(helium pressure 20 psi), by 104–105° (0.1 mm), $n^{25}D$ 1.5037; $[\alpha]^{25}D$ +9.03° (*c* 0.065 g/ml, dioxane); $\lambda_{max}^{dioxane}$ 232 mμ (ϵ 7680); ν_{max} 2955, 2925, 2870, 1690, 1447, 1410, 1377, 1350, 1260, 1133, 1105, 1020, 995, and 628 cm^{-1}; τ 6.89–7.54 (4 H, multiplet), 7.15 (2 H, triplet), 7.66 (3 H, singlet), 8.17–8.55 (5 H, multiplet), 8.72 (3 H, triplet), and 9.08 (3 H, doublet).

Anal. Calcd for $C_{11}H_{20}O_2S_2$: C, 53.18; H, 8.12; S, 25.82. Found: C, 53.43; H, 8.14; S, 25.78.

(*R*)-(−)-6-Acetylthio-4-methylhexanoic Acid (XI). (*R*)-(−)-6-Mercapto-4-methylhexanoic acid (X),[10] 8.2 g (40 mmol), was dissolved in aqueous sodium hydroxide, allowed to react with 4.1 g (66 mmol) of acetyl chloride, and worked up as described above for VIII. Distillation gave 4.6 g (44%) of product, and 36% of the starting material was recovered. The product was found to be homogeneous by vpc on silicone oil (Dow Corning 710), retention time 21 min at 195°, bp 126° (0.07 mm), $n^{25}D$ 1.4870, $[\alpha]^{25}D$ −10.34° (*c* 0.86 g/ml, methanol); ν_{max} 3050 (broad), 2965, 2935, 2875, 1710, 1690, 1450, 1380, 1355, 1283, 1135, 955, and 625 cm^{-1}; τ −1.02 (1 H, singlet), 7.12 (2 H, triplet), 7,64 (2 H, triplet), 7.72 (3 H, singlet), 8.20–8.98 (5 H, multiplet), and 9.07 (3 H, doublet).

Anal. Calcd for $C_9H_{16}O_3S$: C, 52.91; H, 7.90; S, 15.70. Found: C, 52.95; H, 7.78; S, 15.53.

(*R*)-(−)-Ethyl 6-Acetylthio-4-methylthiohexanoate (XII). (*R*)-(−)-6-Acetylthio-4-methylhexanoic acid (XI), 4.4 g (21.5 mmol), was treated with 3.1 g (25.8 mmol) of thionyl chloride according to the method described above for IX. Distillation gave 1.80 g (38%) of (*R*)-6-acetylthio-4-methylhexanoyl chloride, bp 93° (0.08 mm); ν_{max} 1690 (thiol ester C=O) and 1800 cm^{-1} (acid chloride C=O).

The acid chloride, 1.80 g (8.1 mmol), was allowed to react with 0.60 g (9.70 mmol) of ethanethiol in the presence of 1.50 g (8.1 mmol) of tri-*n*-butylamine as described above for IX. Distillation gave 2.0 g (100% from acid chloride); two consecutive fractional distillations under high vacuum produced a sample which was found to be homogeneous by vpc on silicone oil (Dow Corning 200 and 710), retention times 33 min (195°) and 62 min (216°), respectively (helium pressure 20 psi), bp 105° (0.07 mm), bp 74–75° (2×10^{-4} mm), $n^{25}D$ 1.5057, $[\alpha]^{25}D$ −3.21° (*c* 0.22 g/ml, dioxane); $\lambda_{max}^{dioxane}$ 231 mμ (ϵ 8410); ν_{max} 2955, 2925, 2870, 1690, 1447, 1410, 1377, 1350, 1260, 1133, 1105, 1020, 955, and 628 cm^{-1}; τ 6.89–7.54 (4 H, multiplet), 7.15 (2 H, triplet), 7.66 (3 H, singlet), 8.17–8.55 (5 H, multiplet), 8.72 (3 H, triplet), and 9.08 (3 H, doublet).

Anal. Calcd for $C_{11}H_{20}O_2S_2$: C, 53.18; H, 8.12; S, 25.82. Found: C, 53.30; H, 8.04; S, 25.90.

Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Spectra of Five-Membered Aromatic Heterocycles[1a]

Frank J. Weigert[1b] and John D. Roberts

Contribution No. 3622 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91109.

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Abstract: High-resolution ^{13}C nmr spectra have been obtained for the five-membered nitrogen heterocycles and for furan, thiophene, and selenophene. All possible carbon–proton coupling constants have been observed and assigned to the proper protons. The chemical shifts and coupling constants are discussed both empirically and with respect to extended Hückel calculations. The chemical shifts follow variations in the local charge densities and the long-range carbon–proton coupling constants may be correlated with geometrically corresponding carbon–proton and proton–proton coupling constants in substituted ethylenes. Extended Hückel calculations seem uniformly poor in correlating spin–spin coupling constants in these systems.

There have been many nuclear magnetic resonance studies of the five-membered heterocycles because of their utility as models in the testing of semiempirical theoretical predictions. Difficulties arise in the study of the proton spectra of pyrrole and furan because their spectra are deceptively simple and it is not possible to extract the values of the various coupling constants directly from the spectra. Abraham and Bernstein[2] and Hoffman and Gronowitz[3] have studied corresponding substituted heterocycles and inferred values of the coupling constants by suitable interpolation of the observed substituent effects. Reddy and Goldstein[4] used the ^{13}C satellites of the proton spectra of the parent compounds to assign the various proton–proton coupling constants by requiring that the assigned values reproduce the ^{13}C-satellite spectra. In matching the outer satellite spectra by the method of effective chemical shifts, it was necessary to take account of differences between the long-range, carbon–proton couplings, although the outer satellite spectra are not sensitive to the absolute magnitudes of these couplings. Tori and Nakagawa[5] have reported a large number of one-bond, carbon–proton coupling constants for five- and six-membered heterocycles through observations of the ^{13}C satellites in the proton spectra.

Direct observation of ^{13}C spectra has been hampered by the low sensitivity of the ^{13}C nucleus to nmr detection and its low natural abundance. Page, Alger, and Grant[6] 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. In the present research, high-resolution ^{13}C spectra have been obtained for a

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(1) (a) Supported in part by the U. S. Public Health Service, Research Grant 11072-04 from the Division of General Medical Sciences, and in part by the National Science Foundation. (b) National Science Foundation Predoctoral Fellow, 1965–1968.

(2) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 905 (1961).

(3) R. A. Hoffman and S. Gronowitz, *Arkiv Kemi*, **16**, 563 (1960).

(4) G. S. Reddy and J. H. Goldstein, *J. Am. Chem. Soc.*, **84**, 583 (1962).

(5) K. Tori and T. Nakagawa, *J. Phys. Chem.*, **68**, 3113 (1964).

(6) T. E. Page, T. Alger, and D. M. Grant, *J. Am. Chem. Soc.*, **87**, 5333 (1965).

number of five-membered nitrogen heterocycles, furan, thiophene, and selenophene, and some of their methyl derivatives.

Experimental Section

All samples except selenophene, 1,2,3-triazole, and tetrazole were obtained from commercial sources and used without further purification. A sample of selenophene was kindly provided by Professor J. H. Goldstein. Tetrazole was prepared from dicyandiamide and hydrazoic acid;[7,8] 1,2,3-triazole was synthesized by the reaction of acetylene with hydrazoic acid.[9]

The liquid samples were diluted about 10% with acetone to provide an internal proton reference. Spectra of solid samples were taken of saturated solutions in acetone, with the exception of tetrazole, which because of its insolubility in acetone was examined as a saturated solution in dimethyl sulfoxide. Proton spectra were taken with a Varian A-60A spectrometer and ^{13}C spectra with the previously described[10] Varian DFS-60 spectrometer. During heteronuclear decoupling experiments, the field of the DFS-60 was locked to an external water sample. The decoupler consisted of a Hewlett-Packard 5100–5110A frequency synthesizer, a Boonton 230A power amplifier, and a Daven RF attenuation network. Long-range, carbon–proton coupling constants which were determined during double-resonance experiments should be taken as lower limits to the true values. Theoretical spectra were calculated using the computer program LAOCOON II[11] and plotted using a Calcomp plotter.

Results and Discussion

The ^{13}C chemical shifts and couplings for the five-membered nitrogen heterocycles are summarized in Table I. The long-range, carbon–proton coupling constants for pyrrole, furan, thiophene, and selenophene are given in Table II, and Table III 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 I and III) and trial-and-error calculations (Table II). 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 chemical shifts of furan and thiophene agreed with those reported earlier.[6] The carbon resonances of selenophene relative to CS_2 were found to occur at +62.3 ppm (α) and 63.6 ppm (β).

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

Compound	Carbon	Chemical[a] shift	J_{CH-2}[b]	J_{CH-3}[b]	J_{CH-4}[b]	J_{CH-5}[b]
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 parts per million upfield from carbon disulfide. [b] In hertz. [c] The average of these values is 7.6 Hz.

Table II. Long-Range, Carbon–Proton Coupling Constants in the Monosubstituted Five-Membered Heterocycles

Compound	Posn	J_{CH-2}[a]	J_{CH-3}[a]	J_{CH-4}[a]	J_{CH-5}[a]
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 hertz. [b] The average of these values is 7.6 Hz.

Table III. Long-Range, Carbon–Proton Coupling Constants in Some Methyl-Substituted Heterocycles

Compound	Posn	J_{CH-2}[a]	J_{CH-3}[a]	J_{CH-4}[a]	J_{CH-5}[a]
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 hertz. [b] J_{CNH} = 3.3 Hz. [c] J_{CCNH} = 7.1 Ha. [d] The average of these two coupling constants is 6.7 Hz.

The ^{13}C spectra of the polyaza 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.

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 nonzero ^{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).[12] 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 dis-

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(7) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1088 (1950).

(8) R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, **76**, 290 (1954).

(9) R. H. Wiley, K. F. Hussing, and J. Moffat, *J. Org. Chem.*, **21**, 190 (1956).

(10) F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.*, **89**, 2967 (1967).

(11) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964).

(12) In this, and the following descriptions of the multiplicity of the observed patterns, the primary splitting due to the large one-bond, carbon–proton couplings will not be included.

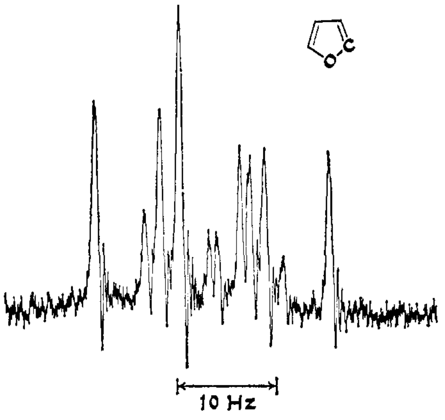

Figure 1. Natural abundance ^{13}C spectrum of the α carbon of furan showing the downfield half, time averaged for 400 scans.

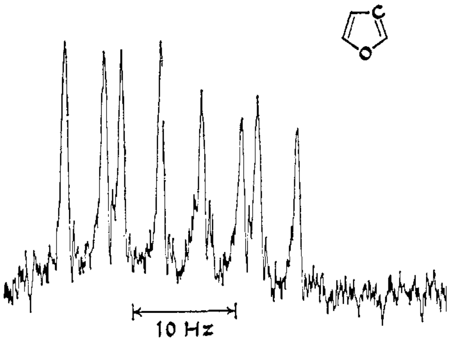

Figure 2. Natural abundance ^{13}C spectrum of the β carbon of furan showing the downfield half, time averaged for 400 scans. The upfield portions of the ^{13}C spectra of the α and β carbons of furan are mirror images of the downfield halves and are not shown.

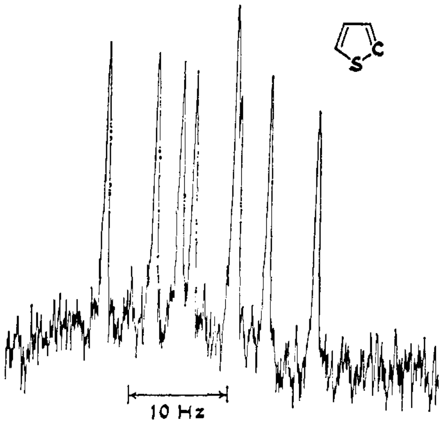

Figure 3. Natural abundance ^{13}C spectrum of the α carbon of thiophene showing the upfield half, time averaged for 150 scans.

appears leaving a triplet of doublets, conclusively showing that $J_{CCNH} = 7.8$ 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 ($J = 7.6$ 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 ($J = 7.1$ Hz) of doublets ($J = 4.6$ 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 1-6. 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.[6] As a result it was not possible to assign the individual transitions to their proper carbon until the spectrum had been completely analyzed using the resolved halves. The spectra calculated using the parameters given in Table II agree quite well with the observed spectra.

The assignments of the long-range coupling constants in Table II 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[13] on the differences between some of the long-range, carbon-proton coupling constants as obtained

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(13) J. M. Read, Jr., C. T. Mathis, and J. H. Goldstein, *Spectrochim. Acta*, **21**, 85 (1965).

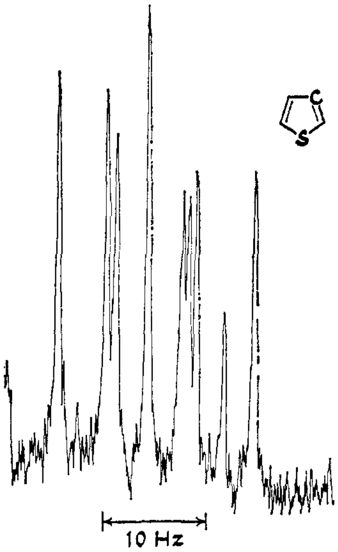


Figure 4. Natural abundance ^{13}C spectrum of the β carbon of thiophene showing the upfield half, time averaged for 150 scans. The downfield portions of the ^{13}C spectra of the α and β carbons of thiophene are badly overlapped and are not shown.

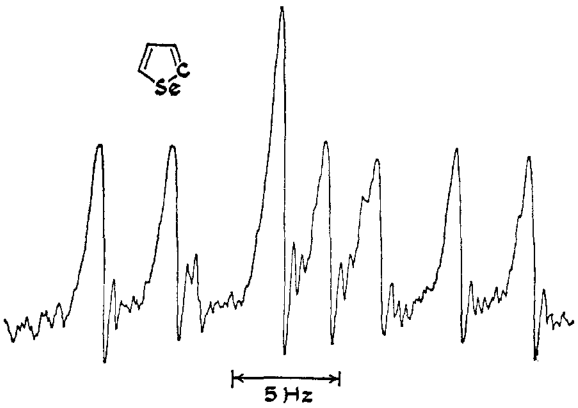


Figure 5. Natural abundance ^{13}C spectrum of the α carbon of selenophene showing the downfield half, time averaged for 400 scans.

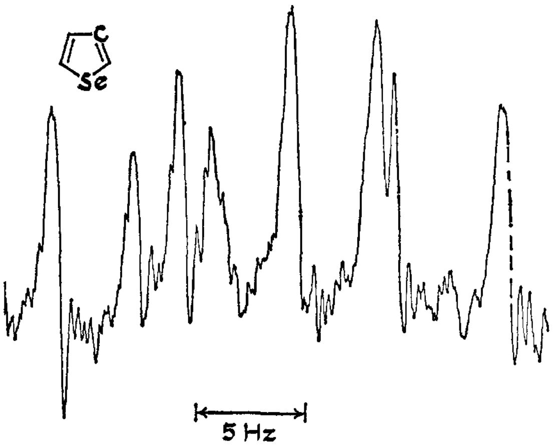


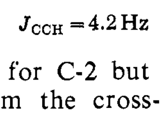
Figure 6. Natural abundance ^{13}C spectrum of the β carbon of selenophene showing the downfield half, time averaged for 400 scans. The upfield portions of the ^{13}C spectra of the α and β carbons of selenophene are badly overlapped and are not shown.

by analysis of the ^{13}C satellites of the proton spectra of the parent compounds. Other evidence was provided by spectra of methyl-substituted derivatives.

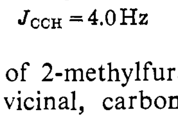
The resonances of the three proton-substituted carbon atoms of the monomethylthiophenes are first order. Goldstein[13] has reported differences between the carbon–proton coupling constants involving the β carbon of thiophene itself as follows: $J_{\text{C-3,H-4}} - J_{\text{C-3,H-2}} \approx 1$ Hz; $J_{\text{C-3,H-5}} - J_{\text{C-3,H-4}} \approx 4$ Hz. For C-3 of 2-methylthiophene, there are two possible assignments of the long-range, carbon–proton coupling constants, $J_{\text{C-3,H-5}} = 8.2$ Hz and $J_{\text{C-3,H-4}} = 5.8$ Hz; $J_{\text{C-3,H-4}} = 8.2$ Hz and $J_{\text{C-3,H-5}} = 5.8$ 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 $J_{\text{C-4,H-3}} = 5.55$ Hz and $J_{\text{C-4,H-5}} = 3.8$ Hz or $J_{\text{C-4,H-3}} = 3.8$ Hz and $J_{\text{C-4,H-5}} = 5.55$ Hz only the first again is consistent with the difference data. Govil[14] has recently determined some long-range, carbon–proton coupling constants in 2-bromothiophene by homonuclear tickling techniques. The magnitudes of the reported couplings are in good agreement with those in the parent compound (Table II) 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 compound 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 II it can be seen that the long-range, carbon–proton coupling constants involving C-2 also fit Goldstein's difference data: $J_{\text{C-2,H-4}} - J_{\text{C-2,H-3}} \approx 3.0$ Hz; $J_{\text{C-2,H-4}} - J_{\text{C-2,H-5}} \approx 6.0$ 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 coupling constants to the "other" β proton. The coupling constants involving the α carbon which

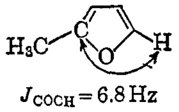


$J_{\text{CCH}} = 4.2$ Hz



$J_{\text{CCH}} = 4.0$ Hz

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



$J_{\text{COCH}} = 6.8$ Hz

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(14) G. Govil, *J. Chem. Soc., A*, 1420 (1967).

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

The chemical shifts of the carbon in nitrogen heterocycles are definitely influenced by the number and positions of the nitrogens. The carbons not connected to nitrogen generally come into resonance at higher fields than those connected to a single nitrogen, which in turn give resonances at higher fields than those carbons flanked by two nitrogens. However, exceptions are known and a four-parameter empirical equation is necessary to describe adequately the variations of the chemical shifts of the nitrogen heterocycles, with tetrazole still remaining anomalous: $\delta_C = N_\alpha C_\alpha + N_\beta C_\beta + N_{\alpha\beta} C_{\alpha\beta} + N_{\beta\beta} C_{\beta\beta}$. Here, δ_C is the chemical-shift difference between a particular carbon atom in the nitrogen heterocycle and the cyclopentadienate anion,[15] the N's represent how many times a particular nitrogen structural feature occurs in the molecule relative to the carbon of interest, while the C's are the chemical-shift increments associated with the structural features. The values for N are taken from the simplest situation in which they occur. Thus for C-2 of pyrrole, $N_\alpha = 1$ and $N_\beta = N_{\alpha\beta} = N_{\beta\beta} = 0$. The results of this calculation are given in Table IV.

Table IV. Correlation of ^{13}C Chemical Shifts in the Five-Membered Nitrogen Heterocycles

Compound	Carbon	N_α	N_β	$N_{\alpha\beta}$	$N_{\beta\beta}$	$\delta_{calcd}{}^{a,b}$	$\delta_{obsd}{}^{a}$
Pyrrole	2	1	0	0	0	−15	−15
	3	0	1	0	0	−4	−4
Pyrazole	3	1	1	1	0	−29	−29
	4	0	2	0	1	−1	-1
Imidazole	2	2	0	0	0	−30	−32
	4	1	1	0	0	−19	−18
1,2,3-Triazole		1	2	1	1	−26	−27
1,2,4-Triazole		2	1	1	0	−44	−44
Tetrazole		2	2	2	1	−51	−41

[a] Chemical shifts are in parts per million upfield from the cyclopentadienate anion[13] (negative values indicate shifts to lower field). [b] Calculated on the basis that $C_\alpha = -15$ ppm, $C_\beta = -4$ ppm, $C_{\alpha\beta} = -10$ ppm, and $C_{\beta\beta} = +7$ ppm.

There are two ways of taking into account the final nitrogen in tetrazole on the basis of the two isomeric triazoles. In general, a second β nitrogen causes a 3-ppm upfield shift (a β effect plus a β–β pairwise interaction). This effect is seen in correlating 1,2,4-triazole with tetrazole. The anomaly seems to be in the other viewpoint. Introduction of an α nitrogen when there is already an adjacent β nitrogen generally causes a 25-ppm downfield shift (an α effect and an α–β pairwise interaction) as seen in the correlation of C-2 of pyrrole with C-3 of pyrazole, of C-4 of pyrazole with 1,2,3-triazole, and of C-4 of imidazole with 1,2,4-triazole. Tetrazole does not follow this trend. The reasons for this are not understood.

Laszlo[16] has shown that for selected compounds the increment in the one-bond coupling J_{C-H} associated with replacing an α carbon by nitrogen is +23 Hz. This relationship works reasonably well for a number of the polyaza 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 the 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.

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 polyaza 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,[17] but in substituted ethylenes some carbon–proton coupling constants are negative.[17] 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 are shown in Figure 7. 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 substituent effects of the other ring atoms. The magnitudes and signs of the carbon–proton coupling constants in benzene have been previously explained in similar terms.[10] The ideal model compounds would be monosubstituted ethylenes in which the substituents are identical with 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 of the carbon–proton coupling constants are known, and whose substituent has an electronegativity close to that of oxygen or nitrogen, is vinyl bromide.[18] Compared with the geminal carbon–proton coupling constant of −2.4 Hz for ethylene[19] the observed geminal carbon–proton coupling constants in vinyl bromide provide evidence for a positive sign for geminal carbon–proton coupling

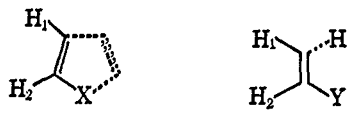

Figure 7.

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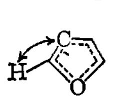
Figure 8.

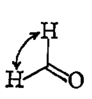
Figure 9.

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 (Figure 8). The geminal carbon–proton coupling constants of *cis*-dibromo- and *cis*-dichloroethylene are both large and positive[14,17] and of similar magnitudes to those for 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 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, $J_{\mathrm{CH}} = 0.4J_{\mathrm{HH}}$.[20] The coupling constants $J_{\mathrm{C\text{-}2,H\text{-}3}}$ and $J_{\mathrm{C\text{-}2,H\text{-}4}}$ in monosubstituted heterocycles seem to be independent of the nature of the heteroatom. The coupling constants $J_{\mathrm{C\text{-}3,H\text{-}2}}$ show the same variation to substituent as the corresponding carbon–proton couplings in monosubstituted ethylenes. The magnitude of $J_{\mathrm{C\text{-}3,H\text{-}2}}$ in furan is possibly reminiscent of the large geminal proton–proton coupling in formaldehyde.[21] The





vicinal coupling $J_{\mathrm{C\text{-}3,H\text{-}5}}$ follows the electronegativity trends of the *trans* proton–proton coupling constants in substituted ethylenes as shown in Figure 9.[22] 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 $J_{\mathrm{C\text{-}2,H\text{-}5}}$ with substituent groups seem to depend on the size of the intervening heteroatom, much as the vicinal carbon–proton coupling across the metal atom in the tetramethyl derivatives of group IV.[23]

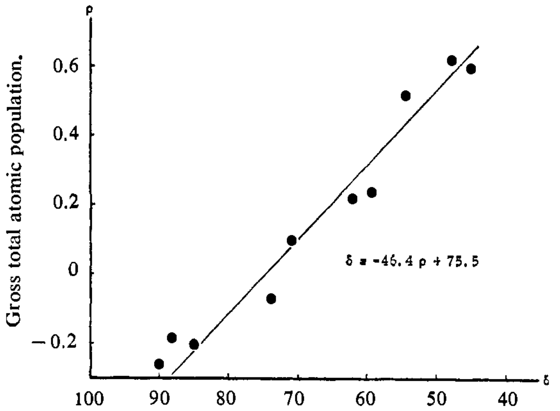


Figure 10. Correlation of total gross atomic populations and ^{13}C chemical shifts for the five-membered nitrogen heterocycles.

Extended Hückel[24] calculations have been performed on some of the heterocycles studied here by Adam, Grimison, and Rodriguez.[25] These workers found that the chemical shifts of some of these heterocycles and their protonated derivatives could be correlated by the relationship

$$\delta = (60 \text{ ppm/electron}) \times \text{charge density}$$

These computations have now been extended to the remaining members of the series, and using the same wave functions, the various carbon–proton coupling constants were calculated. Using the Pople–Santry formalism only the Fermi contact term of the coupling constant was evaluated.[26] The average energy approximation was not invoked in these calculations. 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. 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.[24]

In agreement with Adam, Grimison, and Rodriguez[25] there seems to be a definite correlation between the gross atomic populations and the ^{13}C chemical shifts as shown in Figure 10. There is a similar correlation between the populations of the carbon 2p$_z$ orbital and the chemical shifts (Figure 11). The slopes of these correlations are different, and neither agrees with the 160 ppm/electron observed by Spiesecke and Schneider[15] for various charged aromatic species. This failing is common in Hückel calculations which do not include some self-consistent field treatment in that the charge separation is greatly exaggerated. It is interesting that the charge polarization of the σ framework is calculated to be in the same direction as that of the π system, and is roughly of the same magnitude.

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Bloor and Breen[27] have calculated wave functions for some of the heterocycles studied in the present research by the CNDO/2 method of Pople and Segal.[28] Rather good correlation was found between the ^{13}C chemical shifts and the total charge densities, but not between the chemical shifts and π-electron densities in contrast to the results shown in Figure 10.

The nmr spin-spin coupling constants calculated by the extended Hückel treatment are best characterized as unsatisfactory. 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 I 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.[29] 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 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.

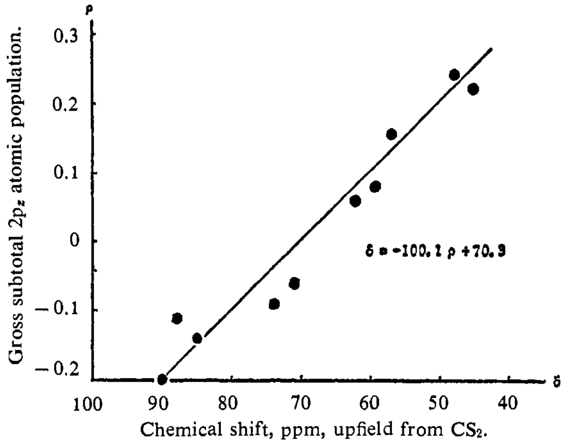

Figure 11. Correlation of calculated gross subtotal $2p_z$ atomic population with ^{13}C chemical shifts for the five-membered nitrogen heterocycles.

The extended Hückel theory does not seem to work well for these compounds as regards predicting of nmr spin-spin coupling constants.

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Conformation of Small Peptides. II. Synthesis and Infrared Studies of Small Peptides[1]

James E. Shields,[2] Samuel T. McDowell,[3] John Pavlos,[4] and Gerald R. Gray[5]

Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106.

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Abstract: The synthesis of several protected peptides containing L-valine, L-alanine, L-isoleucine, L-leucine, and glycine are reported. The absorbance in the N–H stretching region of the infrared spectrum was determined as a function of concentration in deuteriochloroform. Some tetra-, penta-, and hexapeptides show intramolecular hydrogen bonds in this solvent. Evidence was found for the occurrence of the folded β conformation in the tetrapeptide BOC-L-alanyl-L-valyl-L-alanyl-L-valine methyl ester.

In recent years increased interest has arisen in the conformation or *short-range*[6] properties of peptides. This work has been confined, in the greater part, to polymers of essentially infinite length. Since most proteins have relatively short helical segments, more information on equivalent peptides is required. It seems that caution should be exercised in attempting to extrapolate observations of the behavior of high homopolymers to short segments of varied sequences. Goodman and coworkers[7] studied the optical rotatory properties of oligopeptides of γ-methyl-L-glutamate and L-alanine and concluded that secondary structure first occurred in pentapeptides. They interpreted their results as the end-to-end hydrogen bonding of small helical segments at the pentapeptide with progressively greater helical behavior until this property maximized at the nonapeptide and longer chain lengths. However, as pointed out by Schellman,[8] the conformation

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[1] Part I has already appeared as a preliminary communication: J. E. Shields and S. T. McDowell, *J. Amer. Chem. Soc.*, **89**, 2499 (1967).

[2] Address inquiries to The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind. 46206.

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[4] National Science Foundation Summer Research Participant for College Teachers, 1967.

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