Carbon-13 Nuclear Magnetic Resonance Spectra of Uracil, Thymine, and the 5-Halouracils

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Abstract: First-order ^{13}C spectra have been obtained for uracil, thymine, and the 5-halouracils. The ^{13}C chemical shifts in these compounds are correlated reasonably well with π and total electron charge densities calculated with extended-Hückel theory (EHT). In addition, for the 5-halouracils the ^{13}C chemical shifts are correlated quite well with substituent electronegativity, E_X. Substituent effects are discussed for the directly bonded and long-range ^{13}C–H couplings, and correlations are obtained between these couplings and E_X for the halogens. Without exception, three-bond ^{13}C–H couplings are found to be larger than the two-bond couplings for this series of compounds.

Uracil, a major constituent of ribonucleic acid (RNA), and thymine, a naturally occurring heterocyclic base of deoxyribonucleic acid (DNA), have been the subjects of previous proton nmr investigations.[2-5] Also, the 5-halouracils, particularly 5-fluorouracil, which have shown mutagenic, antiviral, and antineoplastic properties,[6-8] have been studied by proton nmr.[4,5,8] However, as yet no complete ^{13}C nmr studies have appeared for this biologically important series of compounds. Because of the experimental difficulties involved, very few long-range ^{13}C–H coupling values are available for any nitrogen heterocyclic molecules.[9,10]

Recent studies of the carbon framework in nitrogen heterocycles by proton-noise-decoupled ^{13}C nmr have proven very valuable.[11-14] In addition, ^{13}C chemical shift studies have now been reported for naturally occurring nucleotides[15] and nucleosides.[16-18] Theory and substituent effects for ^{13}C chemical shifts in aromatic molecules have been presented.[19-22] Recently, ^{13}C chemical shifts have been correlated with carbon electron charge densities calculated by various molecular orbital methods.[17,23,24] Furthermore, one study has attempted to relate electron charge densities in nucleotide bases, including monosubstituted uracils, to anticarcinogenic activity of the compounds.[25]

In the present study, complete first-order ^{13}C spectral data are presented for uracil, thymine, and the 5-halouracils. The ^{13}C chemical shifts are correlated with substituent electronegativity, E_x, for the 5-halouracils, and general correlations are presented here between the ^{13}C chemical shifts and electron charge densities calculated using extended-Hückel theory (EHT). The long-range ^{13}C–H coupling values are discussed, and the substituent effects on ^{13}C–H coupling in the 5-halouracils are related to E_x.

Experimental Section

All compounds used in this study were the commercially available materials requiring no further purification, as shown by their physical properties and nmr spectra. Dimethyl sulfoxide, which has been used extensively by other workers[17] as a solvent for similar compounds, was found to be the only suitable solvent for all compounds studied here. The commercially available DMSO was further purified and dried according to the methods of Reddy.[26] Samples were thus prepared and sealed in 13-mm tubes, under dry nitrogen, as saturated solutions in DMSO. 5-Fluorouracil was the most soluble member of the series at approximately 20 mol %. Saturated solutions of thymine and 5-iodouracil were less than 5 mol %. CS_2, 10% by volume in DMSO, was used as an external reference.

All ^{13}C nmr spectra were obtained in the frequency-sweep mode with a Bruker Scientific HFX-90 spectrometer operating at 22.62 MHz. Since proton noise decoupling was not employed and the complete ^{13}C spectrum was obtained in all cases, it was necessary to accumulate the spectra for up to 12 hr with a Fabri-Tek 1074 signal-averaging system. Proton stabilization on the methyl resonance of DMSO was used in all cases. All chemical shifts were measured using a sweep width of 1 Hz/cm and a sweep rate of 1.5 Hz/sec. Under these conditions it is estimated that the absolute chemical shifts are good to approximately 2.0 Hz or 0.1 ppm, but the uniform conditions employed make the relative chemical shifts internally very consistent, to at least 0.5 Hz or 0.025 ppm. The coupling values are estimated to be good to within 0.1 Hz.

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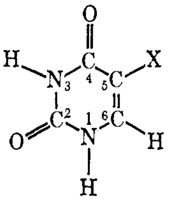
Table I. ^{13}C Chemical Shifts for Uracil, Thymine, and 5-Halouracils[a]



1

X	Carbon positions			
	2	4	5	6
H	921.2;[b] (40.76);[c] [−24.24][d]	639.7; (28.30); [−36.70]	2092.8; (92.60); [+27.60]	1141.8; (50.52); [−14.48]
CH_3	933.6; (41.31); [−23.69]	630.4; (27.90); [−37.10]	1923.8; (85.12); [+20.10]	1245.2; (55.10); [−9.90]
F	964.2; (42.66); [−22.34]	787.2; (34.83); [−30.17]	1195.7; (52.91); [−12.09]	1501.3; (66.43); [+1.43]
Cl	952.3; (42.14); [−22.86]	741.4; (32.81); [−32.19]	1963.1; (86.86); [+21.86]	1198.9; (53.05); [−11.95]
Br	947.8; (41.94); [−23.06]	738.4; (32.67); [−32.33]	2223.8; (98.40); [+33.40]	1143.2; (50.59); [−14.41]
I	937.0; (41.46); [−23.54]	705.5; (31.22); [−33.78]	2830.5; (125.24); [+60.24]	1033.5; (45.73); [−19.27]

[a] Numbering of positions is shown in **1**. [b] Values are given in hertz upfield from external CS_2 at 22.62 MHz. [c] Values in parentheses are in parts per million upfield from external CS_2. [d] Values in brackets are given in parts per million and have been converted to the benzene scale as in ref 17. Positive values indicate higher field.

Calculations

Extended-Hückel theory (EHT) is an LCAO–MO method developed by Hoffmann[27] which simultaneously calculates σ and π electron distributions. In EHT the basis set for the linear combination of atomic orbitals, $\Psi_i = \Sigma_j C_{ij}\phi_j$, is extended to include all valence-shell atomic orbitals. In the case of uracil, for instance, the 1s Slater orbitals for hydrogen and 2s and three 2p Slater orbitals for carbon and nitrogen are used. The 3d and 4d orbitals for bromine and iodine, respectively, were not included in these calculations. Minimization of the total energy, in the Hückel approximation of the total Hamiltonian as a sum of one-electron effective Hamiltonians, gives the secular determinant

$$\det(H_{ij} - ES_{ij}) = 0$$

where i and j go from 1 to n through the total number of valence atomic orbitals. All overlap integrals S_{ij} are retained and are taken from standard sources.[28] The exchange integrals H_{ij} are computed from the approximation

$$H_{ij} = 0.5K(H_{ii} + H_{jj})S_{ij}$$

where $K = 1.75$.[27] The values of the Coulomb integrals H_{ii} are the appropriate valence-state ionization potentials, taken from Pritchard and Skinner[29] and from the tables of Hinze and Jaffé.[30,31] A Mulliken population analysis[32] yields the σ and π electron charge densities. A computer program[33] was used for carrying out these EHT calculations.

The geometry for uracil was taken from the work of Parry.[34] The C–X bond distances for the substituted uracils were approximated by using the corresponding lengths in monosubstituted benzenes.

Results

Table I gives ^{13}C chemical shifts for uracil, thymine, and the 5-halouracils; the structure and numbering of the carbon positions are as indicated in **1**. All chemical shifts are expressed in hertz upfield from external CS_2, in parts per million upfield from external CS_2, and, for comparison with other literature data,[17] in parts per million relative to benzene. ^{13}C–H and ^{13}C–F coupling values for uracil, thymine, and the 5-halouracils, according to the numbering scheme given in **2**, are shown in Table II. For J_{13} in uracil, thymine, and 5-iodouracil it was not possible to observe the value of the coupling directly. However, line broadening in these cases relative to the line widths observed for other comparable resonances indicates that coupling is present and, under the experimental conditions employed, must be less than 1 Hz. Table III presents the π and total ($\sigma + \pi$) electron charge densities for substituted uracils calculated according to the previously described EHT (numbering is indicated in **3**). For comparison, SCF π electron charge densities for this series of compounds[25] are given in parentheses. Further comparisons of π electron charge densities for uracil and thymine calculated by various MO methods are available.[17]

Discussion

In Figure 1 the complete ^{13}C nmr spectrum of 5-fluorouracil is shown. Also shown is a narrow-range 1-Hz/cm spectrum of the indicated resonance and the subsequent first-order splitting pattern observed for 5-fluorouracil. The ^{13}C spectra for all members of this series proved to be first order, and thus all coupling values are shown as positive since their absolute signs cannot be determined. The chemical shifts for the various carbon atoms were not difficult to assign. Substitution at position 5, analogy with ^{13}C shifts for similar compounds,[10,13,35,36] the coupling values available from the spectra, and noticeable broadening of the carbonyl resonance between the two nitrogens were all helpful in making the assignments.

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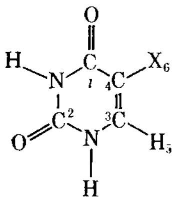
Table II. ^{13}C–H and ^{13}C–F Coupling Values[a] for Uracil, Thymine, and 5-Halouracils[b]

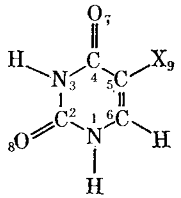


2

X	J_{15}	J_{16}	J_{25}	J_{26}	J_{35}	J_{36}	J_{45}	J_{46}
H	10.9	2.0	9.2	d	180.5	4.1	<1[e]	176.5
CH_3	9.2	3.9[c]	9.2		177.8	5.6[b]	<1[e]	
F	6.7	25.7	9.1	d	182.0	31.7	4.2	227.3
Cl	7.7		9.2		184.0		2.3	
Br	8.5		9.4		184.7		1.8	
I	9.0		8.6		184.5		<1[e]	

[a] All values in hertz. [b] Numbering is shown in **2**. [c] Refers to the coupling between the carbon designated and the protons of $-CH_3$. [d] No coupling observed within experimental error. [e] Line broadening indicates presence of coupling which under the experimental conditions used appears to be less than 1 Hz.

Table III. π and Total Electron Charge Densities in Substituted Uracils as Calculated Using Extended-Hückel Theory[a]



3

X	Atom Positions																	
	1		2		3		4		5		6		7		8		9	
	π	$\sigma + \pi$	π	$\sigma + \pi$	π	$\sigma + \pi$	π	$\sigma + \pi$	π	$\sigma + \pi$	π	$\sigma + \pi$	π	$\sigma + \pi$	π	$\sigma + \pi$	π	$\sigma + \pi$
H	1.4914 (1.898)	5.2224	0.5947 (0.728)	2.6442	1.5378 (1.900)	5.3199	0.6358 (0.754)	2.8677	1.1417 (1.033)	4.2834	0.7938 (0.940)	3.6837	1.9059 (1.368)	7.4269	1.8989 (1.379)	7.4032		
CH_3	1.5006 (1.897)	5.2291	0.6640 (0.728)	2.7134	1.5338 (1.898)	5.3130	0.6616 (0.755)	2.9057	1.0529 (1.046)	3.8915	0.9953 (0.921)	3.8918	1.9067 (1.370)	7.4170	1.9056 (1.380)	7.4100	1.7796	4.9096
F	1.4954 (1.900)	5.2168	0.6124 (0.728)	2.6619	1.5354 (1.898)	5.3111	0.6609 (0.757)	2.9028	1.0484 (1.014)	3.3887	0.8590 (0.977)	3.7598	1.9075 (1.373)	7.4279	1.9008 (1.382)	7.4052	1.9801 (1.971)	7.6614
Cl	1.4963 (1.899)	5.2244	0.6224 (0.728)	2.6719	1.5342 (1.898)	5.3146	0.6644 (0.755)	2.9059	1.0439 (1.032)	3.8003	0.8873 (0.953)	3.7878	1.9074 (1.373)	7.4280	1.9074 (1.382)	7.4280	1.9018 (1.980)	7.4062
Br	1.4964 (1.898)	5.2271	0.6279 (0.728)	2.6774	1.5341 (1.898)	5.3160	0.6607 (0.755)	2.8985	1.0580 (1.039)	3.9739	0.8975 (0.935)	3.7956	1.9070 (1.372)	7.4281	1.9023 (1.381)	7.4067	1.9162 (1.994)	7.0086
I	1.4958 (1.898)	5.2304	0.6311 (0.728)	2.6806	1.5341 (1.899)	5.3178	0.6579 (0.755)	2.8898	1.0575 (1.041)	4.1638	0.9000 (0.928)	3.7962	1.9066 (1.372)	7.4280	1.9025 (1.381)	7.4069	1.9147 (1.999)	6.8177

[a] Numbering is shown in **3**. The values in parentheses are SCF π electron charge densities given by Ladik and Biczó (ref 25).

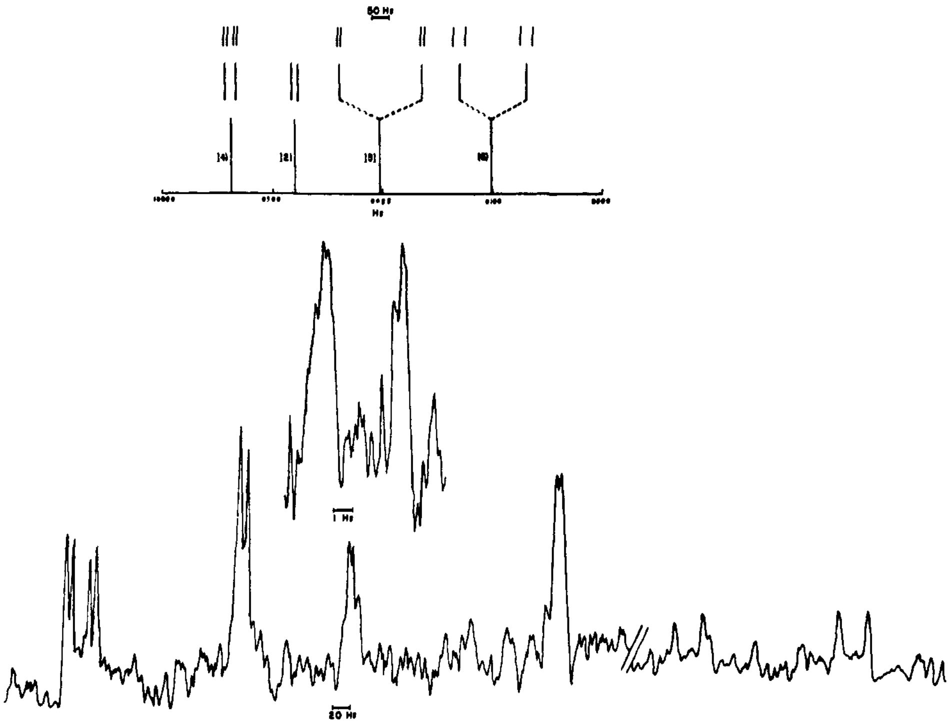


Figure 1. (Lower) The complete ^{13}C nmr spectrum of 5-fluorouracil taken at 20 Hz/cm including a narrow-range (1 Hz/cm) spectrum shown above the corresponding resonance at 20 Hz/cm. (Upper) A stick plot of the first-order splitting pattern observed for 5-fluorouracil.

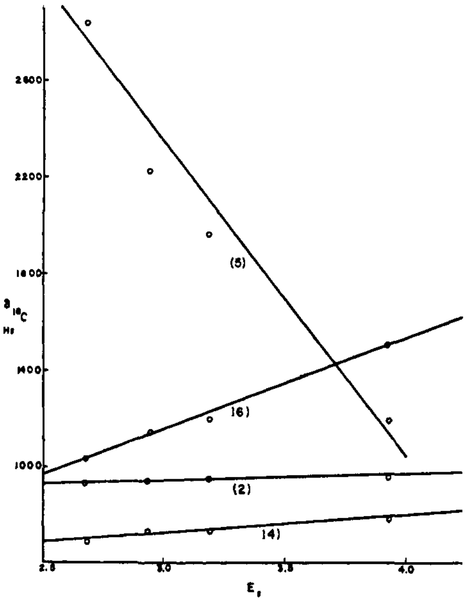


Figure 2. Plot of the ^{13}C chemical shift at the indicated carbon position *vs.* substituent electronegativity, E_X, for the 5-halouracils.

In Figure 2 the chemical shifts observed for the 5-halouracils at each carbon position are plotted against the substituent electronegativity, E_X, values of Shoolery and Dailey.[37] Not surprisingly, C_5, which is directly bonded to the substituent, shows the greatest substituent effect, $\delta(^{13}C)$ decreasing with increasing electronegativity of the substituent. At position C_6, two bonds from the substituent, the substituent effect is somewhat diminished relative to that of carbon-5 and, in addition, $\delta(^{13}C)$ is now observed to increase linearly with increasing E_X. C_4 is also two bonds from the substituent but shows much smaller substituent effect than that observed at C_6, suggesting the importance of the double bond between C_5 and C_6 in transmitting the substituent effect. Again, at C_4, $\delta(^{13}C)$ increases linearly with increasing E_X. At C_2, four bonds from the substituent, the effect of X is very small, but $\delta(^{13}C)$ is observed to increase slightly with increasing substituent electronegativity. It is unfortunate that a carbon three bonds from the substituent is not available in this series to further test these correlations. This same alternating pattern of substituent effects with E_X has been noted in the proton nmr shifts of monohalobenzenes[38] and halobiphenyls.[39]

Recently, Jones, *et al.*,[17] have presented correlations between $\delta(^{13}C)$ and π electron charge densities, calculated by various MO methods, for naturally occurring nucleosides. In Figure 3A are shown the chemical shifts for the compounds of the present series plotted against π electron charge densities calculated by EHT. The scatter in this plot definitely leaves something to be desired, but the correlation does conform approximately to the empirical (160 ppm/electron) relationship proposed by Spiesecke and Schneider.[40] It also appears that parallel lines may be drawn roughly through the set of points for C_2 and C_5 as well as through those for C_4 and C_6. It seems reasonable that C_4 and C_6 should behave similarly since they are both two bonds removed from the substituent, but it is not clear why C_2 and C_5 should correlate together. The points for C_5 and C_6 in 5-fluorouracil are anomalous with respect to these correlations.

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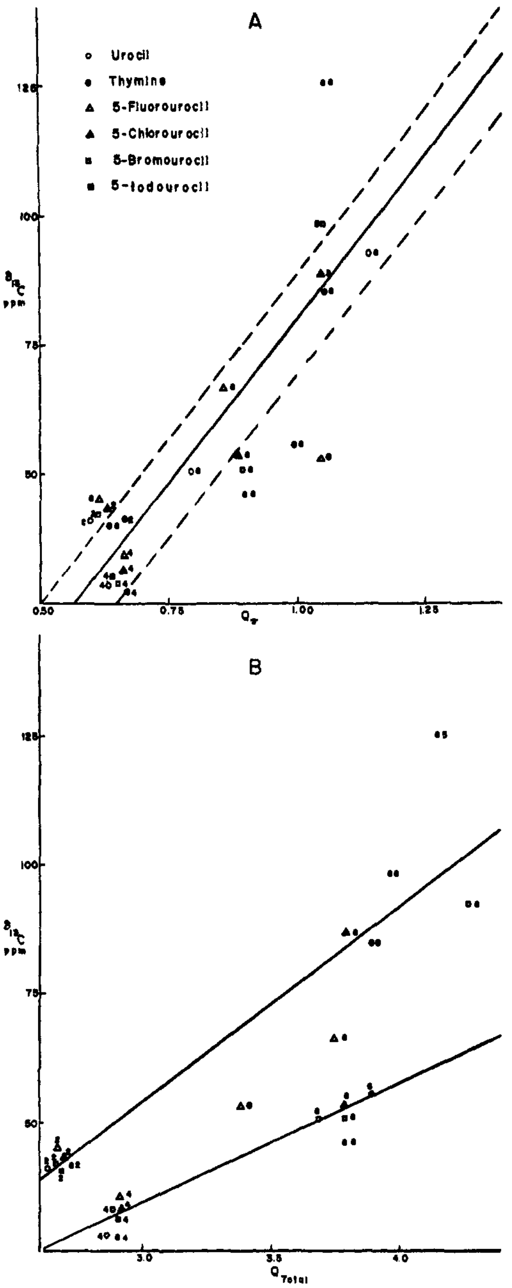

Figure 3. (A) Plot of ^{13}C chemical shifts at the designated carbon positions for the indicated compounds *vs.* the carbon π-electron charge density calculated from EHT. (B) Plot of the ^{13}C chemical shifts at the designated carbon positions for the indicated compounds *vs.* the carbon total electron charge density calculated from EHT.

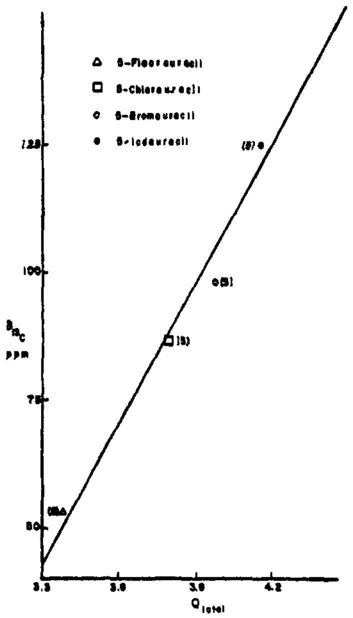

Figure 4. Plot of the ^{13}C chemical shifts at C_5 *vs.* the total electron charge density calculated from EHT at C_5 in 5-halouracils.

Adam, *et al.*,[24] have shown for a series of nitrogen heterocycles (some protonated) that correlation of ^{13}C chemical shifts with total electron charge density is more reliable than correlation with π electron charge density alone. Bloor[23] has arrived at similar conclusions using CNDO/2 calculations. Following these results, the ^{13}C chemical shifts of all carbons in the present series of compounds were plotted against the total electron charge densities calculated from EHT, and the results are shown in Figure 3B. The correlation for all carbons in all compounds is really not improved over that obtained with π electron charge density alone. However, if the C_2 and C_5 pair and the C_4 and C_6 pair are considered separately then these correlations are somewhat improved over the π charge correlations. It is interesting to note that the chemical shifts for C_5 and C_6 in 5-fluorouracil fall between the two correlation lines. Also, the slopes of the correlation lines are not in very good agreement with those reported elsewhere[24] for five- and six-membered ring heterocycles using total electron charge density.

Total electron charge density as calculated from EHT does not account very well for ^{13}C shifts in the 5-halouracils except at C_5. For this position the linear correlation is shown in Figure 4. For the other carbon atoms, as pointed out by Jones, *et al.*,[17] other factors such as variation in bond order[41-43] and average excitation energy terms[44] may be important.

For hydrocarbons the values of the bonded ^{13}C–H coupling constants, J_{CH}, are proportional to the fractional s character of the carbon orbital bonding to the H atom. Substitution of electronegative X for H on the same carbon atom invariably increases J_{CH}.[45-48] This effect may be attributed to two principal causes: rehybridization (increased p participation) of the C orbital to produce the strongest possible bond to X, and the effect of decreased shielding at the C atom on the Z^3 dependence of the Fermi-contact term.[49] In the vinyl halides these two sources essentially account rather well even for the J_{CH} values for the C–H bonds β to the halogen substituent, provided that mesomeric structures are taken into account.[50] In the series C_2H_3X, the cis-β couplings range from 159.2 to 164.1 Hz for

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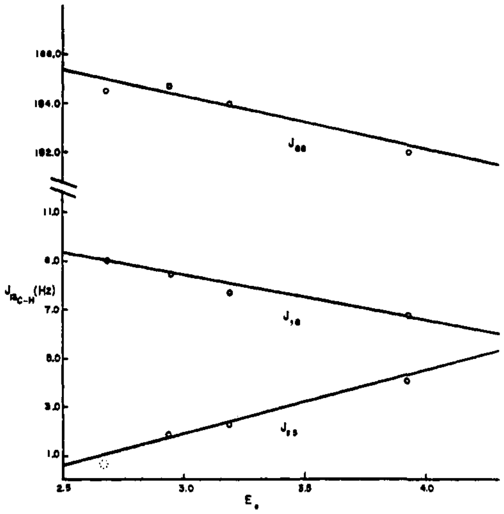

Figure 5. Plots of the indicated $J_{^{13}C-H}$ coupling values (numbering as in **2**) in 5-halouracils *vs.* substituent electronegativity, E_X.

X = F through I,[51] and about the same range and order is observed in the 5-halouracils (182.0–185.5, as shown in Table II). Relative to unsubstituted ethylene and uracil, respectively, the overall effect on the $^{13}C_3$–H_5 coupling (numbering as in **2**) produced by the halogens is very similar. From these observations it can be inferred that both the inductive and mesomeric effects produced by the halogens at C_3 (numbering as in **2**) are reasonably similar in the ethylenes and the uracils. In thymine the reduction of J_{35} by ~3 Hz relative to uracil is in accord with previously reported methyl substituent effects.[52]

Shown in Figure 5 are plots of $J_{^{13}C-H}$ (numbering as in **2**) against substituent electronegativity, E_X, for the 5-halouracils. J_{25}, a three-bond coupling, is not shown in Figure 5 because the carbon in question is four bonds removed from the substituent and thus the changes in the coupling with substituent are relatively not very large. J_{35} is a one-bond coupling and is observed to decrease with increasing E_X. J_{15} is a two-bond coupling and increases in value with increasing E_X. J_{15}, a three-bond coupling, again decreases with increasing E_X for the halogens, as does the one-bond coupling. These trends are somewhat reminiscent of those observed for protons in substituted benzenes,[53] and the alternating pattern of slopes with the even and odd numbers of bonds parallels that observed in the present study for the ^{13}C shifts.

As shown in Table II, the two-bond couplings J_{36} and J_{45} in uracil have quite different values, indicating the influence of the nitrogen heteroatom on C_3 (numbering as in **2**). Also, the one-bond couplings J_{46} and J_{35} are quite different in uracil, again demonstrating the effect of the nitrogen at C_3. In 5-fluorouracil, the two-bond coupling J_{36} is considerably larger than the two-bond coupling J_{16}, indicating either the effects of conjugation or again the effect of the nitrogen on C_3. The ^{13}C–fluorine couplings observed here for 5-fluorouracil are in general agreement with comparable values in substituted fluorobenzene.[54]

It has been noted before that three-bond ^{13}C–H couplings are larger in magnitude than two-bond couplings,[55–60] though exceptions have been observed.[58] In the present study, without exception, it is observed that three-bond couplings are larger in magnitude than are the two-bond couplings. However, compared to four-bond coupling values observed in substituted benzenes,[59,60] it seems very surprising that there is no J_{26} coupling observed for uracil and particularly for 5-fluorouracil.

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