gave the best agreement with each spectrum agreed quite closely. The value found from these two analyses for the five-bond fluorine-fluorine coupling constant is 4.7 ± 0.1 Hz. The sign of the AB coupling constant can not be determined from an ABX analysis. The magnitude is sufficient that, in any future treatment of the proton or fluorine spectrum of this compound, the two rings can not be treated separately. This coupling constant was used subsequently in the analysis of the AA'X spectrum of C-3. Because only three lines are seen, the analysis of the spectrum can not have the same accuracy as the others. The calculated spectrum is quite sensitive to the linewidths as well as the coupling constants, because the pattern is caused by the accidental overlap of some of the lines. Nevertheless, reasonable agreement between the calculated and experimental spectra was achieved. The three line, 1:2:1 pattern for C-4 could be the result of either accidental equivalence of the two carbon-fluorine coupling constants or a deceptively simple spectrum. Given the fluorine-fluorine coupling constant and a zero chemical shift between the two fluorines, the spectrum was calculated for several values of the carbon-fluorine coupling constant, all constrained so that the sum of the two coupling constants is 9.7 Hz. The ^{13}C spectrum was calculated to be a triplet over a considerable range of the carbon-fluorine coupling constants, indicating that it is quite likely that this spectrum is deceptively simple. A summary of the carbon-fluorine coupling constants is given in Table 3.8.

The original purpose of this investigation was to gain some information about the signs of the coupling constants in 1-fluoronaphthalene and the proper assignment of the small cross-ring coupling constants. This is not possible as the introduction of a second fluorine substituent changes the magnitudes of the coupling constants sufficiently to make a correlation between the two compounds impossible. For example, there is a 5.1 Hz or 5.2 Hz cross-ring carbon-fluorine coupling constant in both compounds.

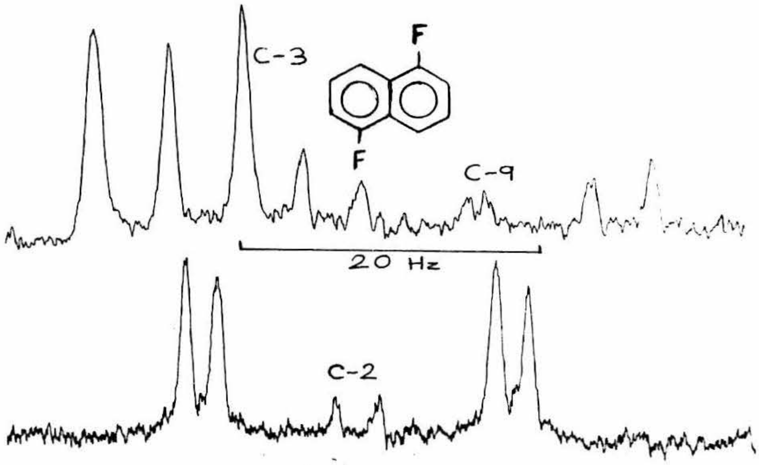


Figure 3.7. ^{13}C spectrum of 1, 5-difluoronaphthalene. Carbons have been sequentially decoupled.

Table 3.8

Carbon-Fluorine Coupling in 1, 5-Difluoronaphthalene

Carbon	J_{CF_1}[a]	J_{CF_5}[a]
1	251	5.2
2	19.6	-1.0
3	8.0	2.2
4	b	b
9	17.6	5.6

a) In Hz.

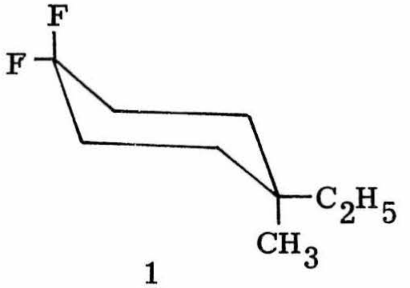
b) The sum of these two coupling constants is 9.7 Hz.

c) The fluorine-fluorine coupling constant as determined by the analyses of C-2 and C-9 is 4.7 ± 0.1 Hz.

In 1-fluoronaphthalene it was assigned to C-8 on the basis of the decoupler shift and the ^{13}C chemical shift of the carbon. In 1,5-difluoronaphthalene it is just as unambiguously assigned to C-5 on the basis of the AMX spectrum of the carbon directly bonded to fluorine. Thus, although C-2 in 1,5-difluoronaphthalene shows a cross-ring coupling of -1.0 Hz and there was a 0.8 Hz cross-ring coupling in 1-fluoronaphthalene (sign unknown) the previous inconsistency with the 5 Hz coupling constant indicates that no definite assignment of the cross-ring coupling can be made at this time.

The ^{13}C spectrum of n-hexyl fluoride obtained with complete proton decoupling consisted of three doublets and three singlets. The three singlets are assigned to C-4, C-5 and C-6 because they show no chemical shift relative to the corresponding carbons in n-hexane (23). The substituted carbon was easily identified by its downfield chemical shift, the downfield shift of the directly bonded protons and the large, carbon-fluorine coupling constant. The β-carbon was identified by the slight downfield shift of the directly bonded protons, the downfield ^{13}C chemical shift and the fact that the relative sign of the coupling constant could be determined by partial decoupling techniques. The remaining resonance, found considerably upfield of C-3 in n-hexane, was assigned to the γ-carbon. The ^{13}C chemical shifts, the substituent effects of the chemical shifts and the carbon-fluorine coupling constants of n-hexyl fluoride are summarized in Table 3.9.

Only three of the carbons of 4-methyl-4-ethyl-1,1-difluorocyclohexane **1** are significantly coupled to the fluorine. Rapid ring inversion between the nearly identically populated conformers (24) renders the average coupling between the carbons and the two fluorines equal to within our experimental error. The α, β, and γ carbons are identified by their chemical shifts, and in the case of the β and γ carbons, their relative intensities. The geminal and vicinal coupling constants are quite similar to those in *n*-hexyl fluoride.



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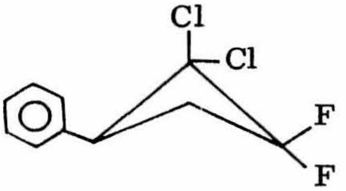

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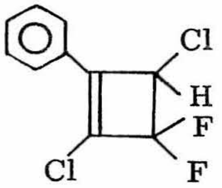


3

The four cyclobutane carbons in 3-phenyl-1,1-difluoro-2,2-dichlorocyclobutane **2** are easily identified. The one-bond and two-bond coupling constants are unexceptional. The only interesting feature would be the difference between the two vicinal carbon-fluorine coupling constants, but there is no way of assigning the couplings to their proper fluorines. Conformational effects probably are the relevant factor as the preference for the phenyl group for a pseudoequatorial position has been estimated as

Table 3.9

Carbon-Fluorine Coupling and ^{13}C Chemical Shifts of Some Continuous-Chain, Primary Fluorides

Compound	Carbon	Chemical Shift[a]	Substituent Effect[b]	J_{CF}(Hz)
Methyl fluoride		53.3[c]	-77.5	158[d]
Ethyl fluoride	1	49.4[c]	-73.4	-
	2	114.1[c]	- 7.7	-
n-Hexyl fluoride	1	44.9	-69.9	166.6
	2	97.5	- 8.3	+19.9
	3	103.0	+ 6.3	5.25
	4	96.4	- 0.3	-
	5	105.5	- 0.3	-
	6	114.6	- 0.2	-

a) In ppm upfield from benzene.

b) In ppm upfield from the corresponding position in the continuous-chain alkane. D. M. Grant and E. G. Paul, J. Am. Chem. Soc., **86**, 2984 (1964).

c) H. Spiesecke and W. G. Schneider, J. Chem. Phys., **35**, 722 (1961).

d) R. K. Harris, J. Mol. Spec., **10**, 309 (1963).

1 kcal/mole (25). Only three of the ring carbons in 1, 1-difluoro-2, 4-dichloro-3-phenylcyclobutene-2 3 are easily identified. The carbon bonded to the fluorine shows the large, characteristic, one-bond carbon-fluorine coupling constants. The two-bond, carbon-fluorine coupling constants identify the two carbons ortho to the fluorines and these two are further distinguished by the sensitivity of C-4 to the decoupling frequency and the chemical-shift difference expected between olefinic and aliphatic carbons. The assignment of C-3 and the substituted carbon of the phenyl ring is somewhat ambiguous. The ortho and meta carbons of the phenyl ring are distinguished from the para carbon by their intensity, and the para carbon from the substituted carbon by its sensitivity to the decoupling frequency. Both the substituted carbon and C-3 are coupled to the fluorines, are insensitive to the decoupling frequency and have similar chemical shifts. The assignment in Table 3.10 was made assuming that the four-bond, carbon-fluorine couplings would be similar in the cyclobutene and cyclobutane derivatives.

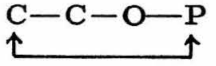
The carbon-fluorine coupling in cyclic geminal difluorides may be sensitive to the hybridization of the carbon orbital. The coupling becomes more *negative* as the s character in the carbon orbital increases. The coupling is 240 Hz in the cyclohexane, 280 Hz in the cyclobutanes and 330 Hz in hexafluorocyclopropane (26).

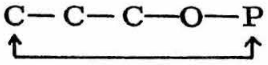
Table 3.10

^{13}C Chemical Shifts of Some Aliphatic Geminal Difluorides

Compound	Carbon	Carbon-Fluorine Coupling, Hz
4-Methyl-4-ethyl-1, 1-difluorocyclohexane	1	240.7
	2	+23.9
	3	5.0
3-Phenyl-1, 1-difluoro-2, 2-dichlorocyclobutane	1	284, 270
	2	26.1, 25.1
	3	15.1, 4.0
	4	23.3, 21.5
	5	2.05, 2.05
	6, 7, 8	0
1, 1-Difluoro-2, 4-dichloro-3-phenylcyclobutene-2	1	281.2, 279.8
	2	28.6, 27.2
	3	17.0, 12.2
	4	26.0, 23.9
	5	3.3, 2.3
	6, 7, 8	0
Diethyldifluoromalonate	CF_2	260
	CO	30.8
	CH_2, CH_3	0

Phosphorus: The ^{13}C chemical shifts and carbon-phosphorus coupling constants of the compounds studied are given in Table 3.11. The protons of a carbon bonded to either phosphorus or oxygen are shifted downfield relative to interior methylene protons. Thus the ^{13}C resonance which sharpens on irradiation of the low-field proton resonance may be assigned to the α carbon. The chemical shift of the α carbon of phosphites and phosphates is similar to that of an α carbon in an alcohol and therefore presents no problem in identification. Methyl protons absorb at high field which identifies the methyl carbon resonances. A methyl carbon appears as a perturbed quartet and a methylene carbon as a perturbed triplet under partial decoupling conditions. This observation is only useful if the carbons are not significantly coupled to the phosphorus, otherwise the partially decoupled spectra are too complicated. The protons on the β and γ carbons appear as one broad band and both methylene carbons appear in the same region of the ^{13}C spectrum. In phosphates and phosphites, the expectation that four-bond, carbon-phosphorus coupling will be negligible identifies the doublet as the β carbon and the singlet as the γ carbon.


C—C—O—P


C—C—C—O—P

The doublet with intensity one-third of the others in the methyltributylphosphonium ion is readily assigned to the unique

Table 3.11

NMR Parameters of Phosphorus-Containing Compounds

Compound	Carbon		Chemical Shift[a]	Carbon-Phosphorus Coupling[b]
Methylphosphine			133.1[c]	9.3
Dimethylphosphine			121.6[c]	11.6
Trimethylphosphine			111.4[c]	13.5
Phosphacyclopentane	2		96.9[c]	5.4
	3		107.4[c]	9.95
Tetramethyldiphosphine			117.3[c]	d
Tri-n-butylphosphine	1		103.5	10.9
	2		99.6	+11.7
	3		100.5	12.5
	4		114.3	0
Triphenylphosphine	1		-9.3	12.4
	2		-5.5[e]	19.55
	3	-0.3	±0.3	6.7, 5.1, 1.6
	4		±0.3	0
Tetrabutylphosphonium bromide	1		109.8	47.6
	2		104.8	4.3
	3		104.4	15.4
	4		115.2	0
Tributylphosphonium chloride	1		-	46.5
	2			-4.7
	3			14.9

Compound	Carbon	Chemical Shift[a]	Carbon-Phosphorus Coupling[b]
	4		0
Methyltributylphosphonium iodide	1	108.1	49.0
	2	104.8	-4.55
	3	104.6	15.7
	4	115.0	0
	methyl	123.4	41.8
Ethyltributylphosphonium iodide	1	110.0	47.7
	2	104.9	5.0
	3	104.6	15.6
	4	115.3	0.83
	a	115.6	49.7
	b	122.4	-5.2
Methyltriphenylphosphonium iodide	1	9.2	88.4
	2	-4.7	10.9
	3	-1.8	12.8
	4	-6.5	2.9
	methyl	119.0	51.7
Trimethyl phosphite		79.8	+10.05
Triethyl phosphite	1	70.7	11.0
	2	111.3	4.9
Triphenyl phosphite	1	-23.4	3.0
	2	7.6	6.85
	3	-1.5	0
	4	4.0	0

Compound	Carbon	Chemical Shift[a]	Carbon-Phosphorus Coupling[b]
Tri-n-butyl phosphate	1	61.5	-5.9
	2	95.7	6.5
	3	109.4	0
	4	114.8	0
Di-n-butyl phosphate	1	63.1	-5.6
	2	95.7	6.0
	3	109.5	0
	4	114.9	0

a) Chemical shifts are in ppm upfield from benzene.

b) In Hz.

c) Relative to external benzene.

d) The average of the magnitudes of the two carbon-phosphorus coupling constants is 4.3 Hz. The spectrum is a deceptively simple AA'X.

e) The value for C-4 disagrees with that found by H. L. Retcofsky and C. E. Griffin, Tetrahedron Letters, 1975 (1966).

methyl carbon. The two carbons of the ethyl group of the ethyltributylphosphonium ion are also identified by their intensity. The α carbon has a large, one-bond, carbon-phosphorus coupling constant. Assuming that the coupling between the phosphorus and the β carbon in a butyl group is similar to the coupling with a β carbon of the ethyl group, all β carbons in butyl groups of phosphonium ions may be identified. The remaining unassigned doublets arise from the γ carbons.

The relative signs of carbon-phosphorus coupling constants can be determined by our partial decoupling techniques if both the carbon and its directly bonded protons are significantly coupled to the phosphorus. This limitation makes it impossible to determine the sign of the three-bond, carbon-phosphorus coupling, because the phosphorus-proton coupling through four bonds is small. Proton decoupling of trimethyl phosphite with our maximum power can not produce a sharp, symmetrical doublet for the ^{13}C resonance. Irradiation of the upfield portion of the proton spectrum sharpens the upfield portion of the ^{13}C spectrum and vice-versa as shown in Figure 3.8. The difference between the proton decoupling frequencies which sharpen each half of the ^{13}C spectrum is the phosphorus-proton coupling constant. The two-bond, carbon-phosphorus coupling in trimethyl phosphite has the same sign as the three-bond, phosphorus-proton coupling. The signs of the carbon-proton and carbon-phosphorus coupling are the same, suggesting that all three are positive.

In cases where interior methylene groups are both coupled to the phosphorus and have similar chemical shifts, the β and γ carbons can be distinguished by the symmetry of the degradation of the ^{13}C resonance when the decoupler is offset from the optimum frequency. The β carbon shows an unsymmetrical effect similar to that shown in Figure 3.8 while both peaks in the γ carbon resonance broaden symmetrically.

Only three lines with relative intensities 1:1:2 are seen for the β and γ carbons of the tetrabutylphosphonium ion. Either the first two lines arise from a single carbon and the line of intensity two represents a carbon with a zero coupling to the phosphorus, or the first and third lines represent one doublet and the second and third lines the second doublet. The latter is the correct assignment as some of the other tributylphosphonium ions have four lines in this region and if the four lines are paired correctly, the coupling constants are very similar to the coupling constants of the tetrabutylphosphonium ion.

The carbon bonded to the substituent in aromatic derivatives is identified by its intensity and its insensitivity to the proton decoupler frequency. The para carbon is also identified by its intensity (except for triphenylphosphine, see below). The absence of four-bond, carbon-phosphorus coupling for triphenyl phosphite identifies the meta carbon and the doublet of intensity two is

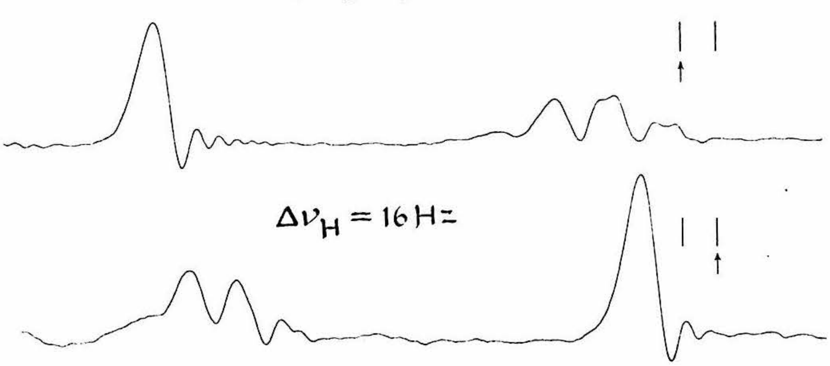


Figure 3.8. ^{13}C spectrum of trimethylphosphite with two different settings of the proton decoupler.

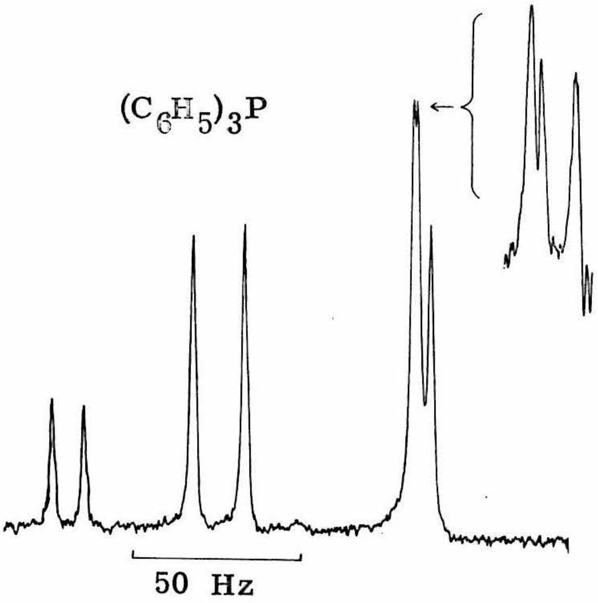
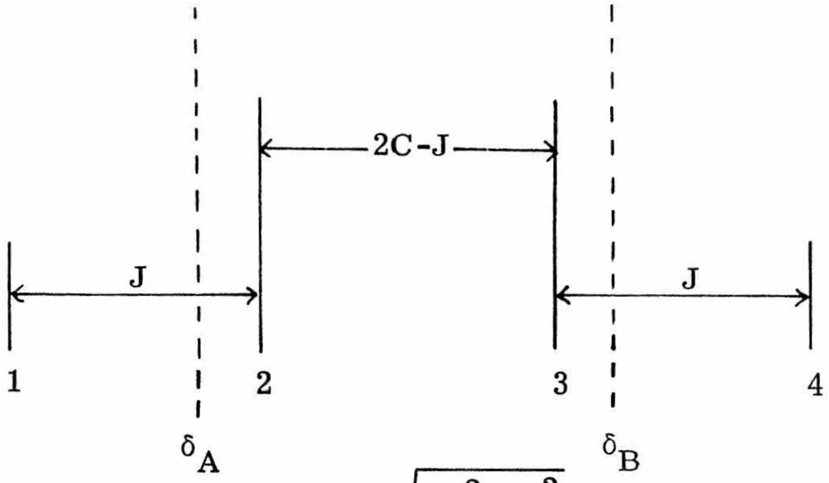


Figure 3.9. ^{13}C spectrum of triphenylphosphine. Inset shows region of meta and para carbons with expanded sweep.

assigned to the ortho carbon. The meta carbon in the triphenylmethylphosphonium ion can be identified by its small chemical shift relative to benzene. The proton decoupled ^{13}C spectrum of triphenylphosphene is shown in Figure 3.9. Three lines of equal intensity are observed in the region of the spectrum where the meta and para carbons of triphenylphosphine are expected. Because the three-bond carbon-phosphorus coupling to the meta carbon is expected to be non-zero, while the four-bond coupling to the para carbon should be small, the three lines are not unexpected, but there are three equally reasonable ways of assigning these lines to the carbons. Partial decoupling experiments are not of any help. The obvious solution, but one which is instrumentally unavailable to us, is to observe the spectrum at a different field strength. Only one of the three spacings will remain the same, thus identifying the coupling constant. The assignment of the para carbon differs from that given previously by Retcofsky (27).

Carbon: The extremely low signal-to-noise ratios for ^{13}C satellites of the ^{13}C spectrum (at best 0.2/1 for a single scan) necessitated some care in verifying the reality of a supposed satellite. The ideal experiment, ^{13}C homonuclear tickling with simultaneous complete proton decoupling, was not practical because of the weakness of the signals of the unlabelled materials and because the modulation and sweep systems of the DFS-60 do not lend themselves to homonuclear decoupling experiments. The possibility of spinning side bands as the origin of the satellites was eliminated because the positions of the satellites were unaffected by changes in spinning rate and more importantly the satellite resonances were in general not symmetrically located about the intense peak of the singly labelled materials.



$$\delta_{AB} = \sqrt{4C^2 - J^2} \qquad (1)$$

The coupling constant can be measured directly from an AB spectrum, but the chemical shifts must be calculated using (1). Neglecting isotope effects, the resonances of the singly labelled species occur at the calculated chemical shift positions of the AB spectrum of the doubly labelled species. The agreement between the chemical shift calculated from the AB spectrum and that observed from the two singly labelled species is additional evidence that the assignment of the satellites is correct.

Anderson and Freeman (28) showed that the X part of an $A_iB_j\ldots X$ system can be collapsed to a single line by a sufficiently strong decoupling field. Because the ^{13}C spectrum of a singly labelled species is the X part of an $A_iB_j\ldots X$ spin system, a single line is expected to result under the decoupling conditions used in our experiments. Any remaining resonances are then due to other species.

The possibility of an impurity at the low concentrations of ^{13}C satellites is very difficult to eliminate, but the probability that impurities would be present in just the correct concentrations and have just the right ^{13}C and proton chemical shifts to simulate carbon-carbon coupling constants is small.

Carbon-carbon coupling constants of substituted cyclopropanes are given in Table 3.12. Litchman and Grant (29) found small, but significant, substituent effects on the carbon-carbon coupling constants in t-butyl derivatives. A similar variation is also seen in the cyclopropane derivatives. The carbon-carbon coupling constants in substituted cyclopropanes are proportional to the carbon-proton coupling constants in substituted methanes as

Table 3.12

Carbon-Carbon Coupling in Cyclopropane Derivatives

Compound	Bond	Coupling Constant, Hz
Cyclopropanecarboxylic acid	1, 2	10.05
	1, α	72.5
Dicyclopropyl ketone	1, 2	10.2
	1, α	54.0
Cyclopropyl cyanide	1, 2	10.9
	1, α	77.9
Methylcyclopropane	1, α	44.0
Cyclopropyl iodide	1, 2	12.9
Cyclopropyl bromide	1, 2	13.3
Cyclopropyl chloride	1, 2	13.9
1, 1-Dichlorocyclopropane	1, 2	16.55

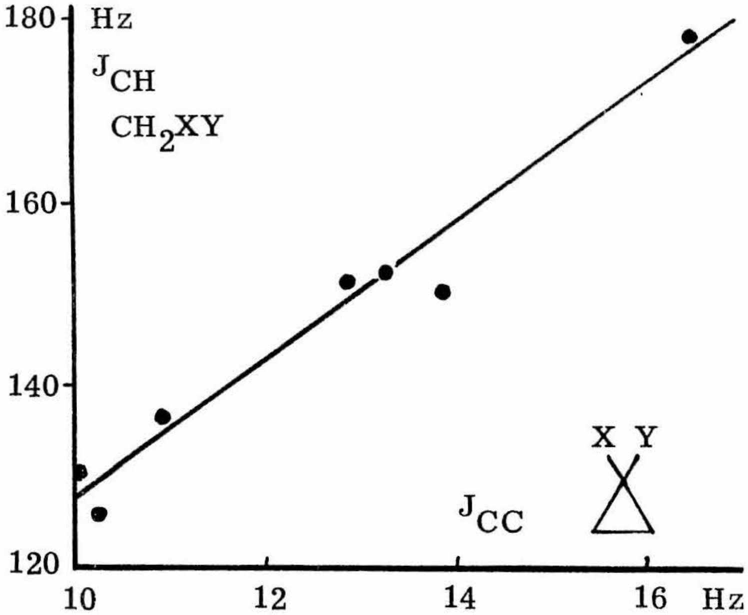


Figure 3.10. Carbon-carbon coupling in cyclopropanes versus carbon-carbon coupling in substituted methanes.

shown in Figure 3.10. Because the coupling constants increase with increasing electronegativity of the substituent, the compounds in which the first atom of a substituent is carbon, such as dicyclopropyl ketone or cyclopropanecarboxylic acid provide the closest models to cyclopropane itself. Thus, the carbon-carbon coupling constant in cyclopropane is probably close to 10 Hz. The magnitudes of the substituent effects on the carbon-carbon coupling constants are quite similar in the cyclopropanes and the t-butyl derivatives (29).

One-bond, carbon-carbon coupling constants which have been obtained for aliphatic and alicyclic compounds are given in Tables 3.13 and 3.14. Consideration of a bromine substituent effect and the further expectation that the substituent effect on a β-γ bond should be negligible, gives an extrapolated value for the carbon-carbon coupling in cyclobutane of 27 Hz.

The coupling constant of the carbonyl carbon in cyclohexanone is similar to the corresponding coupling constant in cyclopentanone. Cyclobutanone, on the other hand, has significantly smaller carbon-carbon coupling constants which are indicative of the rehybridization of the bonding orbitals due to ring strain. The β-γ coupling constant in cyclobutanone is different from that in bromocyclobutane, perhaps being indicative of the difference between a planar ketone and a puckered bromide. The coupling

Table 3.13

Carbon-Carbon Coupling in Aliphatic Compounds

Compound	Bond	Coupling Constant, Hz
Ethanol	1, 2	37.7
2-Propanol	1, 2	38.4
_t_-Butyl alochol	1, 2	39.5[a]
1-Propanol	1, 2	37.8
	2, 3	34.2
3-Pentanol	1, 2	35.0
	2, 3	37.9
Acetone	1, 2	40.6
2-Butanone	1, 2	38.4
	3, 4	37.0
3-Pentanone	1, 2	35.7
	2, 3	39.7
Propyne	2, 3	67.4
Dimethylacetylene-dicarboxylate	C≡CO	123

a) Reference 29.

Table 3.14

Carbon-Carbon Coupling in Alicyclic Compounds

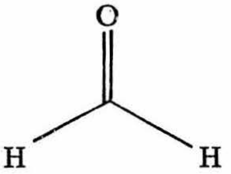
Compound	Bond	Coupling Constant, Hz.
Bromocyclobutane	1,2	29.6
	2,3	27.1
Cyclobutanone	1,2	29.7
	2,3	28.5
Cyclopentanone	1,2	37.2
	2,3	34.4
Cyclohexanone	1,2	37.3
Cyclopentanol	1,2	36.0
	2,3	32.6
Cyclohexanol	1,2	35.8
	2,3	33.0

constant between the carbinyl carbon and C-2 in cyclohexanol and cyclopentanol are also similar. The similarity of the coupling constants in the five- and six-membered rings suggests that there is no angle strain in either series.

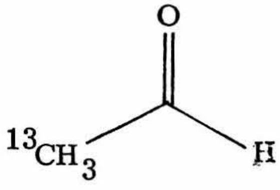
The carbon-carbon coupling constant in ethanol is 3.1 Hz larger than that in ethane. Substitution of a methyl group on the β carbon to form 1-propanol does not alter the value of the coupling constant between the α and β carbons. The β-γ coupling constant in 1-propanol does not differ greatly from that in ethane. However, substituting a methyl at the α position of ethanol to give 2-propanol causes an increase in the one-bond, carbon-carbon coupling constant which is seen again in the addition of a second methyl group to form t-butyl alcohol (29). The coupling in cyclic alcohols is significantly smaller than the corresponding alicyclic compounds, but the origin of this effect is at present unknown.

The only carbon-carbon coupling constant where both carbons involved are in an aromatic ring was obtained by Bernstein (10) who measured the 57.0 Hz carbon-carbon coupling in benzene itself. Ethylene has a carbon-carbon coupling constant of 67.6 Hz (8, 9). The difference between the carbon-carbon coupling constants of benzene and ethylene points out the danger of simplifying the concept of orbital hybridization and its relationship to carbon-carbon coupling to the extend that only the number of atoms bonded to the carbons are considered. Furan, pyrrole and thiophene all have carbon-carbon coupling constants similar to that in ethylene, while the six-membered ring aromatic compounds all have one-bond, carbon-carbon coupling constants similar to benzene. The accuracy of these coupling constants is considerably lower than in the case of the cyclopropane coupling constants because wider sweep ranges had to be scanned. The substituent effects seem much more erratic than those of the aliphatic compounds and may possibly represent subtle changes in the σ bonding with changes in substituent as well as π electron effects. The coupling constants which have been observed in unsaturated compounds are given in Table 3.15.

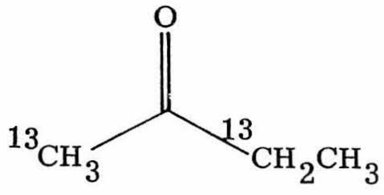
A large proton-proton coupling constant has been observed in formaldehyde (30). Large carbon-proton coupling constants have been observed in aldehydes (31). If carbon-carbon coupling is dominated by similar mechanisms, the geminal, cross-carbonyl, carbon-carbon coupling in ketones would be expected to be large. Acetone, the simplest ketone where this feature could be seen, is not suitable for out studies, because, with complete proton decoupling, the two methyl carbons become magnetically equivalent, and the coupling between them can not be seen. A carbon-carbon coupling of 15.2 Hz was observed in the next higher homologue



$J_{HH} \sim 40$



$J_{CH} \approx 26$



$J_{CC} = 15.2$

Table 3.15

Carbon-Carbon Coupling in Aromatic and Olefinic Compounds

Compound		Aromatic Compounds	
Compound	$J_{C-1,C-2}$	$J_{C-2,C-3}$	$J_{C-3,C-4}$
Benzene	57.0[a]		
Pyridine	-	53.8	53.5
Nitrobenzene	55.4	56.3	55.8
Iodobenzene	60.4	53.4	58.0[c]
Anisole		58.2	56.0
Aniline	61.3	58.1	56.2
Pyrrole		65.6	
Furan		69.1	
Thiophene		64.2[c]	
		Olefinic Compounds	
Ethylene[b]	67.6		
1,1-Dimethylallene		99.5	
Acrylonitrile	70.6		
Acrylic acid	70.4 (1, α)		

a) Reference 10

b) References 8 and 9

c) Only the inner two lines of the AB pattern were seen. The coupling constant was evaluated using

$$J = (\delta^2 - 4C^2)^{1/2}$$

2-butanone. A large, geminal, carbon-proton coupling constant which has no analogy in proton-proton coupling occurs in acetylene (8, 9, 32). The proton-decoupled ^{13}C spectrum of C-1 of propyne labelled with 57% ^{13}C in the methyl carbon is shown in Figure 3.11. The central peak is due to molecules with one ^{13}C, and the two satellites are due to the doubly labelled species. The geminal carbon-carbon coupling constant is 11.8 Hz.

In addition to the satellites due to the one-bond coupling, inner satellites were found symmetrically located about the α and β carbon resonances of pyridine but no satellites of similar magnitude were found about the γ carbon. The vicinal, carbon-carbon coupling constant of 13.95 Hz in pyridine is shown in Figure 3.12. Similar, though smaller, coupling constants were also observed in the spectra of substituted benzenes. The long-range coupling constants which have been observed are given in Table 3.16.

Nitrogen: The observation of spin-spin coupling involving nitrogen is considerably hampered by the fact that the major isotope of nitrogen has a spin of one and most coupling is either partially or completely washed out by quadrupole relaxation. Because the natural abundance of the spin one-half isotope is 0.4%, observation of the coupling using natural abundance

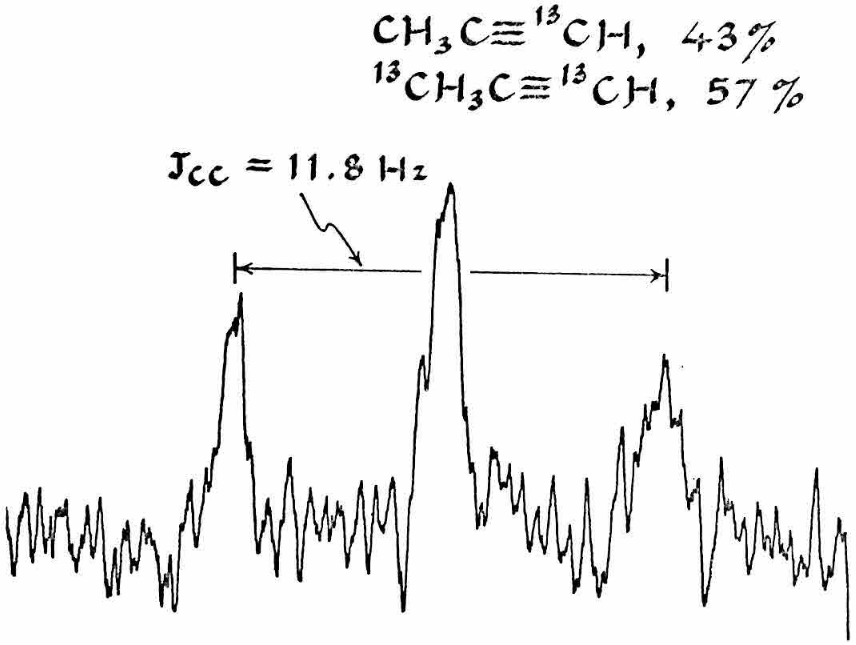


Figure 3.11. ^{13}C spectrum of C-1 of propyne labelled 57% in C-3.

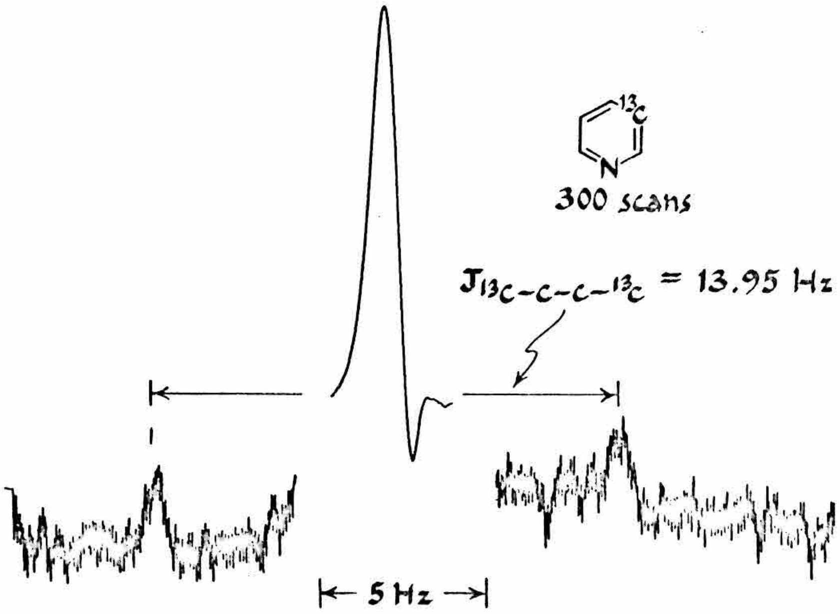


Figure 3.12. ^{13}C spectrum of C-2 of pyridine showing $J_{C-2, C-5}$.

Table 3.16

Long-Range, Carbon-Carbon Coupling

Compound	Carbons	Coupling Constant, Hz
	Geminal	
Propyne	1, 3	11.8
2-Butanone	1, 3	15.2
Cyclobutanone	2, 4	9.5
Bromocyclobutane	2, 4	9.0
	Vicinal	
Pyridine	2, 5	13.95
Aniline	2, 5	7.9
Iodobenzene	2, 5	8.6
Nitrobenzene	2, 5	7.6

materials is impractical. In order to see carbon-nitrogen coupling, either observation of compounds with nitrogens with long relaxation times (33) or isotopic enrichment with ^{15}N is necessary (34, 35). Table 3.17 lists a few carbon-nitrogen coupling constants which have been observed.

The nitrogens in the tetraalkylammonium ions have long relaxation times and nitrogen-proton coupling can be observed in the proton spectrum. In these cases the proton decoupled ^{13}C spectrum is a 1:1:1 triplet and the carbon-nitrogen couplings in the tetramethyl and tetraethylammonium ions could be observed. The lines of the triplets are noticeably broader than the lines from an internal reference, but the coupling is resolvable.

If the relaxation time of the nitrogen is shorter, only a single, broad band is seen for carbons coupled to the nitrogen. Even if the coupling is unresolvable because of quadrupole interactions, some information is still available from the widths of the ^{13}C resonances. Table 3.17 also lists the ^{13}C linewidths of some carbons coupled to ^{14}N. The linewidth of the methyl carbon in acetamide is greater than that of the carbonyl carbon in the same compound. In a given molecule, the relaxation time of the nitrogen is a constant and the differences in the linewidths reflect differences in the carbon-nitrogen coupling constants. The carbon-nitrogen coupling across a carbonyl group might be

Table 3.17

Carbon-Nitrogen Coupling

Compound	Carbon	Carbon Line Width, Hz	$T_1(^{14}N)$[a] msec	$T_1(^{14}N)$[b] msec	J_{CN}
Acetonitrile	CN	4.7	5.0	3.6	17.5[c, d]
Nitromethane	-	9.6	22.0	13.2	
Acrylonitrile	CN	3.5	3.5	2.9	
Nitrobenzene	C-1	6.3	3.5	2.9, 5.3	14.5[d]
Dimethyl-formamide	CO	3.2	1.4	2.8	
Acetamide	CO	1.1	-	0.59	
	CH_3	1.5			
Pyridine	C-2	<0.3	2.3	1.2	
Pyrrole	C-2	2.76	2[f]		
Tetramethyl-ammonium		0.55	-	≈ 60	4.15[e]
Tetraethyl-ammonium	C-α	-	-	≈ 60	2.85[e]

a) Reference 37.

b) Calculated from the linewidth of the ^{14}N resonances assuming $T_1 = T_2$; M. Witanowski, T. Urbanski and L. Stefaniak, J. Am. Chem. Soc., 86, 2569 (1965), and subsequent papers.

c) References 34 and 35.

d) Coupling with ^{15}N.

e) Coupling with ^{14}N.

f) E. Rahkamaa, J. Chem. Phys., 48, 531 (1968).

expected to be large by analogy with the proton-proton coupling in formaldehyde, the carbon-proton coupling in acetaldehyde and the nitrogen-proton coupling in formamide. The linewidth of all carbons in pyridine, including the α carbon, appear to be homogeneity controlled implying small carbon-nitrogen coupling constants.

Pople (36) has derived an expression for the line shape of a spin one-half nucleus coupled to a spin one nucleus undergoing moderately rapid relaxation. Given either the relaxation time or the coupling constant, the other can be calculated from the linewidth. Unfortunately, if the coupling constants are desired, the precision of the available relaxation data (37) is insufficient to give more than an order of magnitude estimate of the coupling constant.

Mercury: The carbon-mercury coupling constants which have been obtained for a series of disubstituted mercury compounds are given in Table 3.18. Irradiation of the low-field portion of the proton spectrum sharpens the upfield portion of the ^{13}C spectrum of the β carbon of dipropylmercury and vice versa, thus showing that the sign of the geminal, carbon-mercury coupling constant is opposite of the vicinal mercury-proton coupling. Because the vicinal coupling is almost certainly positive, the geminal, carbon-mercury coupling is negative. The sign of the vicinal, carbon-mercury coupling could not be determined, but as with mercury-proton coupling, the magnitude of the vicinal coupling is greater than that of the geminal

Table 3.18

Carbon-Mercury Coupling[a]

Substituents	J_{CHg}	J_{CCHg}	J_{CCCHg}	J_{CCCCHg}
Methyl	692			
Ethyl	648	24		
n-Propyl	659	-25.2	102.6	
n-Butyl	656	26.3	100	0
i-Propyl	633.6	32.2		
Phenyl	1186	88	101.6	17.8
Vinyl	+1159±2			

a) In Hz.

coupling. The geminal coupling in divinylmercury could not be determined because it was not possible to simultaneously decouple both β protons.

Boron: Boron also has a quadrupole moment, but in favorable cases boron-proton and boron-fluorine coupling has been observed. The carbons directly bonded to boron in triisopropyl and di-n-propylboron have linewidths of 130 Hz and 80 Hz respectively. This is presumably the result of a large carbon-boron coupling which is incompletely relaxed. The boron of the tetraphenylboride anion is in a symmetric environment and would be expected to have a long relaxation time. With complete proton decoupling all four carbons can be seen and the substituted carbon (insensitive to the proton decoupling frequency) was a 1:1:1:1 quartet with a carbon-boron coupling constant of 49.5 Hz. A coupling of 2.6 Hz was also observed to the meta carbons, but no coupling could be resolved to either the ortho or the para carbons, though both resonances were slightly broadened.

Miscellaneous: Some coupling constants between carbon and cadmium, selenium, silicon, tin and lead are given in Table 3.19. The sign of the geminal, tin-carbon coupling constant was determined by partial decoupling techniques similar to those used with dipropylmercury. Separate resonances could be resolved for the

Table 3.19

Coupling of Carbon and Miscellaneous Elements

Compound	Coupled Nuclei	Coupling Constants, Hz
Selenophene	C-2, Se	113.6
	C-3, Se	-
Tetramethylsilane	C-Si	51
Triethylsilane	C-α, Si	51.5
	C-β, Si	-
Hexamethyldisiloxane	C-Si	59.2
Tetramethyltin	C-Sn	330±5
Tetraethyltin	C-α, Sn	307.4, 321.5
	C-β, Sn	-23.5
Dimethylcadmium	C-^{111}Cd	512
	C-^{113}Cd	537.5
Tetramethyllead	C-Pb	250
Tetraphenylboride	C-1, B	49.5
	C-3, B	2.6

one-bond, carbon-tin coupling to ^{119}Sn and ^{117}Sn. Two-bond, carbon-silicon and carbon-selenium coupling could not be seen in the compounds studied.

Discussion

The best currently operational formalism for calculating the Fermi contact contribution to the spin-spin coupling constant is the molecular orbital theory of Pople and Santry (38)

$$J_{AB} = -64h\gamma_A\gamma_B\beta^2/9 <s_a|\delta_{r_a}|s_a><s_b|\delta_{r_b}|s_b> \sum_i^{occ} \sum_j^{unocc} (1/\Delta E_{i-j}) C_{is_a} C_{js_a} C_{js_b} C_{is_b} \quad (1)$$

where β is the Bohr magneton, γ_A and γ_B are the nuclear magnetic moments, and the matrix elements are the valence shell s electron densities at the nucleus while the coefficient C_{uv} is for a particular s atomic orbital v in molecular orbital u. Because excited-state wavefunctions are needed for the evaluation of (1), the average energy approximation and closure are frequently invoked giving

$$J_{AB} = (16\ h\beta^2\gamma_A\gamma_B/9)\ (1/\Delta E) <s_a|\delta_{r_a}|s_a><s_b|\delta_{r_b}|s_b> P^2{}_{ab} \quad (2)$$

where ΔE is a mean excitation energy and $P^2{}_{ab}$ is the s bond order between atoms a and b. Equation 2 has the advantage that only ground-state wavefunctions are required, however, arbitrary assumptions must be made about the magnitude of ΔE.

Coupling constants have been calculated for a few of the simpler molecules studied here using extended Hückel wavefunctions (39). The carbon and nitrogen parameters used have been described previously (see page 57) and in addition the following parameters were used for oxygen and fluorine (40).

	Fluorine	Oxygen
Orbital Exponent	2.61	2.275
2s Coulomb integral	-39.0 ev.	-32.
2p Coulomb integral	-20.9 ev.	-16.

The results of these calculations are given in Table 3.20.

The one-bond coupling constants are in reasonable agreement with the experimental values, however, the unusual features of the long-range couplings are not reproduced. For carbon-fluorine coupling significant contributions to the coupling constant may arise from interactions other than the Fermi contact term, but for carbon-carbon coupling where it is fairly certain that the Fermi contact term dominates, the poor agreement must be ascribed to the inadequacy of the extended Hückel wavefunctions, at least in this particular application.

Karabatsos (41) extended the valence-bond theory of geminal proton-proton coupling to the case of geminal, carbon-proton coupling. The two couplings could be related by

$$J_{CH} = a \cdot J_{HH} \tag{3}$$

where for sp^3 hybridized carbon a = 0.3; for sp^2, a = 0.4; and for sp, a = 0.61.

Table 3.20

Coupling Constants Calculated from Extended Hückel Wavefunctions

Compound	Coupled Nuclei	J_{CX}(calcd.), Hz
Benzene	C-1, C-2	49.3
Pyridine	C-2, C-3	54.1
	C-3, C-4	48.1
	C-2, C-5	0.8
Propyne	C-1, C-2	126.4
	C-2, C-3	38.8
	C-1, C-3	-4.1
Pyrrole	C-2, C-3	53.0
n-Propanol	C-1, C-2	24.6
	C-2, C-3	23.4
Fluorobenzene	C-1, F	-207.0
	C-2, F	+4.5
	C-3, F	+9.6
	C-4, F	-0.8

Smith (42) following Karabatsos, related the X-C-H geminal coupling in the tetramethyl derivatives of Group IV to the H-C-H coupling in methane. The problem of choosing a form for the central atom s-orbitals is more difficult for the heavier elements. Smith adopted an empirical approach and calculated effective nuclear charges (Z*) for s-like orbitals which gave the best fit with the observed spin-spin coupling constants.

The equations which Smith and Karabatsos formally derived for geminal coupling may be valid for any Fermi contact interaction where the average energy approximation holds. The most general form of such an expression must allow for the variation of both the form and the hybridization of the orbitals used by both atoms in forming the valence bonds. Equation 4 relates the Fermi contact contribution to the one-bond carbon-metal coupling constant in the tetramethyl derivatives of Group IV to the carbon-carbon coupling in neopentane where α^2 is the fractional s-character of the carbon

$$J_{CX} = \left(\frac{\alpha^2_{cx}}{\alpha^2_{cc}}\right) \left(\frac{\Delta E_c}{\Delta E_x}\right) \left(\frac{Z_x{}^*}{Z_c{}^*}\right)^3 \left(\frac{\underline{n}_x}{\underline{n}_c}\right)^3 \left(\frac{g_x}{g_c}\right) \times J_{CC} \qquad (4)$$

orbital forming the carbon-metal bond, ΔE is the average energy approximation term, $\underline{n}$ is the principal quantum number of the period to which the central atom belongs, Z* is the effective nuclear charge of the orbital used by the central atom in forming the carbon-metal bond and g is the magnetic moment of the central atom. For one-bond couplings, eq. 4 is attractive theoretically, because the valence-bond structure which contributes the most to the coupling constant is the perfect pairing structure, and the coefficient of this structure in the valence-bond wavefunction changes insignificantly from unity for the purposes of calculating the coupling constant in covalent molecules for which ionic structures are unimportant.

For the case of one-bond, carbon-metal coupling in the tetramethyl derivatives of Group IV, the hybridization of each orbital of the central atom forming a bond to carbon contains 25% s-character by symmetry. The hybridization of the carbon orbital forming the bond to the metal is not exactly sp^3 since the four substituents on the carbon are not identical. The degree of hybridization of this orbital may be assigned by the method of Juan and Gutowsky (43).

Assuming that a carbon atom uses a single 2s orbital to form its four bonds, the variation of the one-bond, carbon-proton coupling constant was attributed to changes in the hybridization of the carbon orbital forming the carbon-proton bond. This approach has been criticized (44) and, in the cases where electronegative substituents are present, the parameter which most strongly influences the carbon-proton coupling constant is the effective nuclear charge of the carbon 2s orbital rather than its hybridization. When no electronegative substituents are present, the correlation of s-character with the carbon-proton coupling constants seems valid. When the fraction of s-character in the C-H bond is fixed, the remaining s-character, if any, must reside in the carbon-metal bond. The s-characters of the carbon-hybrid orbitals calculated in this way for the tetramethyl derivatives of Group IV have been tabulated by Smith (42).

The Z* values, which Smith found gave the best agreement for the geminal X-C-H coupling constants, were used in this work. A further assumption was made that the average energy approximation term is constant throughout this series.

Typically changes in the "average excitation energy" have been related to bond strengths. A more valid procedure would be to consider electronic transitions. On this basis, although carbon metal bonds have low dissociation energies, they have more normal excitation energies.

The parameters used and the results of the calculations are given in Table 3.21 and show the rather good agreement between the coupling constants calculated in this rather naive way and the experimental values. The agreement, if not fortuitous, tends to justify the belief that the Fermi contact interaction is the dominant coupling mechanism and that, if the average energy approximation holds, simple correlations with bond order and electron density at the nucleus are valid.

Table 3.21

Comparison of the Calculation of the One-Bond Carbon-Metal Coupling by the Method of Karabatsos and Smith with the Observed Values

	J_{CH}	α_{CH}^2	α_{CX}^2	Z_X^*	μ	n_X	J_{CX} calcd.	J_{CX} obsd.
C	124.3	.248	.256	3.29	.70	2	(-)	36.2
Si	118.2	.236	.291	6.02	-.55	3	58.6	51
Ge	124.4	.249	.256	10.9	-.88	4	204	-
Sn	127.7	.255	.137	16.3	~-1.0	5	369	330
Pb	134.2	.268	.196	22.6	.58	6	276	251

The one-bond, carbon-mercury coupling may be calculated from a typical carbon-carbon coupling constant assuming that the mercury orbital forming the carbon-mercury bond is an sp hybrid, neglecting changes in the average excitation energy and carbon orbital hybridization and using Smith's (42) value of 22.7 for Z*. The calculated value is obviously sensitive to the carbon-carbon bond chosen as the model, but assuming a value of 36 Hz from neopentane (29) the calculated value for J_{CHg} is 650 Hz, in very good agreement with that observed. The cadmium-carbon coupling of 330 Hz in dimethylcadmium can be explained on similar grounds.

The one-bond, carbon-mercury coupling in diphenyl- or divinylmercury is particularly influenced by the change in the hybridization of the carbon orbital forming the bond to mercury. The carbon-carbon coupling in neopentane may be related to the one-bond, carbon-proton coupling in isobutane by the relationship $J_{CC} = 0.3 \times \underline{J}_{CH}$. The calculated value of 37.5 Hz agrees well with the experimental value of 36.2 Hz. Similarly, the one-bond, carbon-metal coupling constant should be 0.3 times the one-bond, metal-proton coupling constants in the trimethylmetal hydrides. The results of this calculation are given in Table 3.22. The relationship does not hold for the heavier members of Group IV. The most plausible explanation for the failure of the Karabatsos equation in these cases is that one or more of the assumptions on

Table 3.22

A Comparison of Coupling Constants Involving Carbon with Those Involving Protons

	J_{XH}, in $HX(CH_3)_3$ [a]	J_{XC}, [a] calcd.	J_{HXCH}, in $HX(CH_3)_3$ [a]	J_{HXCH}, [a] calcd.
C	125	36.5	6.8[d]	2.0
Si	202[b]	61	-	-
Ge	-	-	3.8[e]	1.1
Sn	1700[c]	510	2.4[c]	.72
Pb	2397[c]	720	1.5[c]	.45

a) Hz.

b) E. A. V. Ebsworth and J. J. Turner, J. Chem. Phys., **36**, 2628 (1962).

c) H. D. Kaesz and N. Flitcroft, J. Am. Chem. Soc., **85**, 1377 (1963).

d) J. S. Waugh and F. W. Dobbs, J. Chem. Phys., **31**, 1238 (1959).

e) T. Birchall and W. L. Jolly, Inorg. Chem., **5**, 2177 (1966).

which the derivation is based are not valid. In particular, the wavefunctions of the two series of compounds may not be comparable. Chemically, this is reasonable because, although the carbon-proton bond closely resembles the carbon-carbon bond, the metal-proton and metal-carbon bonds are not at all similar in their properties.

A second possibility is that one or both of these coupling constants has a significant contribution from either the orbital or the dipole interactions. Both these contributions are negligible if one of the coupled nuclei is a proton and the results presented above on the one-bond carbon-metal couplings tend to show that these too are dominated by the Fermi contact term.

Reeves and Wells (45) proposed a correlation of the reduced coupling constants with atomic number according to equation 5.

$$\left(\frac{J_{xy}}{\gamma_x \gamma_y}\right)^{\frac{1}{2}} = AZ_x + B \qquad (5)$$

where Z_x is the atomic number of nucleus x, γ is the magnetic moment, and A and B are constants for a single series of atoms y.

The results of applying this correlation to the case of one-bond, carbon-metal coupling constants in the tetramethyl derivatives of Group IV are given in Figure 3.13. Although the equation correlates geminal, metal-proton coupling constants quite well, the

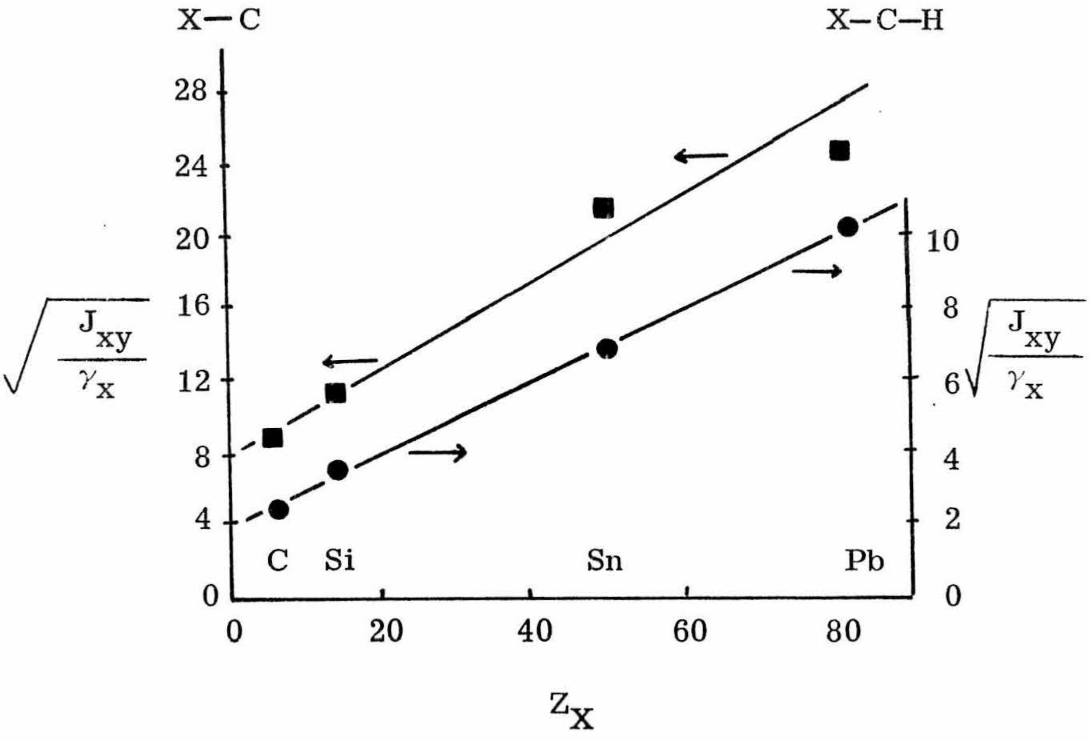


Figure 3.13. Reeves and Wells correlations of the C—X and X—C—H coupling constants in the tetramethyl derivatives of Group IV; ● X—C—H, ■ X—C.

fit for one-bond, carbon-metal coupling constants is less satisfactory.

The main difference between eq. 4 and eq. 5 is in the choice of a form for the s-orbital of the central atom. Both equations have arbitrary constants to absorb this unknown factor. Neither equation can predict the negative sign of the reduced carbon-fluorine coupling constant.

For carbon-carbon coupling the average energy approximation seems valid (38) and it is possible to discuss one-bond carbon-carbon coupling constants in terms of eq. 2.

The carbon orbitals used in forming the carbon-proton bonds of cyclopropane have been assigned 33% s character on the basis of their carbon-proton coupling constants (46, 47). Such correlations of carbon-proton coupling with carbon orbital hybridization seem valid in hydrocarbons; however, when electronegative substituents are present, the parameter which most strongly influences the coupling constant appears to be the effective nuclear charge appearing in the radial function of the carbon 2s orbital (44).

Foote (48) and Lippert and Prigger (49) in studies of carbon-proton coupling in cycloalkanes have suggested that because the carbon orbitals forming the carbon-proton bonds have more s character than normal hydrocarbons, the carbon orbitals forming the carbon-carbon bonds must have more p character. If each carbon uses a single 2s orbital to form all of its bonds (43), and the two exocyclic orbitals have 33% s character each, then 34% s character is left to be divided between the two endocyclic orbitals, i.e., 17% s character in each endocyclic orbital. This is roughly sp^5 hybridization (50).

Assuming that changes in the carbon-carbon coupling constant are entirely due to hybridization effects, the predicted carbon-carbon coupling constant for cyclopropane using the carbon-carbon coupling in ethane as a model for the coupling between two orbitals with 25% s character is $(0.17/0.25)^2 \times 34.6 = 16$ Hz, in contrast to the 10 Hz extrapolated for the parent compound from consideration of the substituent effects.

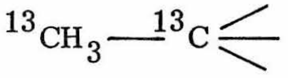
There are several possibilities for rationalizing the above discrepancy. There may be a significant contribution to the coupling constant from terms in the Hamiltonian other than the Fermi contact interaction. The deviation between the simplified calculation and the experimental result is more likely to be due to the approximations used in evaluating the Fermi contact term because with the use of more accurate wavefunctions better agreement is achieved between calculated and experimental values of coupling constants.

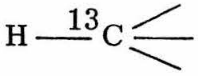
Within the average-energy approximation there are other factors in addition to hybridization which can affect the coupling constant. Qualitatively the effective nuclear charge appearing in the radial function of a 2s orbital should be greater than that appearing in the radial function of a 2p orbital of the same atom because a 2s electron has a greater probability of being found close to the nucleus where it is less shielded than a 2p electron (51). This effect is in the right direction to explain the larger-than-expected coupling in acetylene and the smaller-than-expected coupling in cyclopropane based on the coupling in ethane. Figure 3.14 shows the non linear correlation of carbon-carbon coupling in hydrocarbons with the product of the orbital hybridizations. Variations of 10% in the effective nuclear charge may be sufficient to explain the curvature, and variations of this magnitude are not unreasonable (51).

Spiropentane is a rather special cyclopropane where the central carbon is forced by symmetry to bond with four identical sp^3 orbitals to the surrounding carbons. The carbon-carbon coupling constant involving the quaternary carbon is expected to be considerably larger than a normal cyclopropane coupling constant. The coupling constant found by Grant (52) is consistent with the sp^3-sp^5 nature of the bond involved.

From Figure 3.14 the hybridization of the endocyclic orbitals in cyclobutane corresponding to a 27-Hz coupling constant is 23% s, which is consistent with the 27% s character in the exocyclic orbitals found from studies of the carbon-proton coupling constant (48, 49).

The carbon-carbon coupling in neopentane may be compared with the carbon-proton coupling in isobutane. A comparison of carbon-carbon coupling and carbon-proton coupling is shown in Figure 3.15. The close agreement between the slope of the





correlation line and the value of 0.3 calculated by Karabatsos for the correlation of carbon-proton and proton-proton coupling and the precisely zero intercept strongly suggests that the coupling mechanisms are identical, and furthermore that the average energy approximation suffices to explain all three types of coupling.

Table 3.23 lists the carbon-carbon coupling involving the carbonyl carbon of some esters along with the carbon-proton coupling in ethyl formate. Strict application of the Karabatsos proportionality constants yield calculated carbon-carbon coupling constants which are all slightly too large, but the agreement with the experimental values is still good.

The variations in carbon-proton coupling are most likely due both to changes in the effective nuclear charge and the hybridization of the carbon orbital (44); hence it follows that, because of the proportionality between carbon-carbon and carbon-proton

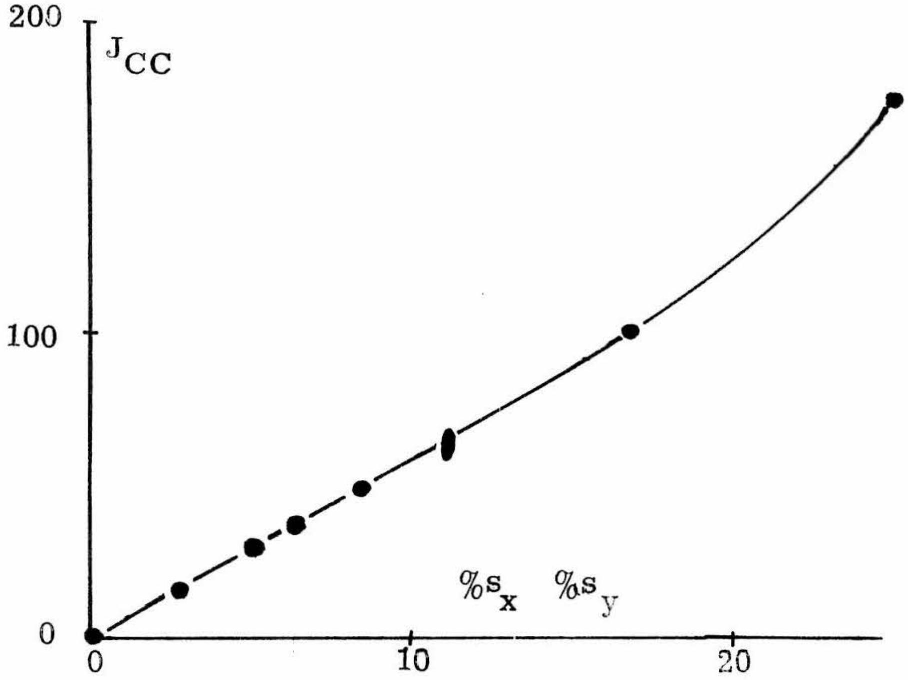


Figure 3.14. Plot of the product of the per cent s-character of carbon versus the carbon-carbon coupling constant.

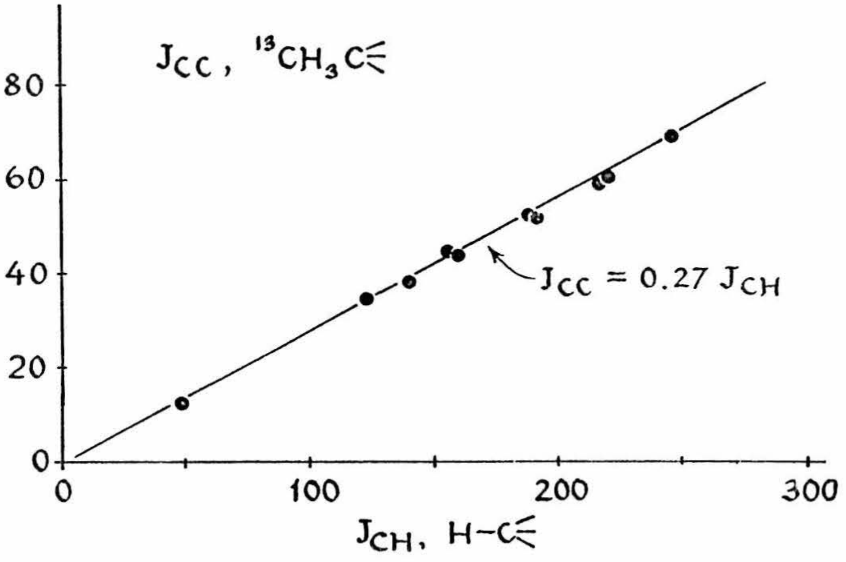
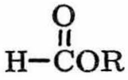
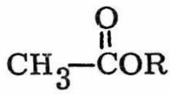
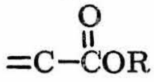
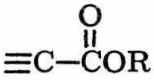


Figure 3.15. Correlation of carbon-carbon coupling of methyl derivatives with carbon-proton coupling.

Table 3.23

Coupling to the Carbonyl Carbon in Some Esters

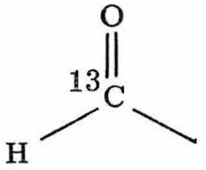
Compound	J_{CC}	J_{CC}/J_{CH} observed	J_{CC}/J_{CH} predicted from hybridization alone
 $\mathrm{H-}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{OR}$ $J_{CH} = 226$			
 $\mathrm{CH_3-}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{OR}$	58.8[a]	0.26	0.30
 $=\mathrm{C-}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{OR}$	76.3[b]	0.34	0.40
 $\equiv\mathrm{C-}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{OR}$	123	0.64	0.61

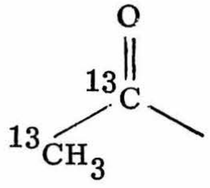
a) G. E. Maciel, private communication.

b) Reference 7.

coupling, similar changes are also seen in carbon-carbon coupling but with reduced magnitudes.

Carbon-carbon coupling in ketones is smaller than would be expected on the basis of carbon-proton coupling in aldehydes. Likewise, carbon-carbon coupling in nitriles is smaller than would be predicted on the basis of carbon-carbon coupling in acetylenes. While formic acid and acetic acid, for example, are both members of the same class of compound, aldehydes and acetylenes may not be valid models for ketones and nitriles.





$^{13}CH_3-^{13}C\equiv N$ $\quad$ $^{13}CH_3-^{13}C\equiv CH$

The magnitudes of the carbon-nitrogen couplings suggest that there is a significant negative contribution to the Fermi contact term which must be evaluated using the complete Pople-Santry theory. From (4) (assuming for the moment that changes in the average-energy term can be neglected) the $^{13}C-^{15}N$ coupling would be predicted to be 0.8 times an analogous carbon-carbon coupling. Comparisons can be made between acetylene (175 Hz) (8, 9) and acetonitrile (17.5 Hz) (34, 35) or neopentane (36 Hz) (20) and the tetramethylammonium ion (5.7 Hz). The one-bond, carbon-phosphorus couplings in phosphonium ions are also smaller than would be predicted by eq. 4. Internally, the one-bond coupling constants may be consistent with a correlation with the s bond order, but when comparisons are made with carbon-carbon coupling the failure of the average energy approximation becomes more obvious. The deficiencies of eq. 4 are accentuated in considering the coupling between two atoms neither of which is a proton.

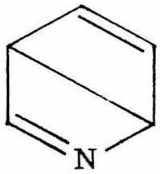
Both fluorine and phosphorus III use nearly pure p orbitals to form bonds with carbon. The valence s orbitals of both phosphorus and fluorine are much more stable than the corresponding p orbitals and thus orbital hybridization is an unfavorable process. Pople and Santry have shown that, under these conditions, the average energy approximation is not valid and negative one-bond coupling can occur (38). Although it appears possible to discuss phosphorus-proton coupling in the phosphines in terms of the small s character of the phosphorus orbitals (53), the negative sign of the carbon-phosphorus coupling invalidates the comparison in this case.

By symmetry, the four orbitals used in forming the carbon-phosphorus bonds in phosphonium ions might be expected to be sp^3 hybrids and the coupling constants might be expected to follow more normal patterns. The signs, at any rate, are in agreement with this expectation, the one-bond coupling being positive and two-bond coupling being negative. While the magnitude of the geminal coupling is in good agreement with that calculated from typical geminal, proton-phosphorus couplings using eq. 3, the one-bond coupling constant is much smaller than would be predicted by application of eq. 3 to the phosphorus-proton coupling in phosphonium ions. The larger coupling between the phosphorus and C-1 of the phenyl group in the methyltriphenylphosphonium ion is, however, presumably due to the increased s character in the carbon orbital.

The search for two- and three-bond, carbon-carbon coupling constants was made in areas in which our knowledge of proton-proton or carbon-proton coupling would predict abnormally large carbon-carbon coupling. The magnitude of the two-bond coupling in 2-butanone is as would be expected from a comparison of formaldehyde and acetaldehyde, but is larger than would be predicted from the correlation in Figure 3.15. If the mechanism of this coupling is as suggested, the sign should be positive. The large magnitude of the geminal, carbon-carbon coupling constants in the cyclobutanes may be due to the effect of the bond angles on geminal coupling. Proton-proton coupling becomes more negative quite rapidly as the H-C-H bond angle is decreased, and at 90° a large, negative, proton-proton coupling would be predicted. If the carbon-carbon coupling occurs via a similar mechanism, this coupling should be negative.

The geminal carbon-carbon coupling in propyne is predicted to be positive by analogy with the carbon-proton coupling in acetylene. This two-bond coupling constant involving a methyl carbon fits the same correlation line as the one-bond coupling constants (Figure 3.15).

Because there is no good analogy in either proton-proton or carbon-proton coupling for the carbon-carbon couplings observed in the aromatic compounds, several possible qualitative mechanisms are proposed to account for their unusually large magnitudes. The coupling is doubly vicinal; that is, there are two equivalent paths for the spin information to be transmitted through the the σ bonds, and the effects are expected to be additive. In elementary π valence-bond theory the five canonical structures for pyridine are the three Dewar structures and the two Kekule structures, The Dewar structure 1 implies pairing between the $2p_z$ electrons of the para carbons of the aromatic ring. Because p electrons do not contribute directly to the Fermi contact coupling, some σ-π interaction in which the spin-pairing of the π system is transmitted to the σ electrons must be postulated. Because the back lobes of the sp^2 orbitals used in forming the carbon-proton bonds contain some 2s character, direct pairing of these orbitals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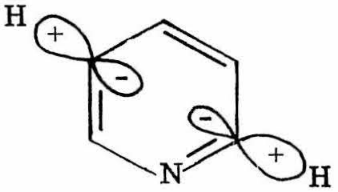
could produce the observed coupling constant by a "through space" mechanism (54).



The two-bond coupling constant in 2-butanone and the three-bond coupling constant in pyridine are both larger than the one-bond coupling constant in some cyclopropanes. This might seem to indicate that there is a greater s bond-order between some formally non bonded carbons than between directly bonded carbons. Because eq. 2 does not explain the large proton-proton coupling constant in formaldehyde or the carbon-proton coupling in acetylene, the "unusual" coupling constants are best considered in terms of eq. 1. Correlations of carbon-carbon coupling with bond-order are at best reserved for one-bond coupling constants.

Couplings in substituted benzenes may be compared to couplings in substituted ethylenes in the same manner as carbon-proton coupling in benzene was compared to proton-proton coupling in ethylene. Using the factor a = 0.4 (see eq. 3) derived by Karabatsos (41) to correlate carbon-proton and proton-proton coupling when the carbon has sp^2 hybridization the values in

Table 3.24 are predicted.

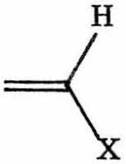
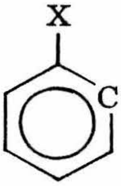
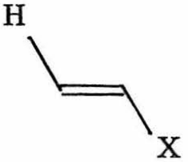
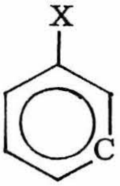
The agreement for carbon-mercury coupling is reasonable, as might be expected because the average energy approximation seems valid for carbon-mercury coupling. The carbon-fluorine couplings are qualitatively in the right direction, but the magnitudes are disappointing. Carbon-phosphorus couplings are not well predicted.

The same correlations may be attempted in the aliphatic series with $a = 0.3$. The results are given in Table 3.25. Geminal coupling seems reasonably well explained for all nuclei for which the average energy approximation holds. The geminal, mercury-proton coupling in diethylmercury of -88 Hz can be used to predict a value of $0.3 \times (-88) = -26$ Hz for the carbon-mercury coupling in very good agreement with the various observed values. The signs and relative magnitudes of carbon-fluorine coupling are predicted correctly by this approach, but the quantitative predictions are less successful.

Vicinal coupling in aliphatic systems does not seem to be explained by this approach for any of the pairs of elements. The nature of the discrepancy has been discussed by Karabatsos (55) for the case of carbon-proton coupling, but no good explanation was proposed. In general, vicinal couplings involving carbon have almost the same magnitude as the corresponding coupling involving protons as shown in Table 3.26.

Table 3.24

Long-Range Coupling to Carbon in Aromatic Derivatives

				
X	J_{CCX}(Hz) Predicted[a]	J_{CCX}(Hz) Observed	J_{CCCX}(Hz) Predicted[a]	J_{CCCX}(Hz) Observed
H	+1.0	+1.0	+7.6	+7.4
F	+33.9	+21.0	+21.0	+7.7
Hg	+52	88	+118	102
P	+4.7	19.5	+12.1	-

a) Using equation 3 with a = 0.4

Table 3.25

Geminal Coupling to Carbon in Aliphatic Derivatives

X	J_{CCX} (Hz) Observed.	J_{CCX} (Hz) Predicted[a]
H	-4	-3.7
F	+19.9	+14
P	+12	+1
P⊕	-4.5	-4.2
Hg	-26	-26

a) Using equation 3 with a = 0.3.

Table 3.26

A Comparison of Vicinal Coupling to Carbon and Protons in Aliphatic Derivatives

X	J_{HCCX} Hz	J_{CCCX} Hz
H[a]	7	5
P	13	12
P⊕	12	15
Hg	115	100
F	25	19

a) Reference 55

Substituent Effects on Carbon-Fluorine Couplings in Substituted Fluorobenzenes

Because the calculation of carbon-fluorine couplings appears impractical, attempts were made to find correlations between the carbon-fluorine coupling constants and other molecular properties.

One-bond, carbon-fluorine couplings in para-substituted fluorobenzenes correlate well with the chemical shifts of the corresponding fluorines as shown in Figure 3.16. The fluorine chemical shifts in these compounds correlate extremely well with σ_p, a well known indicator of π resonance effects (56). The correlation of one-bond, carbon-fluorine couplings with fluorine chemical shift is very good for para derivatives, shows a great deal of scatter for meta derivates and breaks down completely for ortho derivatives. The coupling constants in the ortho derivatives show a fair correlation with the coupling in the para derivatives. The carbon-fluorine coupling constants in the ortho derivatives, unlike the fluorine chemical shifts, are apparently not influenced to a great extent by the steric interactions which govern the chemical shift. The total range of the substituent effects is in the order ortho > para >> meta.

If resonance effects dominate the long-range, carbon-fluorine coupling constants, the substituent effects would be

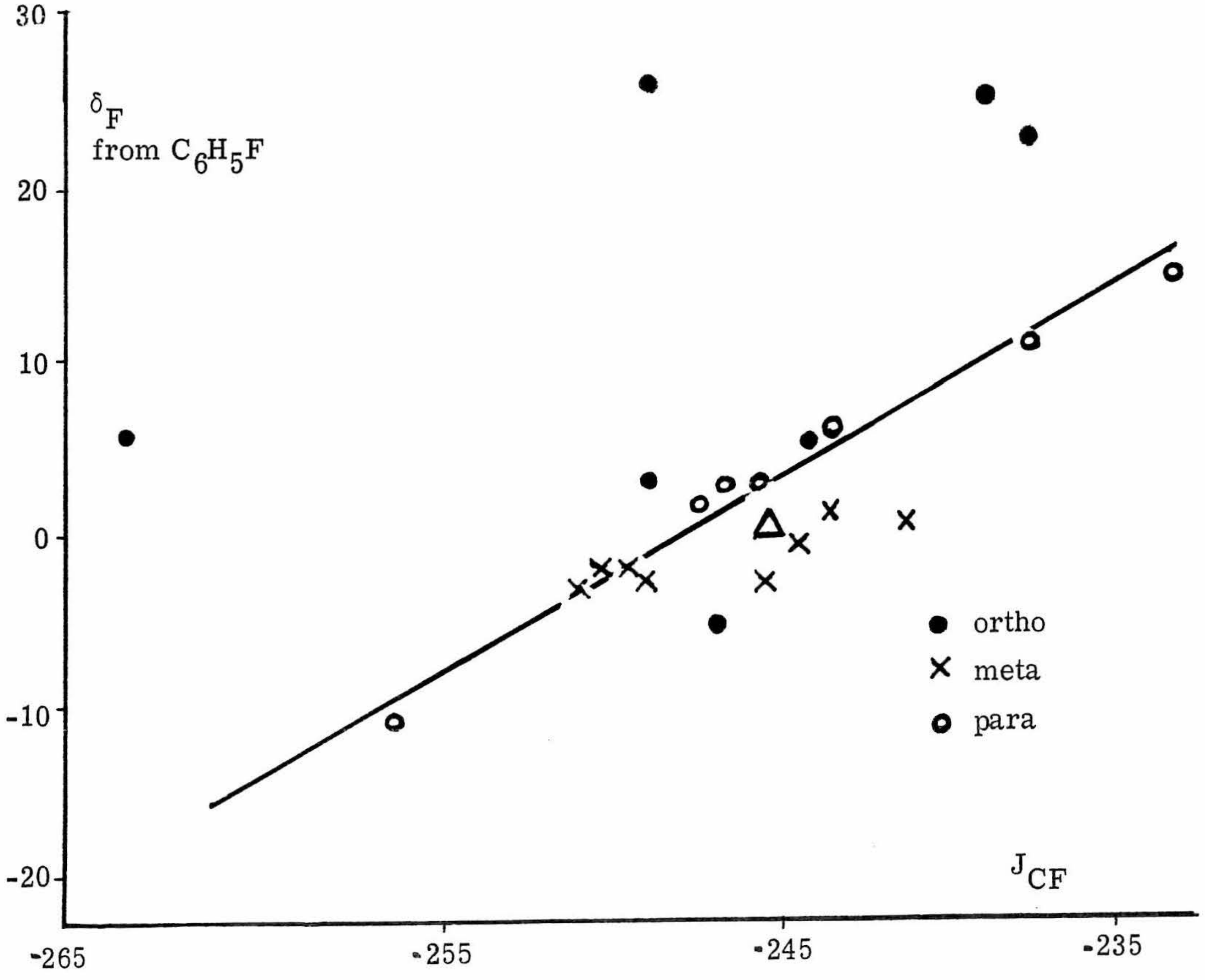


Figure 3.16. Plot of the one-bond, carbon-fluorine coupling in substituted fluorobenzenes versus fluorine chemical shift.

expected to be both positive and negative with nitro and amino at the opposite extremes. Substituent effects for the two-bond and three-bond couplings in the para derivatives are all positive. The ^{13}C chemical shifts of substituted methanes have been shown to be linearly related to the electronegativity of the substituent (with the exception of bromine and iodine) (11). The correlation of the geminal coupling with the ^{13}C chemical shifts of the methyl derivatives is fair. Because no substituents with electronegativities less than protons were studied, all the substituent effects would be expected to be in one direction if electronegativity is the relevant parameter. The same correlation gives much worse agreement with the vicinal coupling constants in the para derivatives. Fluorine no longer has the largest effect and a trend toward larger substituent effects with deactivating groups such as nitro, ammonium and aldehyde is apparent, but because all the substituent effects are in the same direction, resonance effects alone can not explain the trends. All the substituent effects on the four-bond couplings are negative except for fluorine. Electron-supplying substituents such as amino and hydroxyl show the greatest effect, but again because such electron-withdrawing substituents, e.g., aldehyde groups, show effects in the same direction, there can be no simple correlation with resonance effects.

None of the long-range coupling constants in the meta derivatives correlate with σ_p. The geminal, carbon-fluorine couplings involving C-6 are essentially independent of substituent effects. All the coupling constants involving C-2 are larger than that of fluorobenzene itself, but electronegativity effects can not be the whole answer as phenolate and fluoro have widely different effects and nitro has a larger effect than fluoro. The electronegativity of the substituent is a fair explanation of the trends seen for C-3, the substituted carbon. Carbonyl substituents are conspicuous exceptions, having more negative substituent effects than expected on the basis of electronegativity. All substituent effects on the other vicinal coupling constant are positive. Electronegative substituents show the largest effects, however, additional factors must be involved. For four-bond coupling the trend is to lower values, but why the carbon substituents should have the largest effect is not known.

The substituent effects in the ortho derivatives are generally larger than those of the meta or para derivatives. All the substituent effects involving C-2 are negative but they do not correlate with electronegativity because, for example, the substituent effect for amino is greater than fluoro. The other geminal coupling constant shows both positive and negative substituent effects but cannot be correlated with σ_p because nitro and amino have quite similar effects. The variations in the geminal coupling involving

C-6 are smaller than those involving C-2. The largest substituent effects occur in the vicinal coupling constants involving C-3. Because the magnitudes of the coupling constants are all small they can be of either sign and any correlation would be hazardous. Electronegativity may be an important factor because the fluorine substituent effect may be the most negative. The other vicinal coupling constants show much smaller variations with substituents and the effects are of both signs. There seems to be a fair correlation between this coupling constant and σ_p. The variations of the four-bond coupling constants are small and no pattern can be seen here.

Carbon-fluorine coupling cannot be understood by the same sorts of qualitative arguments invoked for carbon-proton or carbon-carbon coupling. There are two theoretical problems; first, because both nuclei have p electrons, both spin-orbit and dipole contributions to the couplings can be significant. Even if the Fermi contact interaction dominates the observed couplings, simple correlations fail because the average energy approximation is not valid for carbon-fluorine coupling.

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IV. Carbon-13 Chemical Shifts in Alcohols and Ketones

Although ^{13}C chemical shifts are quite large compared to proton chemical shifts, the low resolution attainable with rapid-passage, dispersion-mode techniques has hampered the study of other than direct substituent effects in aliphatic systems (1, 2, 3). Complete proton decoupling under slow-passage conditions can give high-quality spectra which allow much smaller effects to be conveniently studied. Non-bonded substituent effects have been observed for continuous-chain and branched-chain alkanes (4), substituted continuous-chain alkanes (5), and methyl-substituted cyclohexanes (6). These effects have been explained in terms of inductive, bond delocalization and steric effects. In this section, a detailed study of oxygen substituent effects in some aliphatic and alicyclic ketones and alcohols is described.

Continuous-Chain Alcohols

The ^{13}C chemical shifts of some continuous-chain alcohols are given in Tables 4.1 and 4.2. Table 4.1 contains the primary shift data while, in Table 4.2, the substituent effects of the hydroxyl groups, the differences in shifts for corresponding carbons in alcohols and alkanes, are shown.

Dioxane was used as internal reference. However, because it was desirable to compare the present results with those of a

Table 4.1

^{13}C Chemical Shifts in Continuous-Chain Alcohols

Alcohol	Chemical Shift (ppm)									
	α	β	γ	δ	ϵ	ζ	η	θ	ι	κ
Methanol	79.4									
Ethanol	71.4	110.8								
1-Propanol	64.8	102.6	118.4							
1-Butanol	67.0	93.4	109.3	114.8						
1-Pentanol	66.6	95.9	100.2	105.8	114.6					
1-Hexanol	66.5	95.6	102.6	96.4	105.6	114.2				
1-Heptanol	66.5	95.5	102.3	99.0	96.3	105.6	114.5			
1-Octanol	66.5	95.5	102.3	98.7	98.8	96.3	105.6	114.5		
1-Nonanol	66.4	95.5	102.2	98.6	98.5	98.8	96.2	105.5	114.4	
1-Decanol	66.5	95.5	102.3	98.6	98.6	98.5	98.8	96.2	105.6	114.4
2-Propanol	65.0	103.3								
2-Butanol	59.7	105.8 C-1 96.4 C-3	118.5							
2-Pentanol	61.4	105.1 C-1 86.8 C-3	109.3	114.4						

Alcohol	Chemical Shift (ppm)									
	α	β	γ	δ	ϵ	ζ	η	θ	ι	κ
2-Hexanol	61.2	105.1 C-1 89.2 C-3	100.1	105.5	114.5					
2-Heptanol	61.2	105.1 C-1 88.9 C-3	102.6	96.1	105.5	114.5				
2-Octanol	61.2	105.0 C-1 88.8 C-3	102.3	98.7	96.2	105.6	114.4			
2-Decanol	61.2	105.0 C-1 88.8 C-3	102.2	98.3	98.4	98.8	96.2	105.5	114.4	
3-Pentanol	54.6	98.7	118.6							
3-Hexanol	56.1	89.0 C-4 98.1 C-2	118.5 C-1 109.0 C-5	114.4						
3-Heptanol	55.8	91.5 C-4 98.7 C-2	118.4 C-1 100.2 C-5	105.4	114.4					
3-Octanol	55.8	91.2 C-4 98.1 C-2	118.4 C-1 102.7 C-5	96.1	105.5	114.5				
4-Heptanol	57.8	88.4	109.3	114.3						
4-Octanol	57.5	90.9 C-5 88.4 C-3	100.2 C-6 109.3 C-2	105.4 C-7 114.4 C-1	114.4					
5-Nonanol	57.3	90.9	100.1	105.4	114.4					

Table 4.2

Substituent Effects of the Hydroxyl Group on the ^{13}C Chemical Shifts of the Continuous-Chain Alcohols[a]

Alcohol	Chemical Shift (ppm)									
	α	β	γ	δ	ϵ	ζ	η	θ	ι	κ
Methanol	-51.4									
Ethanol	-51.4	-11.6								
1-Propanol	-48.3	-10.0	+5.3							
1-Butanol	-48.5	-10.3	+5.6	-0.7						
1-Pentanol	-48.4	-10.2	+6.0	-0.3	-0.4					
1-Hexanol	-48.3	-10.2	+5.9	-0.3	-0.2	-0.6				
1-Heptanol	-48.2	-10.2	+6.0	-0.2	0.0	-0.1	-0.2			
1-Octanol	-48.2	-10.2	+6.0	-0.3	-0.2	0.0	-0.1	-0.1		
1-Nonanol	-48.3	-10.1	+5.9	-0.3	-0.1	-0.1	-0.1	-0.1	-0.3	
1-Decanol	-48.1	-10.2	+6.0	-0.1	-0.1	-0.1	0.0	-0.1	-0.1	-0.1
2-Propanol	-47.6	-9.8								
2-Butanol	-44.0	-9.7 C-1 -7.3 C-3	+3.0							

Alcohol	Chemical Shift (ppm)									
	α	β	γ	δ	ϵ	ζ	η	θ	ι	κ
2-Pentanol	-44.7	-9.9 C-1 -7.4 C-3	+3.2	-0.6						
2-Hexanol	-44.6	-9.7 C-1 -7.5 C-3	+3.4	-0.3	-0.3					
2-Heptanol	-44.5	-9.7 C-1 -7.4 C-3	+3.4	-0.2	-0.2	-0.4				
2-Octanol	-44.5	-9.7 C-1 -7.5 C-3	+3.3	-0.3	-0.1	-0.1	-0.3			
2-Decanol	-44.5	-9.6 C-1 -7.5 C-3	+3.4	-0.1	0.0	0.0	-0.1	-0.1	-0.2	
3-Pentanol	-39.6	-7.4	+3.6							
3-Hexanol	-40.6	-7.7 C-4 -7.6 C-2	+3.7 C-1 +3.3 C-5	-0.4						
3-Heptanol	-40.5	-7.8 C-4 -7.0 C-2	+3.9 C-1 +3.6 C-5	-0.3	-0.4					
3-Octanol	-40.5	-8.7 C-4 -7.6 C-2	+3.7 C-1 +2.8 C-5	-0.2	-0.2	-0.2				
4-Heptanol	-41.4	-7.9	+3.6	-0.5						
4-Octanol	-41.5	-8.1 C-5 -7.9 C-3	+3.9 C-6 +3.6 C-2	-0.3 C-7 -0.3 C-1	-0.3					
5-Nonanol	-41.3	-8.0	+3.8	-0.2	-0.3					

a) The reported values are νalcohol-νalkane in ppm. Negative values are shifts to lower field.

study (5) of neat alcohols referenced to benzene and because the hydrocarbons used for comparison were also referenced to benzene (4), the shifts measured in this work were converted to the benzene scale by the relationship $\delta_c^{\text{benzene}} = \delta_c^{\text{dioxane}} + 61.4$ ppm. The agreement of the shift data (Table 4.1) so obtained with data for shifts of primary alcohols relative to benzene by decoupler shift values (5) is excellent and it appears that dioxane is a suitable internal reference free of errors from solvent or concentration effects to within the stated limits of accuracy of the chemical shifts. Benzene as <u>internal</u> reference was found to shift all of the carbon resonances about 4 Hz downfield relative to the shifts observed using dioxane as internal reference.

For all but the 2-alkanols, the methyl carbon resonances consistently appeared at highest field. In the 2-alkanols the methyls β to the hydroxyl are shifted downfield from one or more of the methylene carbons. Two procedures distinguish between methyl and methylene resonances. First, positions of the various methyl and methylene resonances in the proton spectrum can be used to select particular proton decoupling frequencies as are required to simplify a carbon resonance split by carbon-proton coupling. This technique becomes inapplicable, or at best impractical, when the complexity of the proton spectra is such that the individual proton chemical shifts cannot be distinguished or assigned. The second procedure is to achieve decoupling of the carbons to all protons save the ones to which they are directly attached. This results in perturbed triplets centered at the chemical shifts of methylene carbons and perturbed quartets centered at the chemical shifts of the methyl carbons. It is sufficient to observe the "gap" created by the superposition of a partially decoupled methyl quartet on a completely decoupled methyl singlet to distinguish between methyl and methylene groups.

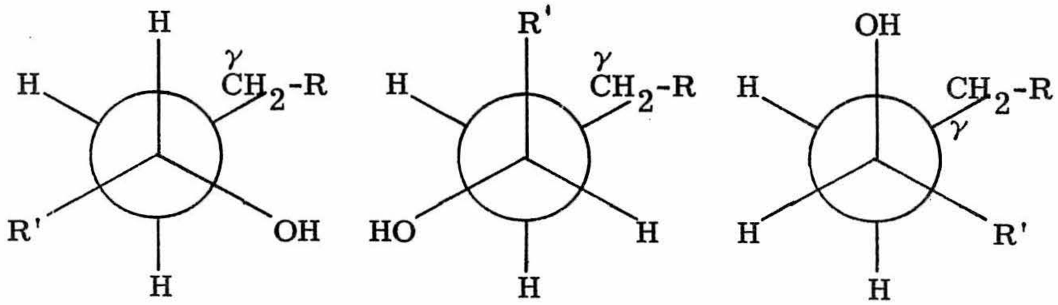
The large α substituent effect of the hydroxyl group uniquely identifies the α carbon in a neat alcohol sample. However, because the α carbon and the dioxane reference sometimes have quite similar chemical shifts, it was occasionally necessary to verify the assignments of these resonances by changing the concentration of dioxane. This was less of a problem in secondary alcohols because, for an as yet unknown reason, the resonance of the α carbon was considerably broader than those of dioxane or the other carbon atoms in the molecule.

Because of the crucial nature of the problem of identifying the various carbon resonances, some of the procedures will be illustrated by examples. For 1-propanol, which is an especially simple case, the methyl carbon resonance is the farthest upfield of the three carbon absorptions and can be decoupled from the attached protons by irradiating at the farthest upfield proton frequency. Furthermore, with partial decoupling, this resonance is seen to be a quartet. The α carbon is uniquely identified by its low-field shift in both the carbon and proton spectrum. The remaining resonance must be that of the β carbon.

In the long-chain alcohols the carbons farther removed from the substituent are essentially unaffected by the substituent and it is not easy to identify the particular methylene resonances. The procedure used here as a tentative identification is to assume minimal substituent effects and to assign the methylene carbon resonances to correspond as closely as possible to the chemical shifts of the carbon in the corresponding alkane. Obviously, this procedure is expected to lead to some ambiguities, but the shift differences associated with the ambiguities are at most a few Hz and reversal of some of the assignments does not affect the arguments to be presented later.

Once resonances are assigned to particular carbons, the substituent effects can be calculated by subtracting from the chemical shift of the alcohol the shift of the corresponding carbon in the continuous chain alkanes (4). The substituent effects so derived are given in Table 4.2. The form of cyclic argument used to obtain the substituent effects is such as to minimize the substituent effects for the interior carbons of long chains and the results show that, despite somewhat different referencing procedures used for the alcohols and alkanes, as well as random errors associated with the measurements of the ^{13}C chemical shifts, the general agreement between the substituent effects of corresponding carbons is within 1-2 Hz and nowhere is there a deviation larger than 4 Hz.

Introduction of a hydroxyl group into a primary or secondary position of a linear hydrocarbon shifts all of the ^{13}C resonances downfield except that of the γ carbon. The large downfield shift of the α carbon can be explained both qualitatively and quantitatively (5) in terms of an inductive effect. The same effect may be associated with the small shifts of the δ- and farther-removed methylene carbons; however, the small magnitude and somewhat erratic nature of these shifts could also arise from other influences. Prediction of the β shift from inductive effects alone would suggest a value only half as large as that observed (5). The remainder of the β shift has been accounted for by a bond-delocalization effect (5) which corresponds to having fewer H-H exchange integrals relative to the corresponding hydrocarbon. The unique upfield shift of the γ carbon in primary and secondary alcohols appears to arise from "spatial crowding" and an associated steric perturbation of the ^{13}C resonance by the proximity of the hydroxyl group to the γ carbon in the *gauche* conformation (**1** and **3**) (Figure 4.1). A more detailed discussion of some of these effects follows.



1 2 3

Figure 4.1. The γ effect in linear primary (R'=H) and secondary (R'=alkyl) alcohols.

Substituent effects at α- and γ-carbons: Inductive effects can be thought to influence chemical shift parameters because inductive transfer of electronic charge from the carbon orbital to an electron-attracting group X increases the "effective nuclear charge" appearing in the radial function of the other carbon orbitals and thereby contracts the remaining orbitals. A downfield shift is expected to be associated with orbital contraction and is expected to be directly related to the electronegativity of X (7). For example, a methyl substituent shifts the ^{13}C resonance of the carbon to which it is attached approximately 10 ppm downfield, while the much more electronegative hydroxyl group causes a shift of 40 to 50 ppm downfield.

The relationship between the "effective nuclear radius" $<\frac{1}{r^3}>$ and the chemical shifts can also be used to account for steric perturbation of ^{13}C resonances. In continuous-chain alkanes, attachment of an alkyl group to the chain two carbon bonds away from a given carbon causes an upfield shift of the ^{13}C resonance of the carbon. Two simple examples are provided by the C-1 resonance in butane which is upfield from C-1 in propane and C-2 in pentane which is upfield from C-2 in butane. This type of shift may be ascribed to steric perturbations associated with 1, 4 gauche interactions. The effect of such interactions may be considered to arise from slight polarizations of the carbon-proton bond(s) caused by non-bonded repulsions between electrons centered on proximate hydrogen atoms. For H-H non-bonded repulsions, the polarization is expected to decrease the effective nuclear charge causing an expansion of the carbon bonding orbitals and a decrease in the paramagnetic term leading to an upfield carbon shift.

Although the data given in Table 4.1 show the upfield chemical-shift effect of 1, 4-alkyl-alkyl interactions for the α carbons of alcohols, this is not so for the data of Table 4.2. However, this is as it should be because Table 4.2 gives the differences between the chemical shifts of corresponding carbons of alkanes and alcohols and therefore the alkyl-alkyl interactions cancel out. Nonetheless, about a 3 ppm upfield shift is found for the α carbon of 1- and 2-alkanols as the chain is extended to include γ (or higher) carbons. An illustrative comparison is of ethanol and 1-propanol, 2-propanol with 2-butanol and, finally, 3-pentanol with 3-hexanol, where no change is expected. Clearly for a three carbon chain 1, 4-gauche, alkyl-alkyl interactions are not present but there is the possibility of 1,4-gauche interactions involving methyl (or methylene) and hydroxyl so that steric perturbation may still be important, although perhaps operating in a somewhat different way.

With 1-propanol and its higher homologs, the γ methyl or methylene group could interact with the hydroxyl either by perturbing the O-H bond or the C-O bond, or both. Such a perturbation of the O-H bond might well be small on the average because the hydroxyl proton can assume a variety of orientations in which it would be well removed from the methyl group. However, regardless of whether the C-O or the O-H bond is implicated, there is an upfield shift of the α carbon. The overall effect of the perturbation would be to diminish the inductive effect of oxygen at the α carbon.

These explanations are consistent with the ^{17}O chemical shift (8) of 1-propanol being 4 ppm upfield from that in ethanol. It will be interesting to see whether this parallelism of ^{17}O and ^{13}C shifts of the atoms of the C-O bond will be observed in other systems. Regardless of mechanism, a substantial upfield shift at the α carbon of a primary or secondary alcohol is associated with lengthening of the carbon chain to include γ carbons. This is accompanied by (and indeed it must be, if the explanation is to be self-consistent) regular and substantial upfield shifts of the γ carbons.

Apparently the effect of a γ methyl group on an α-carbon resonance of an alcohol is somewhat greater than that of a methylene group in the same position. Thus a ^{13}C resonance of 3-pentanol is

1 ppm upfield from that of 3-hexanol and the higher members of the series. With 3-pentanol, there are two methyl groups to interact with the hydroxyl; while with 3-hexanol, there is only one methyl and one methylene. Further evidence on this point is provided by the still smaller upfield shifts associated with the α carbons in 4-alkanols where there are two γ methylene groups.

Considering the ^{13}C resonance positions of γ carbons, primary alcohols show a greater upfield shift of about 3 ppm than for the corresponding carbons of secondary alcohols. This can be rationalized by recognizing that in the primary alcohols (see Figure 4.1) there are three essentially equienergy conformations, two in which the hydroxyl and γ carbon are gauche and one in which they are trans. For secondary alcohols of the two forms in which the hydroxyl and γ carbon can be gauche , one of them (**3**) is of higher energy and less populated because it has three groups other than hydrogen simultaneously gauche to one another. The total of the hydroxyl-alkyl gauche interactions is therefore expected to be less with the secondary alcohols than with primary alcohols. The general correspondence between the α and γ carbon shifts in both primary and secondary alcohols leads credence to this argument.

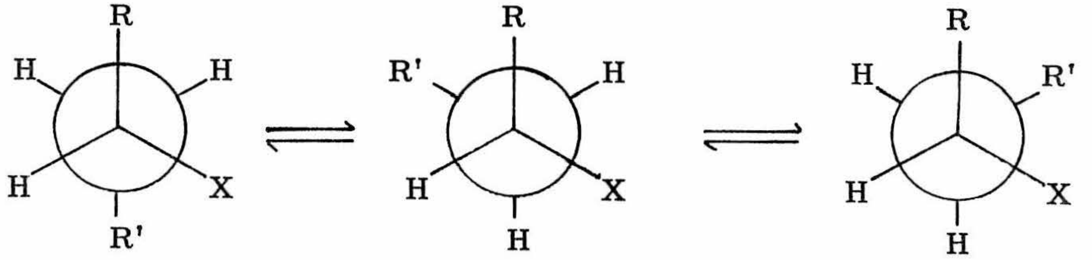
Substituent effects at β-carbons: The β-carbon shift differences are expected to have at least a dual origin--inductive effects and effects which involve changes in the number of hydrogen-hydrogen exchange integrals associated with the β carbon. The nature of the inductive effect and its likely rapid attentuation with increasing distance from the α carbon suggests that it might not be significantly affected by small variations in conformation. Similar insensitivity to conformational changes is not expected for the hydrogen-hydrogen exchange contribution to β shifts which can be evaluated qualitatively by consideration of possible changes in the number of pairwise interactions between hydrogens on the α and β carbons.

Two types of pairwise interactions are possible for staggered conformations, corresponding as to whether the hydrogens on the adjacent carbons are gauche or trans to one another. There seems to be no reason to suspect that the two interactions contribute equally. If they do not contribute equally, then their overall contributions will depend on the number of possible interactions in the various conformations and any existing conformational preferences. Let us first consider the number of interactions for the various possible conformations. We will be only interested now in the three staggered conformers resulting from rotation about the α-β carbon-carbon bond in saturated primary and secondary alcohols. Table 4.3 shows a comparison of the possible number of pairwise interactions for these conformers in alcohols and the corresponding continuous-chain alkanes. This tabulation does not take into account the relative populations of these conformers; this problem will be discussed separately.

Table 4.3

Gauche and *Trans* Hydrogen-Hydrogen Interactions in Various Conformations of the Continuous-Chain Alkanes and Alcohols

Alcohol	Carbon	R	R'	X	Gauche H-Pairs Alkane			Gauche H-Pairs Alcohol		
					1	2	3	1	2	3
Ethanol	C-2	H	OH	H	6	6	6	4	4	4
1-Alkanol	C-2	R	OH	H	4	4	4	2	3	3
2-Alkanol	C-1	R	H	OH	4	4	4	2	2	2
n-Alkanol[b] n>2	--	R	R	OH	2	3	3	1	1	2



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a) The difference in the number of H-H pairwise interactions between alkane and alcohol.

b) Also for 2-Alkanol C-3.

Δ Gauche Pairs Alkane → Alcohol[a]			Trans H Pairs Alkane			Trans H Pairs Alcohol			Δ Trans Pairs Alkane → Alcohol		
1	2	3	1	2	3	1	2	3	1	2	3
2	2	2	3	3	3	2	2	2	1	1	1
2	1	1	2	2	2	2	1	1	0	1	1
2	2	2	2	2	2	1	1	1	1	1	1
1	2	1	2	1	1	1	1	0	1	0	1

For the simple case of ethanol, the three conformers are indistinguishable and each constitutes a third of the mixture. From Table 4.3 one sees that there are two less gauche and one less trans pairwise interactions in ethanol than in ethane, and we can designate the change between ethane and ethanol as 2G + T (where G is a gauche-pair shift contribution and T is the trans-pair shift contribution). The β shift for ethanol is -11.6 ppm, some of which is surely due to the hydroxyl inductive effect and the rest presumably to the difference in pairwise interactions between the hydrogens.

Another simple case where the problem of conformational populations does not arise is 2-propanol and on the basis of differences in the number of pairwise interactions compared to the corresponding alkane, which is 2G + T for each methyl, just as for ethanol, the β shift is expected to be similar to that for ethanol. Actually it is -9.8 ppm, significantly smaller but this may be rationalized on the basis of a "branching" effect associated with secondary hydroxyl substituent. Grant and co-workers (4) have demonstrated that branching of a chain creates additional, as yet undefined, pairwise interactions which consistently produce shifts toward higher field and these will make the β shift more positive for the methyls of 2-propanol compared to ethanol.

For all but the β methyl groups, the three different staggered conformers which are possible by rotation about the α-β carbon-carbon bond are not equivalent and one must know the relative populations for both the alkane and alcohol in order to evaluate the differences in the numbers and kinds of H-H interactions. An illustrative case is provided by 2-butanol for which the populations of the rotational isomers are known for both the alcohol and the hydrocarbon. Here, C-1 is a β methyl and thus the net change in pairwise interactions for C-1 in butane and C-1 in 2-butanol is 2G + T. To obtain the corresponding figures for C-3 we have to consider the conformational populations. With reference to the formulas **1**, **2**, and **3** (see Table 4.3 , where R = R' = CH_3 and X = H for butane and OH for 2-butanol) the populations (9) for butane are 60% of **1**, 20% of **2**, and 20% of **3**, **2** and **3** being mirror images of one another; for 2-butanol (10) the populations are 42% of **1**, 42% of **2** and 16% of **3**. From these data and the figures for the changes in pairwise interactions in Table 4.3, the difference at C-3 between butane and 2-butanol is:

$$2(0.6)G + 2(3)(0.2)G + 2(0.6)T + 2(0.2)T - 2(0.42)G - 2(0.16)G$$
$$- 2(0.42)T = 1.25G + 0.75T$$

This is a smaller change in pairwise interactions than for C-1 and therefore a smaller downfield shift for C-3 is predicted and observed (-7.3 ppm as against -9.7 ppm).

Assuming, within the limits imposed by branching and other as yet unknown effects, that the quantities G and T are transferrable from compound to compound, we can write

$$\beta \text{ shift} = I_\beta + m\,G + n\,T \qquad (1)$$

where I_β is the inductive effect, G is the gauche pair contribution and T is the trans pair contribution, and m and n are factors which can be obtained from the conformer populations and Table 4.3 as in the case of 2-butanol.

Unfortunately, evaluation and testing of specific values for I_β, G and T are difficult because the positions of the conformational equilibria are not known for many aliphatic alcohols. Extraction from specific values for G and T from the data for C-2 and C-3 of 2-butanol requires a numerical figure for I_β.

For linear alcohols, the inductive shift has been calculated to be -5 ppm (or -4 ppm). A value of I_β of this magnitude agrees satisfactorily with the experimental shifts of the β carbons in neopentyl and pinacoyl alcohols as will be discussed below.

These inductive effects were calculated by the relationship

$$I_\beta = \rho_\beta * (-Q \text{ ppm/electron})$$

The charge density at a β carbon ρ_β has been calculated to be 0.025 electrons, independent of the particular substituent (11). The value of Q was taken as -200 ppm/electron (4) or -160 ppm/electron (12).

Unfortunately, the values of G and especially of T which fit the β shifts for C-2 and C-3 of 2-butanol are so sensitive to the choice of I_β as to provide little confidence in their estimated relative magnitudes or even in their relative signs. However, the combination of 2-butanol, 2-propanol and β shifts in axial and equatorial cyclohexanols (see below) suggest that I_β is -4 ± 1 ppm, G is -3 ± 1 ppm and T is 0 ± 1 ppm. It remains to be established whether linear alcohols and cyclohexanols are fairly comparable in this connection.

The precision of these values is too low to permit any useful evaluation of conformational populations of other systems from the β effect but the general constancy of the β shifts for 1-propanol and its higher homologs suggests that these substances all have similar proportions of the conformers **1**, **2** and **3** with respect to rotation about the α-β carbon-carbon bonds. The same seems to be true for the series of 2-alkanols.

Branched alcohols: It is interesting to see to what degree the α, β and γ chemical shift effects derived above can be applied to other types of aliphatic alcohols, particularly those with sufficient symmetry to make the molecular geometry relatively unambiguous. Such cases are provided by the 2-methylpropane and t-butyl alcohol neopentane-neopentanol and neohexane-pinacolyl alcohol pairs, none of which presents problems with respect to conformational populations. The ^{13}C chemical shifts for these alcohols are given in Table 4.4.

The α shift effects of these alcohols are expected to be less than those for analogous continuous-chain alcohols (-48 ppm) because of greater OH-CH_3 interactions. The precise reduction of the α shift cannot be evaluated from our other data on alcohols but

Table 4.4

^{13}C Chemical Shifts and Substituent Effects in Some Branched Alcohols

Alcohol	Carbon	Chemical Shift in ppm relative to benzene	Substituent effect,[a] ppm
t-Butyl alcohol	α	61.3[b]	-42.2
	β	99.2[b]	-5.1
Neopentyl alcohol	α	55.7	-41.5
	β	95.7	-5.1
	γ	102.1	+4.9
Pinacolyl alcohol	α	53.6	-38.4
	β(methylene)	93.4	-4.8
	β(methyl)	110.5	-9.4
	γ	102.9	+3.2

a) Calculated as described for alcohols in Table 4.2.

b) G. B. Savitsky and K. Namikawa, J. Phys. Chem., **67**, 2430 (1963).

the observed shifts are certainly in accord with expectations.

The β shifts are also quite reasonable. For the quaternary carbons there are no H-H pairwise interactions to change on substitution of a hydroxyl group and the β shifts are predicted by eq. (1) to be equal to I_β (-4 ± 1 ppm), as indeed they are. The β shift of the methyl of pinacolyl alcohol (-9.7 ppm) is consistent with those of other secondary alcohols (see Table 4.2).

As regards γ shifts, any one of the γ methyls of these branched alcohols must be gauche to the hydroxyl two-thirds of the time. This is somewhat more than we would expect for ordinary primary and secondary alcohols which have γ shifts of about +6.0 and 3.3 ppm respectively. The observed γ shifts for neopentyl alcohol (+4.9 ppm) and pinacolyl alcohol (+3.2 ppm) are in the right direction but both are rather too small.

Cyclohexanols

The ^{13}C chemical shifts of some alkyl-substituted cyclohexanols are given in Table 4.5. The effects of methyl substitution on the ring carbons of cyclohexane have been discussed in detail by Dalling and Grant (6) and therefore we will be concerned here only with the additional influence of the hydroxyl group on the hydrocarbon system. For many of these substances there is a possibility of two conformers, one with the alkyl equatorial and the hydroxyl axial and one with the alkyl axial and the hydroxyl equatorial. We will assume that the conformational preference of having the alkyl substituent equatorial is sufficiently greater than for having the hydroxyl equatorial, that for practical purposes there will be no appreciable contribution of the conformer with axial alkyl. The perturbation caused by the hydroxyl group on the cyclohexane carbons may be calculated by subtracting from the value of the chemical shifts of the alcohol those of the corresponding alkylcyclohexane as given in Table 4.6.

The rather large differences in the chemical shifts between the ring carbons in methylcyclohexane and _t_-butylcyclohexane are quite consonant with the results obtained by Paul and Grant (4). The 1-carbon of _t_-butylcyclohexane is expected to be susceptible to a large downfield chemical shift relative to cyclohexane from the combined effect of one α carbon and three β carbons of the _t_-butyl group. The 2-carbon is expected to experience effects of opposite sign from the

Table 4.5

^{13}C Chemical Shifts in Cyclohexanols[a]

	C-1	C-2	C-3	C-4	C-5	C-6	Methyl
Cyclohexanol	123.0	157.0	168.1	166.6	-	-	-
trans-2-Methyl	115.9	152.8	158.5	166.7	167.1	157.4	173.7
cis-3-Methyl	122.0	148.5	160.8	157.7	168.1	158.1	170.0
trans-4-Methyl	122.8	b	b	161.1	-	-	170.8
trans-4-t-Butyl	122.4	157.1	167.1	145.5	-	-	c
cis-2-Methyl	121.4	156.7	163.2	168.3	171.0	160.7	176.3
trans-3-Methyl	126.0	151.3	165.9	158.1	172.3	159.7	172.3
cis-4-Methyl	126.6	161.1	163.8	161.9	-	-	171.6
cis-4-t-Butyl	127.8	159.5	171.8	144.6	-	-	d

a) In ppm upfield from carbon disulfide; cis-trans pairs were determined as mixtures.

b) The resonances at 159.4 and 157.7 ppm were unassigned.

c) Quaternary carbon 160.7; methyl carbon 165.3.

d) Quaternary carbon 160.4; methyl carbon 165.4.

Table 4.6

^{13}C Chemical Shifts in Alkyl Cyclohexanes[a]

Compound	C-1	C-2	C-3	C-4	
Cyclohexane	165.5				
Methylcyclohexane	159.3	156.6	165.7	165.8	methyl 169.6
_t_-Butylcyclohexane	143.9	164.6	165.0	165.6	quaternary carbon 160.1
					methyl 165.1
Interior carbons in continuous-chain alkanes	162.5[b] 163.5[c]				

a) Chemical shifts are given in ppm upfield from carbon disulfide.

b) Reference 5.

c) Reference 16.

one β carbon and the three γ carbons giving only a small net shift. The substituent effects calculated are given in Table 4.7.

There are quite obvious differences between the substituent effects of axial and equatorial hydroxyl groups. Bucanan, Ross and Stothers (3) have investigated the variation of the chemical shifts of the carbinyl carbons in a series of 4-substituted cyclohexanols. With the method of average chemical shifts they made estimates of the conformational preference for the hydroxyl group in cyclohexanol itself. While there is no question of the qualitative validity of the approach, our results on high-resolution spectra of cyclohexanols do not agree very well with those of Stothers (3). The discrepancies are clearly in the shifts of the substituted cyclohexanols, because the chemical shifts for the carbons of cyclohexanol agree within the stated experimental errors.

In order to eliminate the possibility that differential solvent effects cause the chemical shift anomalies the resonances of the carbinyl carbons of a solution of a mixture of cyclohexanol, cis and trans-4-t-butylcyclohexanols were determined. Relative to dioxane (125.5 ppm upfield from carbon disulfide) the carbinyl carbon resonances were found for cyclohexanol at 123.0 ppm, trans-4-t-butylcyclohexanol at 122.1 ppm and cis-4-t-butylcyclohexanol at 127.6 ppm. These values agree with the chemical shifts determined on the separate substances, but do not agree with the values given by Stothers.

Table 4.7

Hydroxyl Substituent Effects in Substituted Cyclohexanols

Substituent	C-1	C-2	C-3	C-4	C-5	C-6
None	-42.5	-8.5	+2.6	+1.1	-	-
trans-2-Methyl	-41.0	-6.5	+1.5	+1.0	+1.3	-8.3
cis-3-Methyl	-43.7	-8.1	+1.5	+1.1	+1.4	-7.7
trans-4-Methyl	-43.0	b	c	+1.8	-	-
trans-4-_t_-Butyl	-43.2	-7.9	+1.1	+1.6	-	-
cis-2-Methyl	-35.2	-2.6	+6.6	+2.6	+5.2	-5.0
trans-3-Methyl	-39.7	-5.3	+6.6	+1.5	+7.1	-6.1
cis-4-Methyl	-38.9	-4.6	+7.2	+2.6	-	-
cis-4-_t_-Butyl	-37.8	-5.5	+6.8	+0.7	-	-

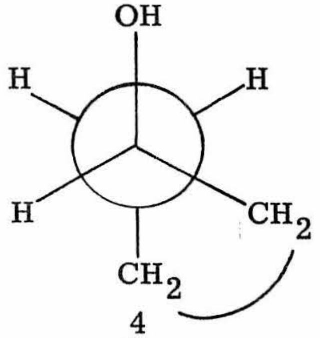
a) In ppm.

b) Either -6.3 or -8.0 ppm.

c) Either +1.1 or +2.8 ppm.

Some of the changes in chemical shift of α carbons which have been noted between various alcohols have been postulated to arise from *gauche* interactions between the hydroxyl groups and the alkyl chains. The same effect appears to be present also in cyclic alcohols when proper account is taken of the restrictions on the conformations of the cyclic alcohols. For the continuous-chain, secondary alcohols conformations 1 and 2 (see Fig. 4.1) are expected to be the most favored because they have only one non H ... H *gauche* interaction, while conformation 3 has two such interactions. The -39 ppm effect on the ^{13}C chemical shift of introducing a hydroxyl group between the ends of a continuous-chain is suggested to be associated with conformations 1 and 2.

In cyclohexanol the conformation analogous to 1 is expected to be negligibly important because of ring strain. Conformation 4, analogous to 2 in the continuous-chain alcohols has the equatorial hydroxyl while 5 has the axial hydroxyl. The conformation 5 is, of course, analogous to 3. The additional *gauche* interaction in 5 is expected to cause an upfield shift of the α carbon relative to the



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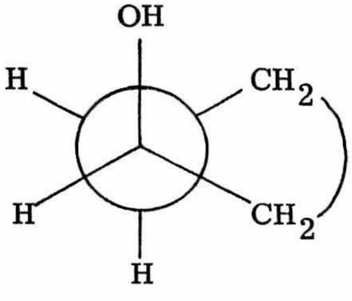

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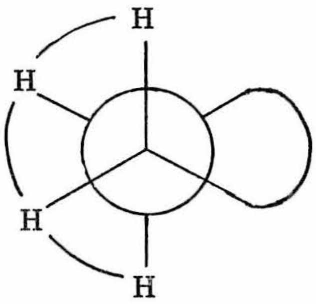
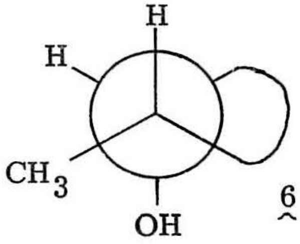
α carbon of 4 and also with respect to secondary open-chain alcohols.



In cyclohexane there are three *gauche* pairs of protons. An equatorial substituent has two less of these interactions (4) while an axial substituent has only one less (5). As a result the β effect is expected to produce a more negative shift for an equatorial than an axial substituent.

The *cis* and *trans* isomers of 2-methylcyclohexanol presumably exist most favorably as conformations 6 (*cis*) and 7 (*trans*). For 6



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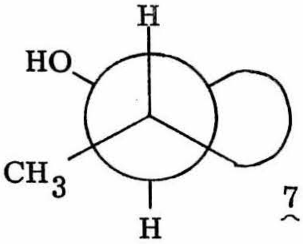

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there is the same number of pairs of *gauche* H-H interactions as in methylcyclohexane itself (methyl taken to be equatorial) while 7 has one less *gauche* pair. As a result the *trans* compound is expected to show a more negative shift for the β carbon,and for both 6 and 7 the shift of the β carbon should be reduced by the same amount relative to a corresponding cyclohexanol without a 2-substituent and the same hydroxyl configuration (compare, for example, the differences in the β carbon shifts of cyclohexanols with *trans*-2-methyl and *trans*-4-*t*-butyl, 2.4 ppm, with *cis*-2-methyl and *cis*-4-*t*-butyl, 2.9 ppm). The 2.6 ppm downfield shift of C-2 of *cis*-2-methylcyclohexanol unlike that of the trans-2-methylcyclohexanol relative to methylcyclohexane is not associated with any change in the number of β interactions and may be indicative of the magnitude of the hydroxyl inductive effect.

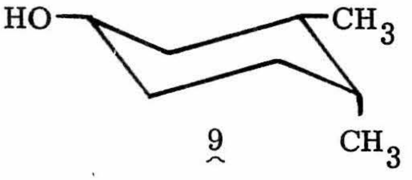
The γ substituent effect on the carbon chemical shift has been rationalized in terms of gauche interactions (4, 5, 6, 7). An axial methyl group γ to a cyclohexane carbon shifts the resonance of the carbon 5 ppm upfield, while an equatorial methyl has no effect (6) (see also the negligible effect of equatorial alkyl substituents on the position of the α carbon resonance of cyclohexanols in Table 4.7).

A purely steric interaction can only be part of the story for hydroxyl substituents because as Table 4.7 shows, there is on the average about a 1.3 ppm upfield shift of carbon when an equatorial hydroxyl is in the γ position. The effect of an axial γ hydroxyl is larger (about 7 ppm) as expected for a proximity effect but the results with γ equatorial hydroxyls are clear in suggesting a significant upfield shift when close proximity is not important. The larger γ effect of axial hydroxyl than axial methyl is of course not quite as expected for a pure steric repulsion effect because a hydroxyl group is expected to have less bulk than a methyl group. Some kind of an electronegativity effect may need to be considered for both the trans and gauche influences on ^{13}C chemical shifts produced by γ substituents.

There is also an upfield δ substituent effect in cyclohexanols which, although fairly constant for equatorial hydroxyl, appears a bit more erratic for axial hydroxyl. Nothing comparable is observed for open-chain alcohols, so apparently this is the result of forced proximity of the 1-and 4-carbons in the cyclohexane ring. Because this effect is not observed for methyl groups (6) it is probably related to the polarity of the substituent.

The methyl carbon in all favorable conformations of both the 2-methylcyclohexanols is expected to be gauche to the hydroxyl group. As expected, these methyl groups are shifted upfield relative to methylcyclohexane by the γ effect.

In connection with other work it was desirable to determine the composition of a mixture of the four possible 3,4-dimethylcyclohexanols (9-12) (13). The ^{13}C spectrum of the carbinyl carbons of these alcohols is shown in Figure 4.2. The presence of all four isomers is clearly indicated and in combination with the data already discussed only one additional fact is needed to identify each isomer unambiguously. Oxidation of the alcohol mixture gave a mixture of cis and trans 3,4-dimethylcyclohexanones and from the ^{13}C nmr spectrum of this mixture (the rationale of this analysis will be



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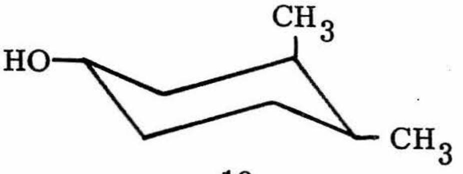

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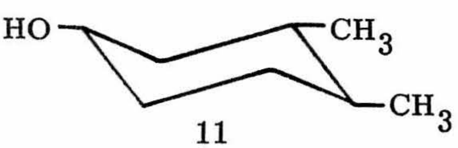

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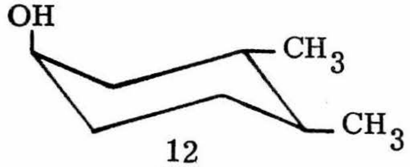

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discussed later) it was concluded that the ketone with *cis* methyl groups was present to the extent of 75%. The only assignment of the ^{13}C carbinyl resonances of the alcohol mixture consistent with this is to have peaks 1 and 4 correspond to the alcohols with *cis* methyl groups and peaks 2 and 3 to those with *trans* methyl groups. To a first approximation the conformations of these molecules will be favored wherein two or three of the substituents are equatorial, and further, as suggested earlier, methyl groups will be expected to have a greater preference for equatorial locations than hydroxyl groups. Now, a 3-axial methyl group is expected to shift C-1 upfield by 5 ppm relative to the corresponding equatorial isomer. This means that peak 1 corresponds to **9** and peak 4 to **10**. An axial hydroxyl shifts the α carbon upfield by 5 ppm relative to its equatorial isomer, which permits peak 2 to be assigned to **11** and peak 3 to **12**.

Conclusions as to the quantities of each form are on shakier grounds. If the chemical shifts of the protons directly bonded to the carbinyl carbon in all four isomers are not within about 4 Hz of each other, the efficiency of the decoupling will be different for each isomer. Because significant nuclear Overhauser effects are expected, the relative intensities of the peaks will depend on the offset from the optimum decoupling frequency.

To demonstrate the quality of spectra obtained by this method for a simpler case, a survey spectrum of a mixture of *cis* and *trans* 2-methylcyclohexanol is shown in Figure 4.3. With one "aliphatic" decoupling frequency and a sweep rate of 10 Hz/sec, the resonances

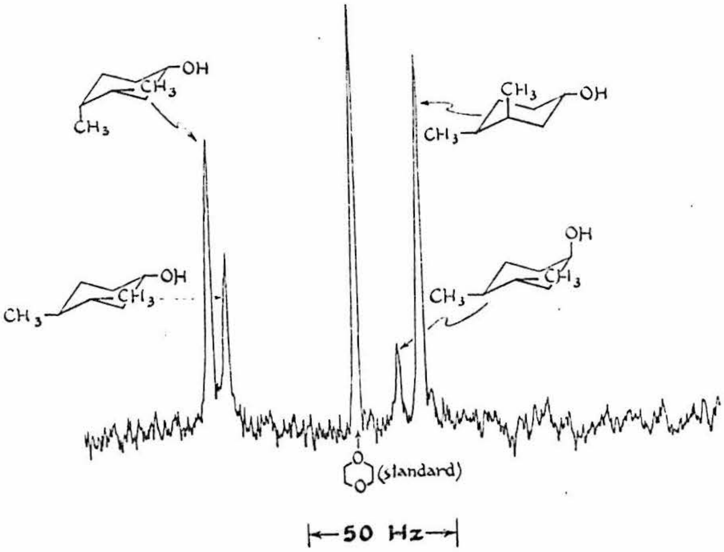


Figure 4.2. Proton decoupled ^{13}C spectrum of the carbinyl carbon of a mixture of the four isomeric 3,4-dimethylcyclohexanols.

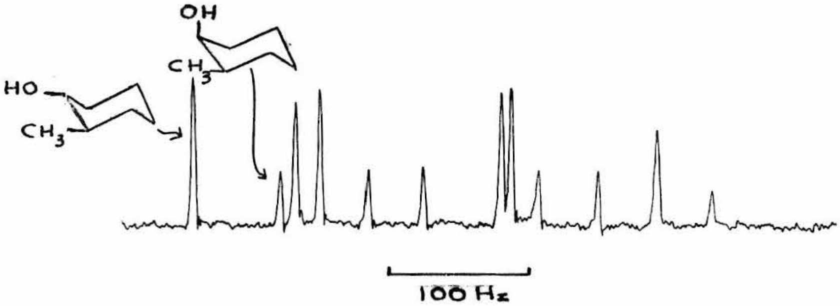


Figure 4.3. Proton decoupled ^{13}C spectrum of a mixture of cis- and trans-methylcyclohexanol. Carbinyl carbons are at much lower field and are not shown.

are ca. 5 Hz wide. Because the methyl protons are upfield from the ring protons decoupling of the methyl protons is less efficient and therefore the ^{13}C resonances are broader. Slower sweep rates and optimization of the individual decoupling frequencies results in line-widths of less than one Hz.

Other cyclic alcohols: In the continuous-chain alcohols and cyclohexanols the important conformations are those which have groups on adjacent carbon atoms staggered. With many ring systems more-or-less eclipsed interactions become unavoidable, and the number of possible favorable conformations of the basic ring system, to say nothing of the possible sites for the substituent groups to reside, become larger. For this reason the elucidation of the conformations of ring systems other than cyclohexane is difficult and challenging. To see if new light could be shed on such problems the ^{13}C spectra of the cyclic alcohols with $n = 5, 6, 7$, and 8 have been obtained and the chemical shifts and substituent parameters are summarized in Table 4.8. The chemical shifts of the cyclic hydrocarbons were those of Lauterbur and Burke (14).

Cyclopentane is not planar (15) but pseudorotation rapidly equilibrates all of the reasonably possible conformers. No one conformation appears to dominate and thus the observed nmr effects will represent the weighted average of the various conformations. In most conformations of cyclopentanol, the dihedral angle between the hydroxyl group and the cis-β proton is likely to be small and it seems

Table 4.8

^{13}C Chemical Shifts in Cyclic Alcohols

Compound	C-α	C-β	C-γ	C-δ	C-ϵ
Cyclopentanol	119.2	157.5	169.1		
	-48.0	-9.7	+1.9		
Cyclohexanol	123.0	157.0	168.1	166.6	
	-42.5	-8.5	+2.6	+1.1	
Cycloheptanol	120.1	154.8	169.2	163.9	
	-44.1	-9.5	+4.9	-0.4	
Cyclooctanol	121.2	157.8	169.5	(167.0	164.7)
	-44.7	-8.1	+3.6	(+1.1	-1.2)

a) The upper line of figures for each alcohol are the experimentally determined chemical shifts in ppm upfield from carbon disulfide, while the lower line gives the substituent effects obtained by subtracting the chemical shifts in ppm of the corresponding cycloalkanes (16).

b) Values in parentheses have not been assigned to specific carbons.

a reasonable first approximation to take cyclopentanol as representing an eclipsed type of structure. The γ effect of hydroxyl to carbon in cyclopentanol is +1.9 ppm which is comparable to the corresponding value of +1.3 ppm found for equatorial hydroxyl in cyclohexanol and similarly cannot be due to a simple steric effect.

It appears likely that for cyclopentane derivatives no single conformation gives an adequate description of the average properties of the molecules. The situation with medium-sized ring compounds is less clear and the available experimental evidence is not always sufficient to distinguish between a single favored conformation involved in a pseudorotation itinerary or a mixture of nearly equally favored conformations.

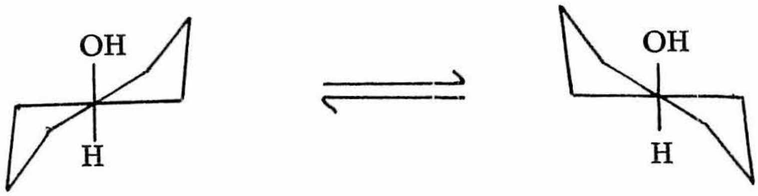
For cycloheptane itself Hendrickson (16) has calculated that the twist-chair conformation should be more stable than the chair, boat or twist-boat by more than 1.4 kcal/mole. As a result, cycloheptane can fairly reasonably be considered as a rapidly pseudorotating mixture of the various possible twist-chair forms. For methylcycloheptane the situation is not simple. Hendrickson (16b, c) has suggested that there should be four nearly equal energy forms with a single methyl group substituted on a twist-chair conformation. These have the methyl at the isoclinal (16) or "axis" position (1) and the 2, 3 and 4 equatorial positions. All axial-type positions are calculated to be less favorable by 1.3 kcal/mole or more. If these predictions are valid, and there is no *a priori* reason to expect they are not, cycloheptanol which has a substituent with a smaller steric effect than methyl is likely to be a mixture of the several equatorial and isoclinal (and possibly even axial) conformations.

The chemical shift of the ^{13}C carbons in cycloheptane is expected to be the statistically weighted average of the chemical shifts of the four different carbons of a twist-chair form. Therefore, the observed chemical shift is

$$\nu = (\nu_1 + 2\nu_2 + 2\nu_3 + 2\nu_4)/7$$

where the subscripts refer to the position number of the twist-chair conformation as defined by Hendrickson (16). It is, of course, not known at present how different the various ν_N values are, but the differences are likely to be small.

For cycloheptanol, the ^{13}C chemical-shift parameter which appears to be most useful for conformational analysis is the γ shift which amounts to +4.9 ppm. Judging from cyclohexanols (Table 4.7) this is somewhat intermediate between what would be expected for a pure axial or pure equatorial orientation of the hydroxyl on a cyclohexane. However, before embracing the notion that cycloheptanol is a complex mixture of conformations with hydroxyl axial or equatorial it is well to point out that the optimized (16) position for equatorial methyl of the twist-chair form have rather larger steric interactions than those of cyclohexane and, furthermore, the axial positions generally have very much greater interactions so that some upfield shift is expected for the carbons γ to the hydroxyl even if the hydroxyl is very largely equatorial. The shift data of the γ carbons by no means rule out a substantial contribution of the conformation with the hydroxyl at the isoclinal carbon. The two enantiomeric conformations with isoclinal hydroxyl 13 and 14 (which are expected to be in rapid equilibrium) have the hydroxyl intermediate in character between axial and equatorial--for either 13 or 14 the 3, 6-carbons have one essentially *trans* and one essentially *gauche* hydroxyl interaction. If we take +1.3 ppm to be the intrinsic effect of an equatorial γ hydroxyl on the shift of carbon and about +6.6 ppm to be the effect of a corresponding axial hydroxyl, then the average of 4 ppm is not greatly different from the observed shift of 4.9 ppm. Clearly what is needed is more information on substituted cycloheptanols with favored and known or predictable conformations.



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For cyclooctanol there is such a large number of possible conformations that it is not really practical to attempt a detailed analysis. Hendrickson (16a, b) has reviewed the recent literature and has made rather refined calculations of the energies of a variety of conformations of cyclooctane and monomethylcyclooctane.

Although the recent low-temperature nmr studies of Anet and St. Jacques (17) on cyclooctane suggest that the boat-chair conformation is favored (a result also supported by Hendrickson's calculations) (16) it is very likely that there are several other conformations which are very close in energy and may contribute substantially to the equilibrium at room temperature (18). The pattern of ^{13}C chemical shifts of cyclooctanol at room temperature is rather similar to that of cycloheptanol. The only positive conclusion seems to be that cyclooctanol is on the average rather congested judging from the general upfield shift of all of the ^{13}C resonances, but from the shift of the γ carbons, the hydroxyl is on the average in a more equatorial-like environment than for cycloheptanol. Obviously more work also needs to be done on substituted cyclooctanols with reasonably predictable conformations.

Cyclohexanones: The ^{13}C chemical shifts observed for a number of substituted cyclohexanones are shown in Table 4.9. In order to determine the value of these data for qualitative and conformational analysis, additivity relations have been investigated for the methyl-, dimethyl- and t-butylcyclohexanones. The simple procedure was used of summing the algebraic differences between the shifts of the respective carbons of alkylcyclohexanes as referenced to cyclohexane and cyclohexanone. The degree of correlation between calculated and observed shifts can be judged from Figure 4.4. In general, the deviations turned out to be small over a shift range

Table 4.9

^{13}C Chemical Shifts in Alkyl Cyclohexanones[a]

Substituent	C-1	C-2	C-3	C-4	C-5	C-6	Methyl
None	-16.0	152.1	166.0	168.7	-	-	-
2-Methyl	-17.5	148.5	157.3	168.3	165.5	151.9	179.0
3-Methyl	-15.6	143.7	159.8	160.3	168.3	152.7	171.7
4-Methyl	-16.2	153.0	158.7	162.4	-	—	172.6
2-t-Butyl	-17.9	132.6	162.6	166.3	163.8	148.5	b
3-t-Butyl	-16.2	149.5	143.6	166.0 or 166.5	166.5 or 166.0	151.8	c
4-t-Butyl	-16.5	151.4	164.8	145.7	-	-	d
trans-3, 4-Dimethyl	-16.6	145.6	154.8	151.4	157.8	152.6	172.3, 173.6
cis-3, 5-Dimethyl	-15.4	143.4	159.4	149.8	-	-	170.2
cis-3, 4-Dimethyl	-16.8	143.4	155.9	159.1	161.9	153.5	176.3, 176.6
trans-3, 5-Dimethyl	-15.8	144.0	163.0	152.9	-	-	171.7
4, 4-Dimethyl	-16.6	154.8	153.3	162.6	-	-	165.0

a) All shifts are in ppm upfield from carbon disulfide.

b) Quaternary carbon, 160.7 and methyl, 164.8.

c) Quaternary carbon, 160.2 and methyl, 165.3.

d) Quaternary carbon, 160.0 and methyl, 164.8.

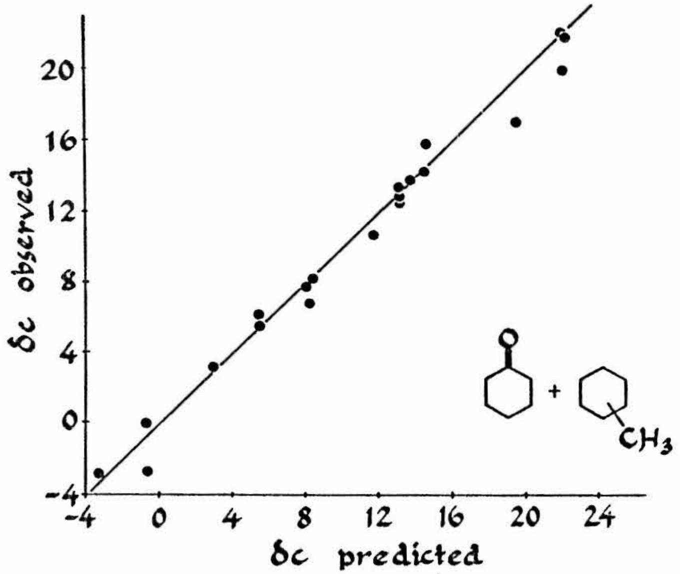
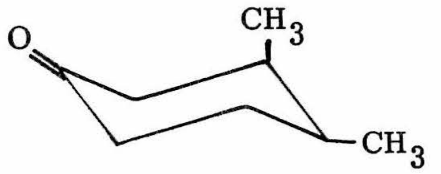


Figure 4.4. Plot of calculated and observed ^{13}C chemical shifts in alkylcyclohexanones.

of more than 20 ppm for alkylcyclohexanones which have a favored conformation with all equatorial alkyl groups. For 4,4-dimethyl-*cis*-3,4-dimethyl and *trans*-3,5-dimethylcyclohexanone, where all of the chair-form conformations have one axial methyl group, the additivity correlation works less well--there being upfield deviations on the order of 2 ppm for those carbons carrying axial methyls and also the γ ring carbons with which they are expected to be sterically involved. Examples include the 2-, 4- and 6-carbons of 4,4-dimethylcyclohexanone and the 3- and 5-carbons of *trans*-3,5-dimethylcyclohexanone. The situation with *cis*-3,4-dimethylcyclohexanone is more complex because the two most favored chair-like conformations **15** and **16** are unlikely to be equally favored. At first



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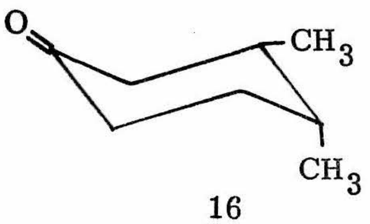

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sight **16** appears to have fewer axial-axial interactions than **15** and, hence, should be favored. This does not agree with the experimental results which show the 5-carbon to have a reasonably normal ^{13}C shift. On the other hand, if **15** is favored, then the shifts of the 2-, 4- and 6-carbons should be abnormally upfield, as in fact they are. The only problem is the sizeable upfield shift of the 3-carbon which indicates that it is substantially axial-like at least part of the time.

It must be remembered that the above effects of axial methyls in the cyclohexanones are relative to the same kind of effects observed in cyclohexanes with axial methyl groups and probably reflect the very substantially greater flexibility of cyclohexanone rings as compared to cyclohexane rings (19).

A somewhat different approach to correlating the chemical shifts of the alkylcyclohexanones and one which is similar to that used for cyclohexanols is to subtract from the chemical shifts of the alkylcyclohexanes those of the alkylcyclohexanones to derive substituent effects for the carbonyl group in alkylcyclohexanones (see Table 4.11). In general, the carbonyl substituent effects for the alkylcyclohexanones fall into a pattern which is similar to that of cyclohexanone itself. Nonetheless, there are sizeable deviations from additivity which are rather more apparent and, to some degree, more easily correlated with structural features than the alkyl substituent effects of Table 4.10.

The shifts of the carbonyl carbon with methyl substitution are small. The relative insensitivity of the resonance of this carbon to substituent effects could be due to the lack of directly bonded protons which make the normal mechanisms of long-range substituent effects inoperative.

The values of the β effect at C-2 and C-6 of 2-methylcyclohexanone seem quite analogous to (but quite a bit larger than) the corresponding equatorial hydroxyl effect (see Table 4.7). The γ effect at the 3- and 5-carbons of cyclohexanones is apparently normally

Table 4.10

Substituent Effects on the ^{13}C Chemical Shifts of Alkyl Cyclohexanones Relative to Cyclohexane[a]

Substituent	C-2	C-3	C-4	C-5	C-6
2-Methyl	-19.6	-8.4	+3.4	+0.8	-13.2
	(-17.0)	(-8.2)	(+2.8)	(0.0)	(-13.6)
3-Methyl	-22.3	-5.7	-5.7	+0.7	-13.1
	(-21.8)	(-5.7)	(-5.2)	(+2.8)	-12.8
4-Methyl	-13.2	-8.4	-3.0	-	-
	(-12.5)	(-6.8)	(-3.1)	-	-
2-<u>t</u>-Butyl	-35.0	-0.4	+2.6	+0.6	-13.9
	(-33.0)	(-2.9)	(+0.8)	(-1.7)	(-17.0)
3-<u>t</u>-Butyl	-14.3	-21.1	+2.3	0.0	-13.3
	(-16.0)	(-21.9)	(+1.0)[b]	(+0.5)[b]	(-13.7)
4-<u>t</u>-Butyl	-13.9	-0.4	-18.4	-	-
	(-14.1)	(-0.7)	(-19.8)	-	-
4,4-Dimethyl	- 8.9	-12.3	-0.2	-	-
	(-10.7)	(-12.2)	(-2.9)	-	-
<u>cis</u>-3,4-Dimethyl	-17.9	-6.9	-4.2	-4.0	-10.0
	(-22.1)	(-9.6)	(-6.4)	(-3.6)	-12.0
<u>trans</u>-3,4-Dimethyl	-22.4	-12.0	-9.3	-8.5	-13.2
	(-19.9)	(-14.1)	(-10.7)	(-7.7)	(-12.9)
<u>cis</u>-3,5-Dimethyl	-21.7	-5.3	-14.4	-	-
	(-22.1)	(-6.1)	(-15.7)	-	-
<u>trans</u>-3,5-Dimethyl	-20.2	+0.5	-11.2	-	-
	(-21.5)	(-2.5)	(-12.6)	-	-

a) The values given are in ppm upfield from cyclohexane. The non-parenthesized values are calculated by simple additivity of the hydrocarbon and cyclohexanone shifts.

b) Assignments uncertain.

Table 4.11

Carbonyl Substituent Effects on the ^{13}C Chemical Shifts of Alkyl Cyclohexanones[a]

Substituent	C-2	C-3	C-4	C-5	C-6	Methyl
H	-13.4	+0.5	+3.2	-	-	-
2-Methyl	-11.0	+0.5	+2.3	+0.5	-14.1	+9.4
3-Methyl	-13.1	+0.3	+3.5	+2.3	-13.5	+2.1
4-Methyl	-13.0	+1.9	+2.9	-	-	+3.0
4-*t*-Butyl	-13.4	-0.2	+1.8	-	-	-
3-*t*-Butyl	-15.1	-0.3	+1.0 or +0.5	+1.9 or +1.0	-13.8	-
cis-3,4-Dimethyl	-17.7	-2.3	+0.9	+0.8	-15.4	-0.5, -0.2
cis-3,5-Dimethyl	-13.8	-0.4	+1.8	-	-	+0.5
trans-3,4-Dimethyl	-11.0	+1.8	-1.6	+1.2	-13.1	0.0, +1.3
trans-3,5-Dimethyl	-14.7	-2.6	+0.7	-	-	-0.4
4,4-Dimethyl	-15.2	+0.5	0.0	-	-	+1.3

a) Substituent Effects are in ppm upfield from the corresponding hydrocarbon (7).

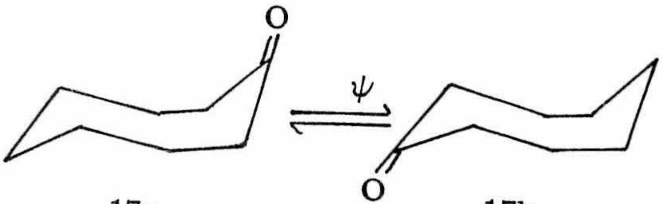
small as might be expected because of the expected smallness of any direct steric perturbation involving the carbonyl group and the 3- and 5-carbons.

The influence of the carbonyl group on the ^{13}C chemical shifts of the methyl groups in monomethylcyclohexanones (Table 4.11) relative to methylcyclohexane is only moderate except for 2-methylcyclohexanone. The methyl in this compound comes at +9 ppm relative to the hydrocarbon whereas the corresponding shift in open-chain methyl ketones is +5 ppm. This difference could well arise because in 2-methylcyclohexanone, but probably not in aliphatic ketones, the methyl group and carbonyl group are expected to be nearly eclipsed in the only favorable chair conformation.

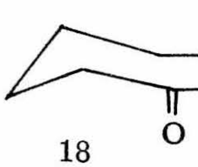
Most of the cyclohexanones in Table 4.11 show an upfield δ effect on the 4-carbon of the ring of 2-3 ppm. No similar effect is noted for open-chain ketones (20) so that this effect seems to arise from the geometric constraints in the ring. A similar but rather smaller effect was noted for cyclohexanols.

Other cyclic ketones: Experimental values for ^{13}C chemical shifts of the simple cycloalkanones $C_nH_{2n-1}O$ with n = 4, 5, 6, 7, 8, 10 and 12 are presented in Table 4.12. The chemical shifts of the carbonyl carbons are similar to those found in the aliphatic methyl ketones and agree moderately well with the values determined by rapid passage techniques (21). The substituent parameters were obtained by subtracting from the chemical shifts of the cyclic hydrocarbons from those of the ketones (14).

Cyclobutanone is likely to be a special case in that there is a substantial change in conformation associated with introduction of a carbonyl group into the four-membered ring because cyclobutanone is much more planar than cyclobutane (22). For this reason the large upfield γ effect in cyclobutanone is unlikely to involve steric interactions. The general upfield "ω effect" involving the carbon farthest away from the carbonyl group in the cycloalkanones with n = 4, 6, and 8 may have a common origin involving special orientation or proximity of the ω carbon (or hydrogens on the ω carbon) with respect to the carbonyl group. If this is so, we can speculate as to which of the possible conformations of cyclooctanone would qualify as being consistent with this result. Anet (23) has concluded on the basis of low-temperature nmr studies of 4-H-cyclooctanone-d_{13} that cyclooctanone exists either as an equal mixture of conformations 17a and 17b or conformation 18 with the latter possibility favored. The ω effect of cyclooctanone also appears to be more consistent with 18 than with 17.



17a 17b



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The shifts for cyclodecanone are less informative because at present there is no way of assigning the shifts to the middle carbons.

Table 4.12

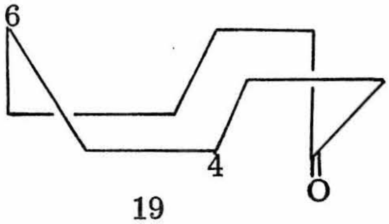
^{13}C Chemical Shifts and Substituent Effects on Cyclic Ketones[a, b]

	C-1	C-2	C-3	C-4	C-5	C-6
Cyclobutanone	-15.4	145.9	183.8			
	-185.5	-14.6	+13.4			
Cyclopentanone	-21.1	155.8	170.5			
	-188.3	-11.4	+3.3			
Cyclohexanone	-16.0	152.1	166.0	168.7		
	-181.9	-13.4	+0.5	+3.2		
Cycloheptanone	-18.9	150.1	(163.1,	169.3)		
	-183.2	-14.3	(-1.2,	+5.0)		
Cyclooctanone	-23.1	151.6	(166.0,	167.7)	168.5	
	-189.0	-14.3	(+0.1,	+1.8)	+2.6	
Cyclodecanone	-19.6	151.5	(168.2,	168.3,	169.9)	168.1
	-187.1	-16.0	(+0.7,	+0.8,	+2.4)	+0.6
Cyclododecanone	-15.9	153.0	(170.6,	168.37,	168.45,	168.9)
	-185.2	-16.3	(+1.3,	-0.9,	-0.8,	-0.4)

a) The upper line of figures for each ketone are the experimentally determined chemical shifts in ppm upfield relative to carbon disulfide, while the lower line gives the substituent effects obtained by subtracting the chemical shifts in ppm of the corresponding cycloalkanes (16).

b) The values in parentheses have not been assigned to specific carbons.

The cyclodecanone ring seems most favorable in the boat-chair-boat conformation as judged by X-ray diffraction investigations of several amine hydrochlorides (24). The rather small value of the ω effect may well indicate that the 6-carbon is not in close proximity to the carbonyl group as expected for a conformation such as **19**, but not conformation **20** in which C-1 and C-6 are rather close together. It will be noted that one of the middle carbons shows a 2.4 ppm upfield shift which is similar to that found for the ω carbon atom in cyclohexanone and cyclooctanone. If conformation **19** is favored then this substituent effect might reasonably be attributed



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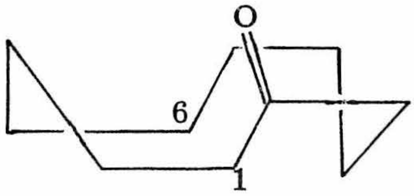

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to C-4 because of its relative proximity to the carbonyl group.

In the cyclic ketones where *n* is odd, there is no difference in signal intensity which uniquely identifies the ω carbon and at present it is not possible to assign the resonances of cycloheptanone.

Comparison of ^{13}C Resonances of Aliphatic and Alicyclic Hydrocarbons

In correlations of substituent effects one has to be careful to distinguish between effects which are intrinsic to the nature of the substituent and those which result because the substituent brings about a change in the position of the conformational equilibrium. The ^{13}C chemical shifts of the linear and cyclic hydrocarbons indicate an upfield shift for a carbon in a chain when there is a γ methyl *gauche* to the carbon under examination. Such a substituent should be and is zero in an equatorial methylcyclohexane but becomes about +5.5 ppm in an axial methylcyclohexane. An intermediate value of +2.5 ppm is found in a continuous-chain alkane such as *n*-butane which will in general be a mixture of conformers with γ methyl in both *trans* and *gauche* positions. If the γ methyl shifts in cyclohexane are applicable to *n*-butane, we can conclude that there must be approximately equal amounts of *gauche* and *trans* isomers present, which agrees well with electron-diffraction results (55 ± 15% of the *trans* isomer) (9).

The ^{13}C resonance of cyclohexane appears 2.5 ppm upfield from that of an interior methylene group of a continuous-chain alkane. Now if we associate a +2.5 ppm shift with the proportions of *gauche* and *trans* conformations usually present in continuous-chain alkanes, then the ^{13}C chemical shift of cyclohexane relative to a hypothetical all-*trans* continuous-chain alkane then is +5 ppm which is in good agreement with *gauche* interactions inherent in the cyclohexane ring. Similar considerations explain why the substituent effects in continuous-chain, secondary alcohols are intermediate between axial and equatorial cyclohexanol.

Other Substituents

Introduction of any substituent into a γ position shifts a ^{13}C resonance upfield (5). The methyl substituent effect has been suggested to occur through proton-proton interactions which are transmitted to the carbons in the gauche conformations (7). This mechanism is not possible for a fluorine substituent because there is no proton on the fluorine. The size of a fluorine is comparable to that of a proton, so there may be no steric effect (25). Furthermore, the interaction between two vicinal fluorines also causes an upfield shift of the fluorine resonance (26).

The ^{13}C chemical shift of C-8 in 1-fluoronaphthalene is 5.1 ppm upfield of the corresponding shift in naphthalene itself. The two other carbons which are three bonds removed from the fluorine but which are not in close proximity to it are shifted downfield by 2.2 and 4.0 ppm. The methyl carbon of 2-fluorotoluene is shifted upfield relative to the methyl carbon in toluene by 7.3 ppm. The corresponding effects in the meta and para derivatives are +1.5 and +0.9 ppm (27). Clearly a carbon is shifted upfield by a γ fluorine which is either eclipsed or gauche to the carbon in question. The desirability of further theoretical investigations into the nature of the γ effect is clearly indicated.

The chemical shift of C-1 in pentafluoroiodobenzene actually appears upfield of the methyl resonance in methyl fluoride. This large shift is explained on the basis of additive substituent parameters for fluorobenzene and iodobenzene (18), where $^1\delta_1$ is the substituent

$$\delta = {}^{1}\delta_{1} + 2({}^{2}\delta_{F}) + 2({}^{3}\delta_{F}) + {}^{4}\delta_{F}$$

$$+63.5 = +32.3 \quad +28.6 \quad -1.8 \quad +4.4$$

effect of iodine on C-1 of iodobenzene, ${}^{2}\delta_{F}$ is the substituent effect of fluorine on the ortho carbon of fluorobenzene, etc. The predicted value of +63.5 ppm agrees fortuitously well with the observed shift of +63.5 ppm. Additivity relations predict the ^{13}C chemical shifts in most aromatic compounds, but not usually to this precision.

Phosphorus: The ^{13}C chemical shifts in the methylphosphines parallel those in the series ethane, propane and isobutane (4). Adding a methyl group in the β position causes a 10 ppm downfield shift of the methyl carbon resonance.

CH_3CH_3	$(CH_3)_2CH_2$	$(CH_3)_3CH$
122.8	113.1	104.3
CH_3PH_2	$(CH_3)_2PH$	$(CH_3)_3P$
134.3	122.9	112.5

This same downfield shift is observed in the difference between the ^{13}C chemical shifts of methanol and dimethyl ether (79.4 and 69.3 ppm) and methylamine and trimethylamine (101.9 and 81.2 ppm) (2, 5) and may also be seen with other intervening atoms.

The constancy of this β-methyl effect suggests a reinterpretation of Bucci's (29) correlation of the ^{13}C chemical shifts in compounds $(CH_3)_nM$ with the electronegativity and the number of lone pairs of atom M. The parameter "b" which was related to the number of lone pairs may also be related to the number of β-methyl groups. In fully methylated derivatives, which were the only ones considered by Bucci, there is no change in the numerical analysis, but with the interpretation presented here, less highly methylated derivatives can be included in the same correlation. The upfield shift in the parameter b from permethyl to perethyl derivatives may be associated with the presence of carbons γ to the methylene carbon in question (4).

If the ^{13}C chemical shifts of mono-substituted methanes are most strongly influenced by the electronegativity of the substituent, (2, 5), only a small chemical shift would be expected for methyl phosphine relative to methane because phosphorus has almost the same electronegativity as a proton. The observed shift is +3.5 ppm in contrast to the -30 ppm shift for methylamine.

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Materials

Most compounds used in this thesis were either available from commercial sources or from previous work in these laboratories.

1, 2, 3-Triazole was synthesized from acetylene and hydrazoic acid (1).

Tetrazole was synthesized from dicyandiamide and hydrazoic acid followed by reduction with hypophosphorus acid (2, 3).

A sample of selenophene was kindly provided by Professor J. H. Goldstein.

Fluoroanilinium ions were prepared by dissolving the corresponding anilines in methanolic nitric acid. Fluorophenolate ions were prepared by dissolving the corresponding phenols in methanolic potassium hydroxide.

Phosphonium ions were prepared by the reaction of the corresponding trialkylphosphines with appropriate alkyl halides (4).

A sample of propyne labelled with 57% ^{13}C at C-3 was kindly provided by Dr. J. N. Shoolery.

Methylcyclopropane labelled with 20% ^{13}C at the methyl carbon was a sample prepared by E. Renk (5).

Samples of di-n-propyl- and di-isopropylmercury were provided by Dr. B. M. Monroe.

A sample of 1, 5-difluoronaphthalene was supplied by J. B. Dence.

The six isomeric methylcyclohexanols were prepared by

Vernon Cormier by the method of Noyce and Denney (6).

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Abstracts of Propositions

I. Torsional effects have been suggested as a possible explanation for the specificity of exo attack on norbornane derivatives. Although the steric hindrance on the endo sides of bicyclo [x. 2. 2] derivatives is similar, torsional considerations in bicyclononene (x = 3) favor endo attack. Experiments are proposed to test this prediction.

II. Silver ion assisted acetolysis of 1-chlorobicyclopropyl yields as the major product 1-acetoxybicyclopropyl. Experiments are proposed to determine whether the acetoxy group in the product is bound to the same carbon as the chlorine in the starting material.

III. The insertion of ketene into the carbon-oxygen bond of cyclic esters leads to cyclic esters with two more carbons in the ring. An investigation of the stereospecificity of this reaction with respect to the ether substituents is proposed.

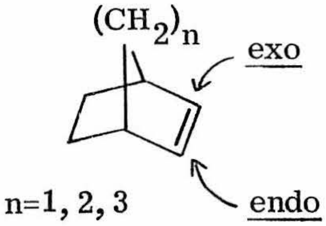
IV. Three possible isomers of 2, 2'-dicarboalkoxybicyclobutanes can exist: exo-exo, exo-endo, or endo-endo. Experiments are proposed which can identify these isomers and find their relative thermodynamic stability.

V. Cis-2-deuteriovinylcyclopropane rearranges to the trans isomer faster than the ring expands to the cyclopentene. The isomerization can occur by rotation about either or both of the carbon-carbon bonds in the diradical intermediate. Experiments are proposed which will distinguish between these possibilities.

Proposition I

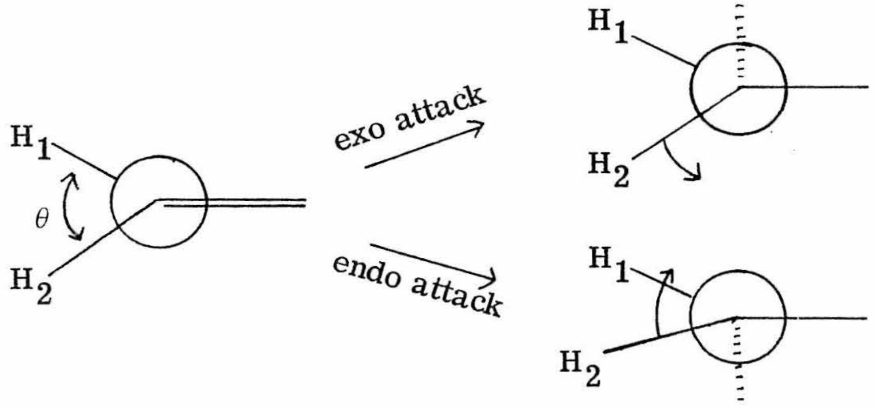
Torsional Factors in the Reactions of the [3.2.2] Bicyclononane Ring System

Most reactions of bicyclo [2.2.1] heptane take place preferentially on the exo side of the molecule. Addition of carbenes yields exclusively the exo adduct (1). The removal of one proton α to the carbonyl group of 2-norbornanone is stereospecifically the exo proton (2). The addition of mercuric acetate (3), hydrogen chloride (4), and borohydride (5) to norbornene are exclusively exo. Reduction of norbornanone with borohydride occurs preferentially from the exo side to yield the endo alcohol (6).



Bicyclo [2.2.2] octene, a reasonable steric model for the endo side of norbornene, undergoes carbene additions (1), though no relative rate data were given. Reduction of the ketone with borohydride proceeds at the same rate as endo attack on norbornanone (6). There is no exo-endo distinction in the [2.2.2] system; both sides of this molecule are equivalent.

Schleyer (7) has proposed the concept of torsional strain along the reaction coordinate as being capable of explaining the specificity of exo attack in the norbornyl system. The dihedral angle between H-1 and H-2 in norbornene is such that endo attack forces the dihedral



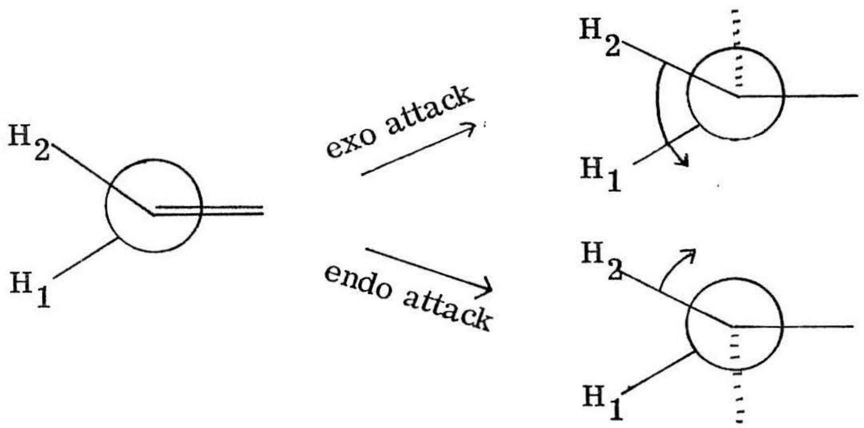
Torsional Behavior of the [2.2.1] System

angle θ to become smaller and the non bonded interaction between H-1 and H-2 increases in the transition state. Some strain is relieved by *exo* attack because the dihedral angle increases in the transition state. The differences in the non bonded repulsions between H-1 and H-2 in the ground state and the two possible transition states may be enough to explain the observed specificity (7).

The H-1, H-2 dihedral angle in bicyclo [2.2.2] octene is zero. In bicyclo [3.2.2] non-6-ene (**1**⇄**2**) the relative positions of H-1 and H-2 are reversed; *exo* attack forces eclipsed hydrogen-hydrogen interactions in the transition state while *endo* attack relieves some torsional strain.

There is a possible complication due to the flexibility of the three-carbon bridge in the bicyclononene. The relative stabilities of the two possible conformations **1** and **2** are not known. The steric

Torsional Behavior of the [3.2.2] System



1 2

hindrance in 2 should not deter an otherwise favored *exo* attack by some reagents. The predominance of *endo* attack by lithium aluminum hydride on bicyclo [3.2.2] nonan-6-one (8) has been attributed to steric approach control (9), hindered by the three-carbon bridge. This selectivity could also arise from torsional effects. The presence of 7,7-dimethyl substituents on the norbornane ring system does not change the stereochemistry of proton abstraction (2), or the addition of mercuric acetate (3) and hydrogen chloride (4), but does slow the rate of reduction of 7,7-dimethylnorbornanone with borohydride (6).

It is proposed that various additions to the bicyclo [3.2.2] ring system be attempted. If Schleyer's (7) theory of torsional strain is correct, a significant proportion of the reactions should occur via pathways involving endo attack on the substrate. On the other hand, if the more traditional views of steric hindrance and/or anchimeric assistance are correct, the exo reactions should still be favored.

Synthetic entry to the bicyclo [3.2.2] nonane ring system is through Diels-Alder reactions of a substituted ethylene with 1,3-cycloheptadiene (10) or a ring expansion of a bicyclooctane (8).

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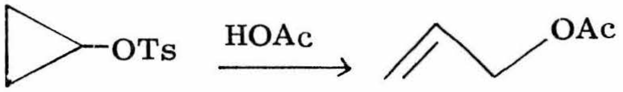
Proposition II

The Solvolysis of 1-Chlorobicyclopropyl

Cyclopropane derivatives **1** undergo a slow solvolysis to give exclusively ring-opened products (1). Cyclopropylcarbinyl systems **2** undergo rapid solvolysis to give a mixture of products with the cyclopropylcarbinyl, cyclobutyl and allylcarbinyl skeletons (2). Studies using labelled compounds have shown that the "unrearranged" cyclopropylcarbonyl product has undergone extensive carbon scrambling during the solvolysis.



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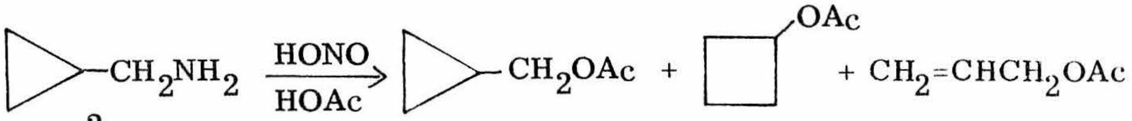

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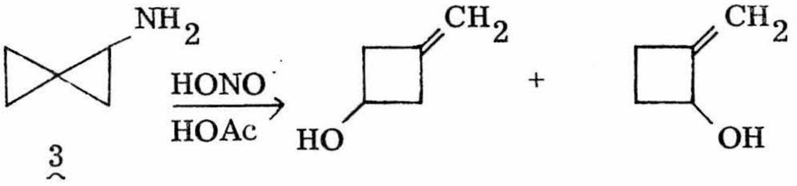
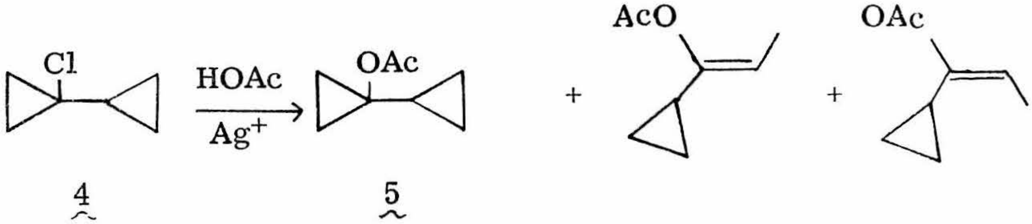
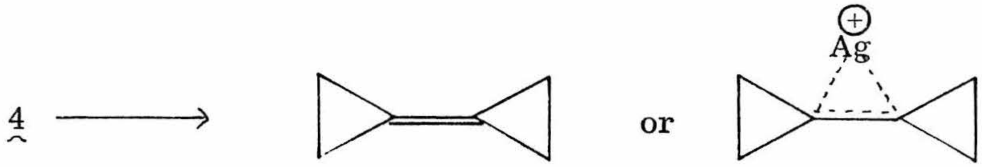
Two systems which incorporate both features of **1** and **2** in a single molecule have been studied. Applequist (3) has investigated the solvolysis of the spiropentane derivative **3** and found that it undergoes slow solvolysis to give exclusively ring enlarged products. Landgrebe (4) has studied the silver ion assisted acetolysis of 1-chlorobicyclopropyl **4**. The rapid reaction gave 1-acetoxybicyclopropyl **5** as the major product along with several other products in which one ring had been cleaved. In apparent contrast to all other cyclopropyl solvolyses the major product has not undergone





either ring opening or ring expansion.

The "unrearranged acetate" could have undergone a number of rearrangements, but this could not have been inferred from the data available since the authors (4) presented no evidence that the acetate group is bonded to the carbon from which the chloride departed. One possible mechanism to scramble the carbons without affecting the basic ring skeleton is loss of a proton from C-1' and a statistical capture of solvent at each of the now equivalent sites. If the alkene 6, or a silver ion complexed form, is involved, solvolysis carried out in deuterated acetic acid CH_3COOD would introduce deuterium into the product as in 7. The introduction of a deuterium could be determined either by nmr or mass spectroscopic examination of the product.



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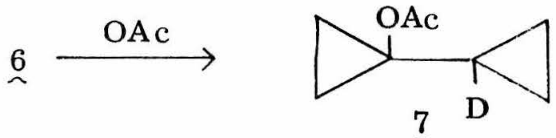
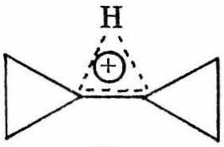
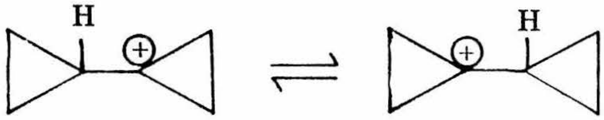


7

The two carbons 1 and 1' can become equivalent without loss of a proton, perhaps through a symmetrical ion 8a or a rapid equilibration of the classical forms 8b and 8c. This type of a mechanism has been shown to be unimportant in aliphatic compounds (5).



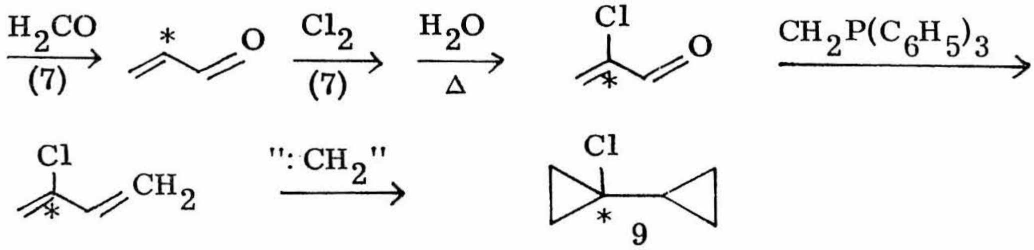
8a



8b 8c

Distinguishing whether this type of a mechanism is operating requires an appropriate carbon labelled compound. A possible synthesis is outlined below.

$$^*CH_3COOH \longrightarrow {}^*CH_3CONH_2 \xrightarrow[(6)]{LiAlH(OEt)_3} {}^*CH_3CHO$$



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It is proposed to determine whether the acetate in **5** is bonded to the same carbon which was bonded to the chloride in **4** by the solvolysis of the labelled compound **9**. The method of product analysis would depend on the type of carbon label introduced. Labelling with ^{13}C and determination of the product composition by ^{13}C nuclear magnetic resonance appears to be a convenient method.

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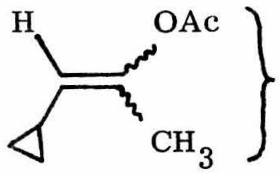
8. The structures assigned to Landgrebe's ring opened products are probably incorrect. The coupling constants involving the methyl protons and the vinyl proton are too small to be vicinal coupling, but are just right for *cis* and *trans* allylic coupling (9) suggesting the two possible pairs



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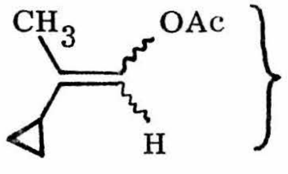

11

The chemical shifts of the vinyl protons (10) suggest that the correct structures are the isomers 11.

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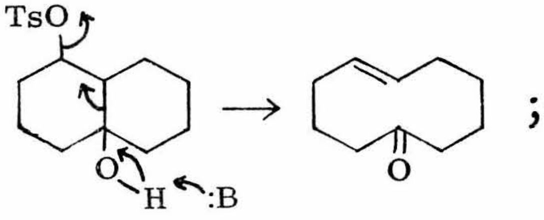
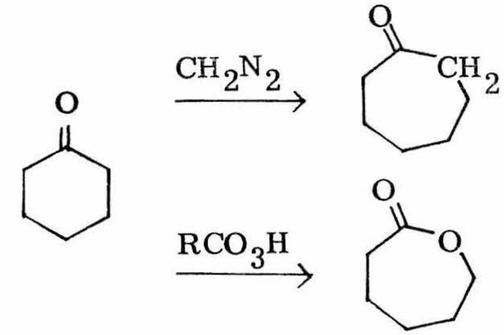
Proposition III

Ring Expansion of Cyclic Ethers

The synthesis of medium-sized rings has been a challenging problem. The unfavorable entropy of bringing two ends of a linear molecule close together makes the syntheses unfavorable. Two approaches have been developed to the syntheses of these compounds which do not depend on entropy factors. Cleavage of a bond between two rings of a bicyclic system forms a single larger ring as in method A (1). Ring enlargement of a monocyclic compound by insertion reactions produces a ring with one or more members according to method B (2, 3).



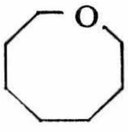
Method A



Method B

The medium-sized heterocycles have been much less studied than the corresponding carbocycles, primarily because of synthetic difficulties. Oxocane 1 was synthesized only recently by a six-step type A synthetic sequence (4).

A two step synthesis for the two carbon ring expansion of



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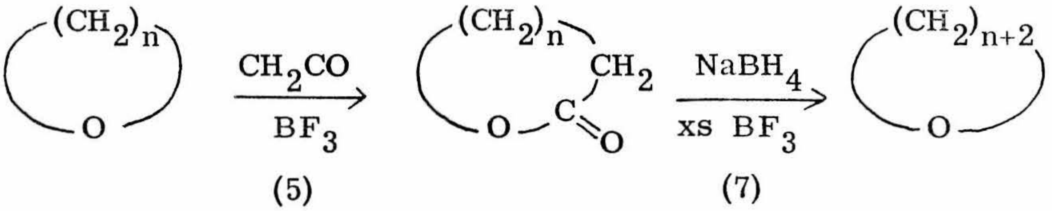
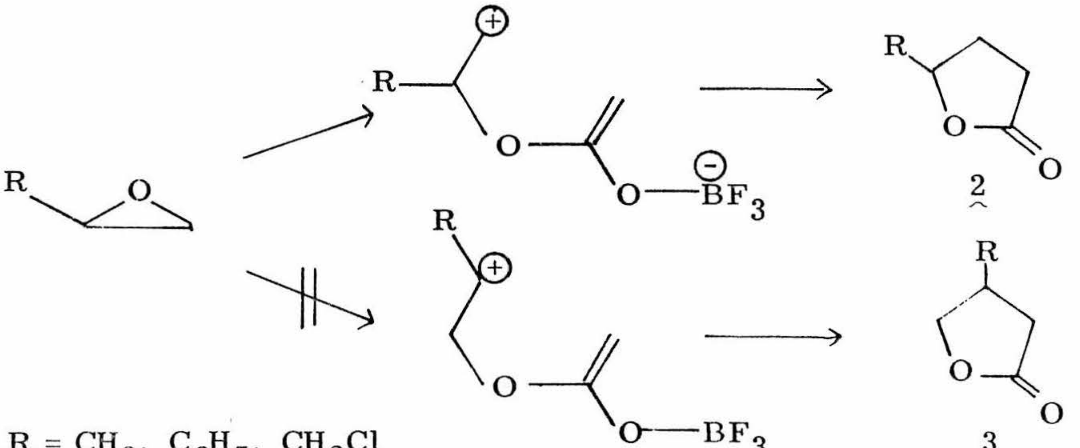
cyclic ethers has been discovered (5), but has not been exploited because of low yield. However, although the yield is low, the conversion based on the ether may be quite reasonable (6, 7). The reaction has been used only with oxiranes (6) and tetrahydrofuran (5); application to



pyran would yield oxocane.

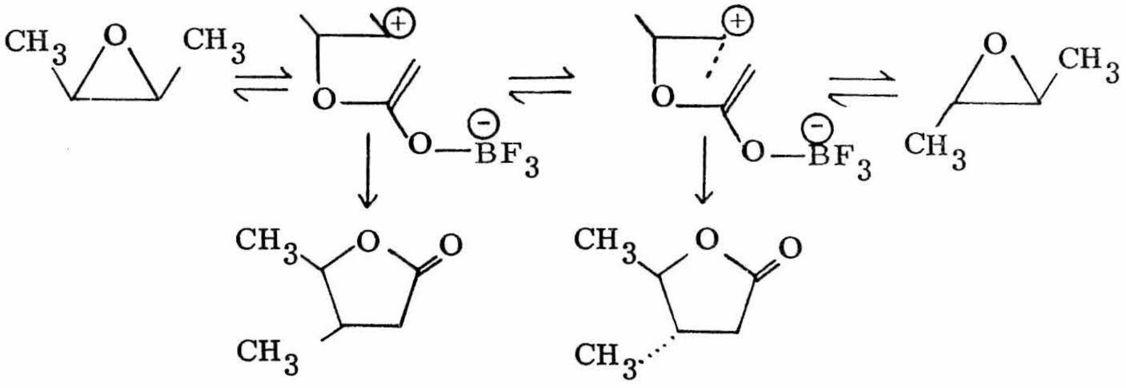
The reaction with substituted oxiranes occurs through what is formulated as the least stable carbonium ion to give 2 exclusively (6). None of the other isomer 3 was found, but a careful search



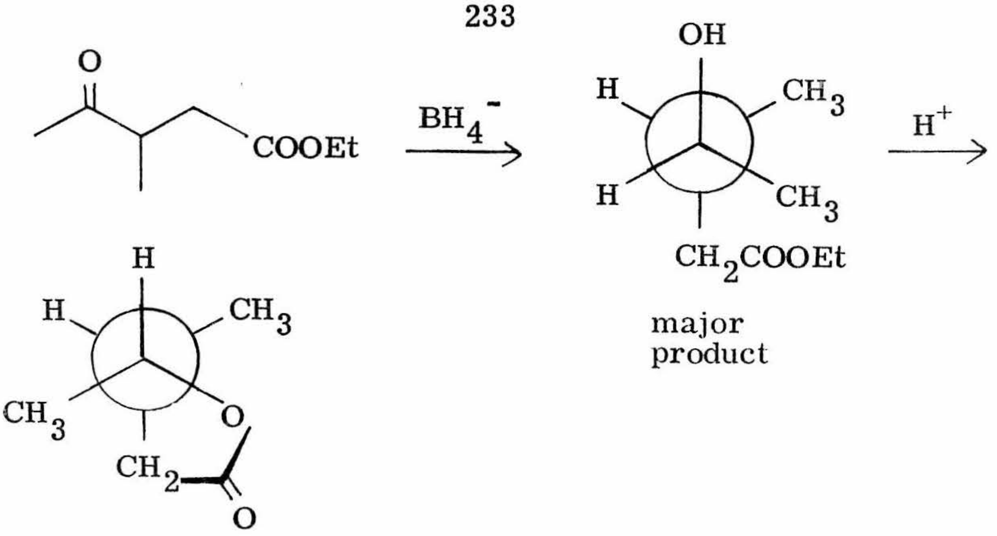
R = CH_3, C_6H_5, CH_2Cl

should be made before concluding that it is definitely absent.

The proposal of a dipolar intermediate (6) has also not been checked. If the lifetime of the intermediate is sufficiently long, rotation about the carbon-carbon bond may occur before closure. It is proposed that cis- and trans-1, 2-dimethyloxirane be treated with ketene in the presence of boron trifluoride. If the reaction is concerted or if rotation in the intermediate is slow a single product should be formed from each starting material. If rotation does occur a mixture of the two products should be formed from each starting material. If formation of the initial adduct is reversible and rotation occurs, interrupting the reaction before completion and reisolating the oxirane would give a mixture of the two isomers.



Authentic samples of the two isomeric lactones may be synthesized from 3-methyllevulinic acid (8). Asymmetric reduction (9) leads preferentially to the alcohol which yields the trans-dimethyllactone.



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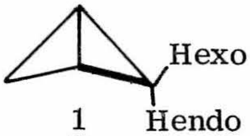
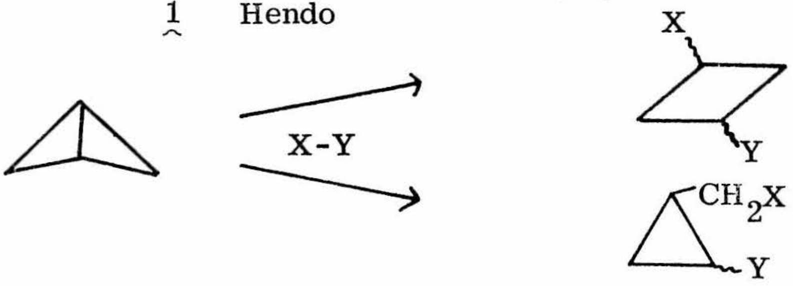
Proposition IV

Base Catalyzed Epimerization of 2, 2'-Dicarbomethoxy-bicyclobutane.

The chemistry of bicyclobutane 1 is quite limited (1). Most reactions proceed by addition across one of the single bonds to destroy the bicyclic ring system.



1

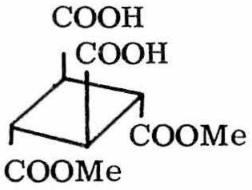


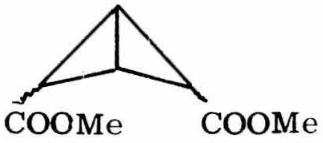
The bicyclobutane ring system is extremely acid sensitive and 1-bicyclobutylmethanol rapidly adds water at pH 4 to give a cyclobutane. The ring system is stable to strong bases.

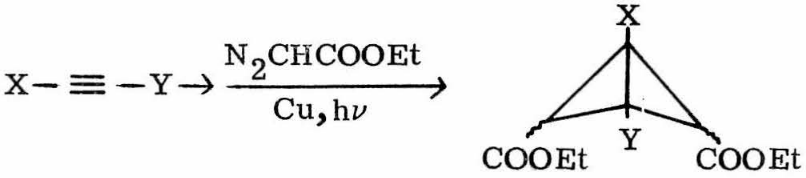
The proton on C-1 is acidic enough to permit metallation (3), and facile deuterium exchange. Reduction of 1-carbomethoxy (4) or cyano (5) bicyclobutanes have been carried out with lithium aluminum hydride without affecting the ring skeleton.

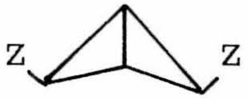
The two methylene protons at C-2 are not equivalent because the bicyclobutane molecule is puckered. If carbon-proton coupling constants are reliable indicators of carbon orbital hybridization, the orbital bonding to the exo proton (see 1) has a higher s character than the orbitals in cyclopropane and the orbital bonding to the endo proton has a lower s character (1).

Two synthetic methods have been developed which lead to 2, 2'-dicarboalkoxybicyclobutanes. Griffin (6) has electrolyzed trans, trans, trans-1, 3-dicarboxy-2, 4-dicarbomethoxycyclobutane and some Russian workers (7) have treated acetylenes with ethyldiazoacetate in the presence of copper catalysts. Both groups claimed to have obtained a single isomer. However, the Kolbe electrolysis can be expected to lead to two reasonable isomers (6); likewise, since additions of carbomethoxycarbene are usually not stereospecific (8), a mixture of isomers would be expected.









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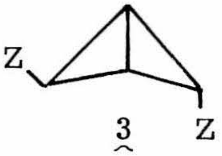

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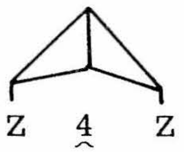

4

Z = COOR

In neither case was the orientation of the carboalkoxy groups determined, nor was it shown whether the single product was actually thermodynamically favored. Determining which isomer is formed is quite straightforward. The two protons on C-2 and C-2' in 3 are in different environments and should give separate signals.

From the nmr Griffin was able to exclude **3** as the structure of his adduct (6). Both **2** and **4** should give singlets for the two protons, but in the *exo* isomer **2** the two *endo* protons would not be coupled. On the other hand, in the *endo* isomer **4** the two *exo* protons should be significantly coupled. This coupling could be seen in the ^{13}C satellites of the proton spectrum. The magnitude of the carbon-proton coupling would also be useful in this respect.

It is proposed that the base catalyzed epimerization of 2, 2'-dicarboalkoxybicyclobutanes be attempted. By carrying out the reaction in deuteriomethanol (9) the rate of proton abstraction can be determined independent of any possible inversion of the carbanion at C-2. If deuterium incorporation occurs without any epimerization either inversion of the carbanion is unusually slow or the initial ester is the thermodynamically favored isomer.

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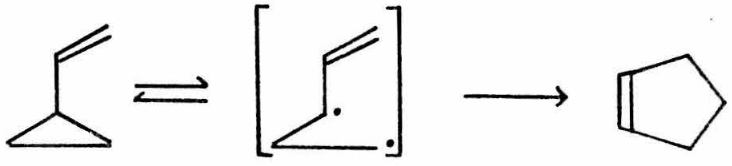
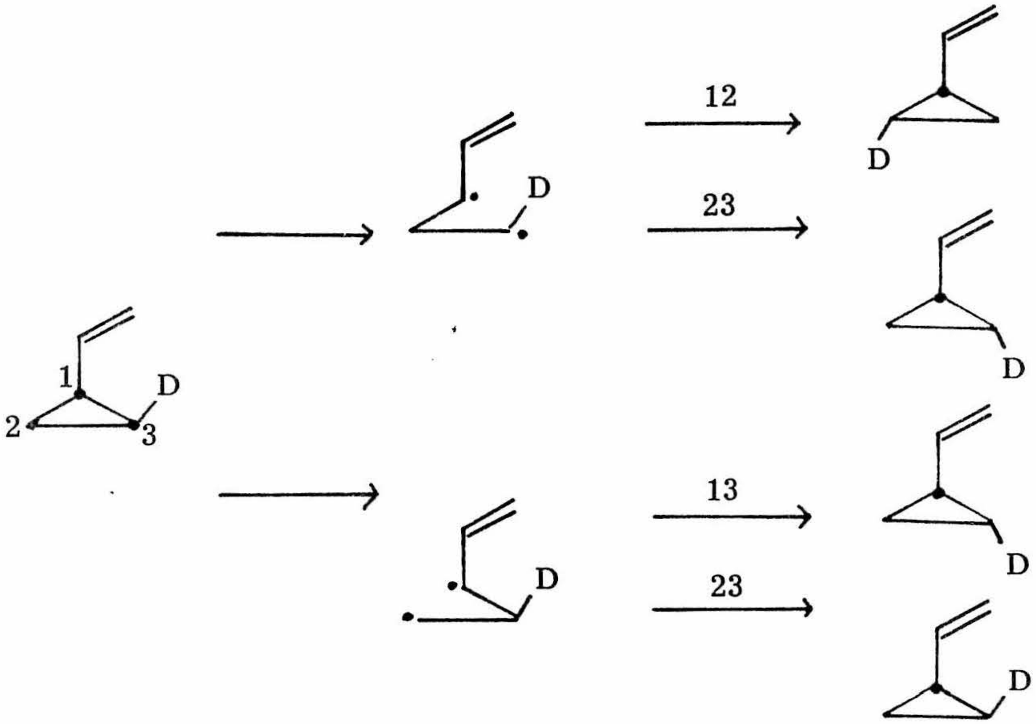
Proposition V

Internal Rotation in the Diradical Intermediate of the Vinylcyclopropane Rearrangement

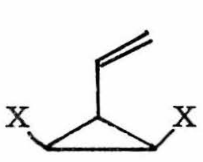
Although most alkylcyclopropanes produce alkyl propenes on pyrolysis with an activation energy of 64 kcal/mole (1), vinylcyclopropane undergoes a ring expansion to yield cyclopentene with an activation energy of 50 kcal/mole (2). The lower activation energy for the vinylcyclopropane rearrangement has been attributed to the resonance stabilization of the transition state which resembles an allyl radical.



In favor of the diradical intermediate is the observation that <u>cis</u>-2-deuteriovinylcyclopropane rearranges to the <u>trans</u> isomer faster than the ring expands to the cyclopentene (3). It should be noted that the rate of bond breaking leading to the rotation may be as much as 25% faster than the observed isomerization rate because rotation about the 2-3 bond leads to the <u>trans</u> isomer only 50% of the time while rotation about the 1-2 bond always leads to the <u>trans</u> isomer.



With 2, 3-disubstituted vinylcyclopropanes it is possible to observe the two rotations independently. There are three structural isomers of this type of compound: the two substituents *cis* to each other and *cis* to the vinyl group 1, the two substitutents *trans* 2, and the two substituents *cis* to each other but *trans* to the vinyl group 3. The possible optical isomerism of 2 will not be relevant to the discussion.



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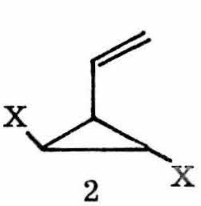

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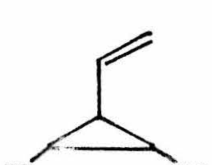
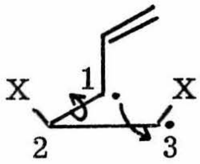


3

Starting with 1 the two possible initial diradicals are identical. Rotation about the 1-2 bond and subsequent ring closure leads to 3



while rotation about the 2-3 bond leads to 2. Similar considerations for 2 and 3 lead to the following interconversion pattern:

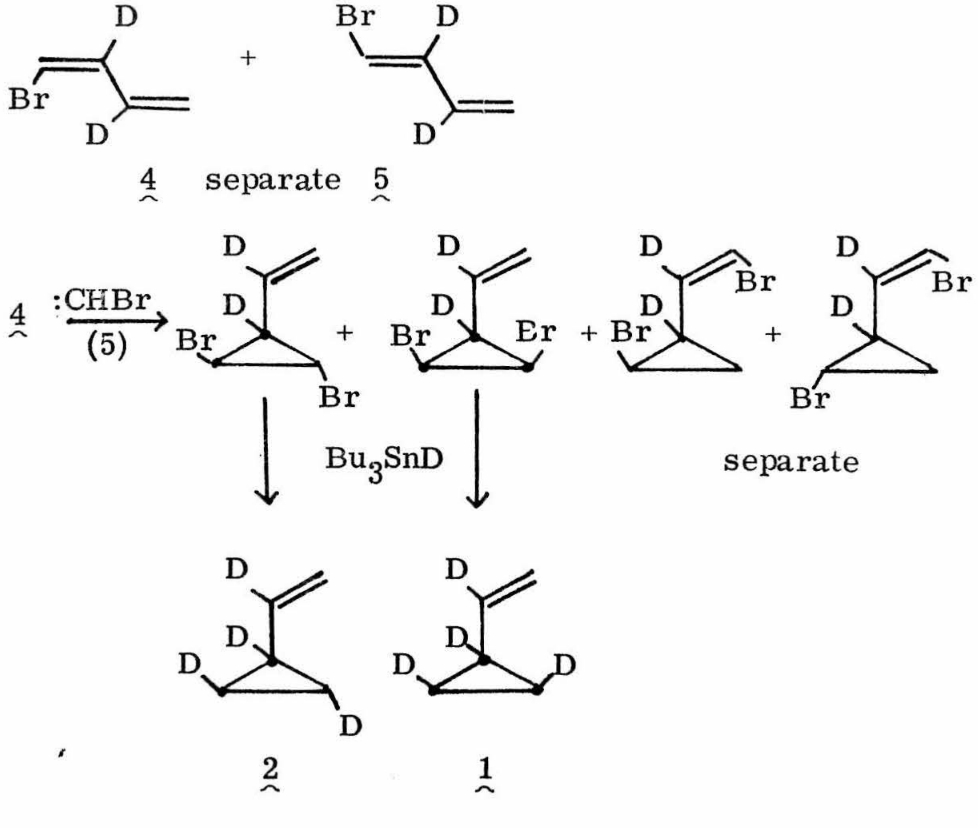
Starting Material	Rotation	Product
1	12	3
	23	2
2	12	2
	23	1, 3
3	12	1
	23	2

Rotation about the 1-2 bond in 2 gives back starting material while rotation about the 2-3 bond leads to either 1 or 3 depending on which bond was initially broken.

It is proposed that the pyrolysis of the three 2, 3-dideuteriovinylcyclopropanes (X=D) be carried out in order to determine the difference, if any, in the barriers to internal rotation about the 1-2 and 2-3 bonds in the diradical intermediate of the vinylcyclopropane rearrangement. Proton nmr provides a convenient analytical method (3). If one neglects isotope effects, then 1 and 3 show singlets for the 2, 3 protons while the spectrum of 2 is an AB pattern with the chemical shifts being identical to those of 1 and 3. Integration of the spectrum of recovered starting material provides the rates of interconversion of the three isomers.

The synthesis of the three deuterated vinylcyclopropanes requires some separations which may be difficult in practice, but a similar synthetic scheme was successfully employed in the synthesis of the monodeuterated material (3).

$$\mathrm{CH_2BrC{\equiv}CCH_2Br} \xrightarrow{\mathrm{D_2}} \mathrm{CH_2BrCD{=}CDCH_2Br} \xrightarrow[(4)]{\mathrm{KOH}}$$



The *trans* bromide **5** will yield a mixture of **2** and **3** by a similar sequence.

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