An Experimental Study of Carbon-13 Isotope Effects on Proton Nuclear Magnetic Resonance Chemical Shifts

Jeremy R. Everett *
Beecham Pharmaceuticals Research Division, Brockham Park, Betchworth, Surrey RH3 7AJ

Small negative, one-bond, carbon-13 isotope effects on proton n.m.r. chemical shifts, *i.e.* ${}^1\Delta{}^1H({}^{13}C)$ values have been measured for a variety of compounds. A linear correlation between ${}^1\Delta{}^1\Delta H({}^{13}C)$ and ${}^1J_{CH}$ was discovered. Three compounds with short C–H bonds were found to deviate from the correlation. The behaviour of ${}^1\Delta{}^1H({}^{13}C)$ was compared with that of ${}^1\Delta{}^{19}F({}^{13}C)$ and ${}^1\Delta{}^{13}C({}^2H)$.

Carbon-13 isotope effects (Δs) on n.m.r. signals were first recognised in ${}^{19}F$ n.m.r. spectra in 1959.[1] Since that time numerous reports of both one-bond [${}^1\Delta{}^{19}F({}^{13}C)$] and two-bond effects [${}^2\Delta{}^{19}F({}^{13}C)$] in ${}^{19}F$ n.m.r. spectra have appeared.[2–8] The situation was reviewed in 1967.[9] One bond ${}^{13}C$ isotope effects have also been found in the n.m.r. spectra of a variety of other nuclei. These nuclei include ${}^{59}Co$,[10,11] ${}^{77}Se$,[12,13] ${}^{125}Te$,[12,13] ${}^{13}C$,[14–22] ${}^{31}P$,[16,23] ${}^{113}Cd$,[24] ${}^{111}Cd$,[24] ${}^{199}Hg$,[25,26] and ${}^{15}N$.[27] Carbon-13 isotope effects in ${}^1H$ n.m.r. spectra were first reported in 1960[28] and since that time many other reports have appeared.[29–39]

Most ${}^{13}C$ Δs are small and upfield but there are a number of exceptions to this generalisation. The few reported ${}^1\Delta{}^{113}Cd({}^{13}C)$, ${}^1\Delta{}^{111}Cd({}^{13}C)$, and ${}^1\Delta{}^{199}Hg({}^{13}C)$ values [24–26] have all been downfield. Downfield ${}^1\Delta{}^{13}C({}^{13}C)$ and ${}^2\Delta{}^{13}C({}^{13}C)$ values have also been reported[17,21,22] when the *observed* carbon atom is substituted by an oxygen atom. The magnitude of the ${}^{13}C$ isotope effect over one bond varies widely with the observed nucleus. The smallest ${}^1\Delta$s are ${}^1\Delta{}^1H({}^{13}C)$ values which vary from 0 to -3 p.p.b. By contrast ${}^1\Delta{}^{77}Se({}^{13}C)$ values have been reported to range between -12 and $-1\,099$ p.p.b. As a consequence of their small magnitude no systematic and precise study of ${}^1\Delta{}^1H({}^{13}C)$ has been reported to date. In this work a large number of organic compounds have been studied in order to obtain more precise ${}^1\Delta{}^1H({}^{13}C)$ values for protons attached to *sp*^{3} carbon atoms.

Table. ${}^1J_{CH}$ and ${}^1\Delta{}^1H({}^{13}C)$ values

Compound	${}^1J_{CH}$ Hz	${}^1\Delta{}^1H({}^{13}C)$ (p.p.b.)
$CHCl_3$	210.09	−2.28
	210.06 ± 0.01[a]	−2.35 ± 0.02
$CHBr_3$	205.73	−2.42
CH_2Cl_2	177.82	−2.56
	178.00 ± 0.02[a]	−2.6 ± 0.6
$CHDCl_2$	177.58	−2.73
	177.91 ± 0.02[a,b]	−2.85 ± 0.03
CH_2I_2	172.64	−2.91
Cl_3CCH_2OH	151.44	−2.01
CH_3I	150.95	−1.99
	151.114 ± 0.004[a]	−2.13 ± 0.05
CH_3OCOCl	149.81	−2.13
CH_3NO_2	145.85	−1.85
CH_3SO_2Cl	142.83	−1.99
CH_3OD	140.80	−1.76
	140.52 ± 0.04[a]	−1.98 ± 0.04
CH_3OH	140.77 ± 0.12	−1.79 ± 0.33
$(CH_3)_2SO$	137.17	−1.67
CH_3CN	135.95	−1.24
	135.94 ± 0.01[a]	−1.92 ± 0.13
CH_3COCl	132.77	−1.60
CH_3CO_2H	129.34	−1.55
$(CH_3)_2CO$	126.61	−1.18
	126.74 ± 0.02[a,c]	−1.5 ± 0.2
$(CH_3)_4Si$	118.11	−0.54
	118.14 ± 0.06[a]	−0.94 ± 0.12

[a] WM-250 instrument. [b] ${}^2J_{HD}$ *ca.* 1.09 ± 0.01. [c] ${}^4J_{H,H}$ 0.55 ± 0.01.

Results

The Table gives all the experimental ${}^1\Delta{}^1H({}^{13}C)$ and ${}^1J_{CH}$ values for the compounds studied.

Experimental

All the compounds are commercially available and were used without further purification as 5M solutions in C_6D_6. The ${}^1H$ n.m.r. spectra were taken at ambient temperature, in 5 mm tubes, at 200 MHz on a Varian XL-200 or at 250 MHz on a Brüker WM-250 instrument. The WM-250 experiments were conducted with a sweep width of 250—400 Hz. 16—1 300 scans were accumulated into 4 K of computer memory. The F.I.D.s were zero-filled to 16 or 32 K prior to line broadening of up to 0.1 Hz and Fourier transformation. Each experiment was repeated between eight and 17 times and the results were averaged. The errors given are $\pm 2\sigma$ where σ is the standard deviation.

The XL-200 experiments were conducted with a sweep width of 300—600 Hz. The acquisition time was 8 s except for $CHDCl_2$ (2 s). The f.i.d.s were acquired in double precision (32 bit words) and were zero filled to 16 K prior to Fourier transformation using floating point mathematics. The number of scans was 32 except for $CHCl_3$ (16) and $CHDCl_2$ (4 300, measured as impurity in CD_2Cl_2). Each experiment was repeated five times except for $CHCl_3$, CH_3CO_2H, and CH_3OD (10 times) and the results were averaged. The experiment on CH_3OH was repeated 30 times in order to establish meaningful error limits. The errors on all the XL-200 results were then taken to be plus and minus twice the standard deviation found in the CH_3OH experiments. These error limits are thought to be generous.

Discussion

Figure 1 shows the experimental ${}^1\Delta{}^1H({}^{13}C)$ values plotted as a function of ${}^1J_{CH}$ for each molecule studied. With the exception of the data for $CHCl_3$, $CHBr_3$, and CH_2Cl_2 it was found that a linear correlation existed between ${}^1\Delta{}^1H({}^{13}C)$ and ${}^1J_{CH}$. This relationship is described by equation (1). The correlation

$$ {}^1\Delta{}^1H({}^{13}C) = 3.35 - 3.64 \times 10^{-2}.{}^1J_{CH} \text{ p.p.b.} \quad (1) $$

coefficient for the 19 data points in the regression was -0.93 (valid at $>99.9\%$ confidence level). This correlation has an interesting parallel in the work of Frankiss,[6,8,9] who discovered

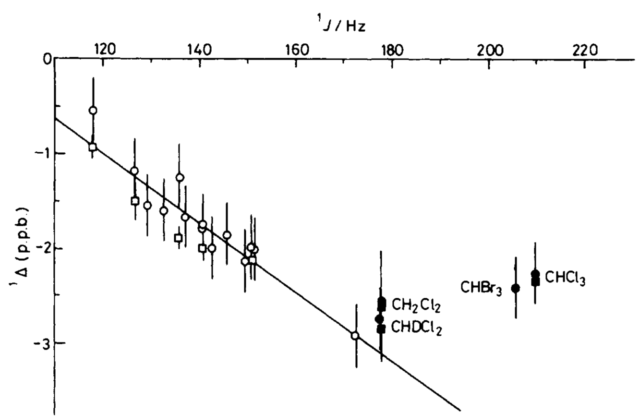

Figure 1. $^1\Delta^1H(^{13}C)$ (p.p.b.) *versus* $^1J_{CH}$ Hz. ○, XL-200 instrument; □, WM-250 instrument

a similar correlation between $^1\Delta^{19}F$ (^{13}C) and $^1J_{CF}$ for both sp^3 C–F and sp^2 C–F bonds. The equation for sp^3 C–F bonds was (2). The magnitudes of $^1J_{CF}$ and $^1J_{CH}$ reflect both the

$$^1\Delta^{19}F\,(^{13}C) = -(7 + 0.436\,^1J_{CF})\text{ p.p.b.} \qquad (2)$$

hybridisation and the electron distribution of the C–F and C–H bonds respectively. The fact that $^1\Delta$ correlates with ^1J may indicate that these two factors are also important in determining the magnitude of $^1\Delta$.

As stated above, the points for CH_2Cl_2, $CHCl_3$, and $CHBr_3$ fall above the plotted line and show a *positive* deviation from equation (1). It may be significant that these three compounds have the shortest C–H bond lengths of any of the compounds studied. Sutton[40] gives these bond lengths as *ca.* 1.07 Å, whereas the majority of the other compounds studied have C–H bond lengths between 1.09 and 1.10 Å. The C–H bond length in CH_2I_2 could not be discovered. Another interesting parallel with the work of Frankiss[6,8] now presents itself. In this latter work *negative* deviations (−40 to −20 p.p.b.) from the plot of $^1\Delta^{19}F$ (^{13}C) *versus* $^1J_{CF}$ were seen for CF_2Cl_2, $CFHCl_2$, $CFCl_3$, and $CFBr_3$. Three of these four compounds have longer C–F bonds (*ca.* 1.40—1.44 Å)[40] than the majority of the other compounds studied (*ca.* 1.32—1.36 Å) although CF_2Cl_2 seems to have a normal C–F bond length (*ca.* 1.34 Å). Thus, in *this* work polyhalogenation (halogen = Cl or Br), with the accompanying shortening of C–H bonds, leads to a positive deviation from the $^1\Delta^1H(^{13}C)$ *versus* $^1J_{CH}$ correlation. By contrast, in the work of Frankiss,[6,8] polyhalogenation, with the accompanying lengthening of C–F bonds, lead to a negative deviation from the $^1\Delta^{19}F(^{13}C)$ *versus* $^1J_{CF}$ correlation. The positive deviation of $(CF_3)_2Hg$ from the correlation of $^1\Delta$ with $^1J_{CF}$ may be due to hybridisation changes at the carbon atoms.

Direct plots of $^1\Delta^1H(^{13}C)$ against r(C–H) or $^1\Delta^{19}F(^{13}C)$ against r(C–F) gave scattered plots but this may have been due to the inaccuracy of some of the bond length data. Recent work in other systems has shown up relationships between $^1\Delta$ and bond length. Gombler[13] found $^1\Delta^{77}Se(^{13}C)$ to be inversely dependent upon $r(sp^3$C–Se) but directly dependent upon $r(sp^2$C=Se) in two small groups of compounds. This result may be compared with an inverse dependence of $^1\Delta^{13}C(^{18}O)$ upon r(C=O), found[41] in a series of acetophenones.

The results for $^1\Delta^1H(^{13}C)$ may also be compared with those previously found for $^1\Delta^{13}C(^2H)$. $^1\Delta^{13}C(^2H)$ values are *ca.* two orders of magnitude larger than $^1\Delta^1H(^{13}C)$ values and a much larger body of literature exists. However, much of the literature data is imprecise[42] and must be viewed with caution. Figure 2 shows a graph of a collection of literature $^1\Delta^{13}C(^2H)$ values against $^1J_{CH}$. Although the data sp^3 carbon atoms is quite scattered, a positive correlation of $^1\Delta$ with ^1J can just be discerned [correlation coefficient 0.42 (>99% confidence) for 43 selected, higher accuracy points, excluding $CHCl_3$, $CHBr_3$, and CH_2Cl_2]. This has been reported previously[43] but for a limited set of four cycloalkanes. Figure 2 shows that the effect is more general. The data for sp^2 carbons is rather less scattered and shows a positive correlation of $^1\Delta$ with ^1J according to equation (3). The correlation coefficient for 26 points was 0.72

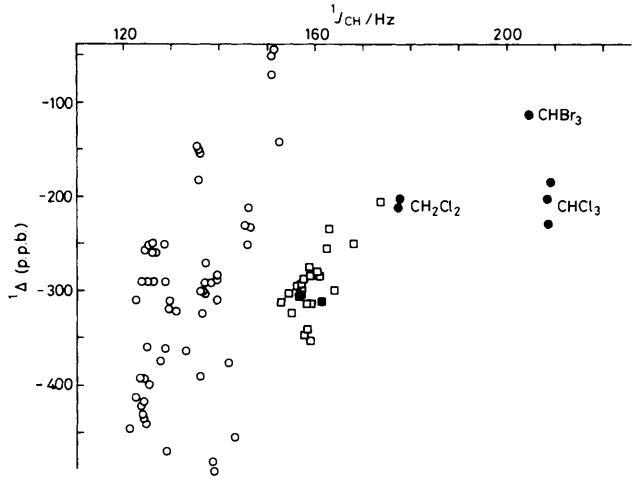

Figure 2. $^1\Delta^{13}C(^2H)$ (p.p.b.) *versus* $^1J_{CH}$ Hz for sp^3 (○) and sp^2 (□) hybridised carbon atoms. The solid square is the data point for cyclopropane

$$^1\Delta = 5.92\,^1J_{CH} - 1\,240\text{ p.p.b.} \qquad (3)$$

(>99.9% confidence). The line for the sp^2 carbons is displaced towards larger $^1J_{CH}$ relative to the crude line for sp^3 carbons and again this is analogous to the behaviour found by Frankiss in his correlations of $^1\Delta^{19}F(^{13}C)$ against $^1J_{CF}$. It is also clear from Figure 2 that the points for CH_2Cl_2, $CHCl_3$, and $CHBr_3$ deviate markedly from the other sp^3 points. It is proposed here that these differences in behaviour may be due to bond length differences in the molecules concerned. It has already been mentioned that r(C–H) in CH_2Cl_2, $CHCl_3$, and $CHBr_3$ is shorter than r(C–H) in any of the other sp^3 hybridised molecules. The marked deviation of the data points for CH_2Cl_2 in Figure 2 was taken as additional support for treating the CH_2Cl_2 and $CHDCl_2$ data points in Figure 1 as deviant when in fact they are borderline.

Finally, the opposed variation of $^1\Delta^1H(^{13}C)$ and $^1\Delta^{13}C(^2H)$ with ^1J has been briefly commented on previously[44] but no explanation has been advanced.

Conclusions

A correlation has been shown to exist between $^1\Delta^1H(^{13}C)$ and $^1J_{CH}$. Compounds with unusually short C–H bond lengths were found to deviate from this correlation. Analogous behaviour was found for $^1\Delta^{19}F(^{13}C)$ and $^1\Delta^{13}C(^2H)$ upon examination of the literature $^1\Delta$ values.

Acknowledgements

I am indebted to Professors A. S. Perkin and A. Shaver for support and encouragement during my stay at McGill University, Montreal.

References

1 G. V. D. Tiers, *J. Phys. Soc. Jpn.*, 1960, **15**, 354.
2 G. V. D. Tiers, *J. Chem. Phys.*, 1961, **35**, 2263.
3 G. V. D. Tiers, *J. Phys. Chem.*, 1962, **66**, 945.
4 G. V. D. Tiers and P. C. Lauterbur, *J. Chem. Phys.*, 1962, **36**, 1110.
5 N. Muller and D. T. Carr, *J. Phys. Chem.*, 1963, **67**, 112.
6 S. G. Frankiss, *J. Phys. Chem.*, 1963, **67**, 752.
7 J. Bacon and R. J. Gillespie, *J. Chem. Phys.*, 1963, **38**, 781.
8 R. K. Harris, *J. Mol. Spectrosc.*, 1963, **10**, 309.
9 H. Batiz-Hernandez and R. A. Bernheim, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1967, **3**, 63.
10 P. C. Lauterbur, *J. Chem. Phys.*, 1965, **42**, 799.
11 A. Loewenstein and M. Shporer, *Mol. Phys.*, 1965, **9**, 293.
12 G. Pfisterer and H. Dreeskamp, *Ber. Bunsenges. Phys. Chem.*, 1969, **73**, 654.
13 W. Gombler, *J. Am. Chem. Soc.*, 1982, **104**, 6616.
14 F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.*, 1972, **94**, 6021.
15 P. S. Nielsen, R. S. Hansen, and H. J. Jakobsen, *J. Organomet. Chem.*, 1976, **114**, 145.
16 R. Paasonen, J. Enqist, M. Karhu, E. Rahkamaa, M. Sundberg, and R. Uggla, *Org. Magn. Reson.*, 1978, **11**, 42.
17 J. Jokisaari, *Org. Magn. Reson.*, 1978, **11**, 157.
18 V. Wray, L. Ernst, T. Lund, and H. J. Jakobsen, *J. Magn. Reson.*, 1980, **40**, 55.
19 H. Booth and J. R. Everett, *Can. J. Chem.*, 1980, **58**, 2709.
20 P. E. Hansen and J. J. Led, *Org. Magn. Reson.*, 1981, **15**, 288.
21 M. Stöcker, *J. Chem. Res.* (*S*), 1982, 124.
22 M. Stöcker, *Org. Magn. Reson.*, 1982, **20**, 175.
23 P. S. Pregosin and R. Kunz, *Helv. Chim. Acta*, 1975, **58**, 423.
24 J. Jokisaari, K. Räisänen, L. Lajunen, A. Passoja, and P. Pyykkö, *J. Magn. Reson.*, 1978, **31**, 121.
25 J. Jokisaari and K. Räisänen, *Mol. Phys.*, 1978, **36**, 113.
26 K. Grishin and Y. A. Ustynyuk, *Zh. Strukt. Khim.*, 1982, **23**, 163.
27 R. E. Wasylishen, *Can. J. Chem.*, 1982, **60**, 2194.
28 J. N. Shoolery, L. F. Johnson, and W. A. Anderson, *J. Mol. Spectrosc.*, 1960, **5**, 110.
29 H. Dreeskamp and E. Sackmann, *Z. Phys. Chem.*, 1961, **27**, 136.
30 J. M. Read, R. E. Mayo, and J. H. Goldstein, *J. Mol. Spectrosc.*, 1967, **22**, 419.
31 J. M. Read, R. W. Crecely, and J. H. Goldstein, *J. Mol. Spectrosc.*, 1968, **25**, 107.
32 E. W. Garbisch and M. G. Griffith, *J. Am. Chem. Soc.*, 1968, **90**, 6543.
33 H. Jensen and K. Schaumberg, *Mol. Phys.*, 1971, **22**, 1041.
34 G. Schrumpf, *Chem. Ber.*, 1973, **106**, 246.
35 G. Schrumpf, G. Becher, and W. Lüttke, *J. Magn. Reson.*, 1973, **10**, 90.
36 J. M. A. Al-Rawi, J. A. Elvidge, J. R. Jones, and E. A. Evans, *J. Chem. Soc., Perkin Trans. 2*, 1975, **449**.
37 V. A. Chertkov and N. M. Sergeyev, *J. Am. Chem. Soc.*, 1977, **99**, 6750.
38 P. Diehl and H. Bösiger, *J. Magn. Reson.*, 1979, **35**, 367.
39 J. Runsink and H. Günther, *Org. Magn. Reson.*, 1980, **13**, 249.
40 L. E. Sutton, 'Tables of Interatomic Distances and Configuration in Molecules and Ions,' Special Publications, Nos. 11 and 18, The Chemical Society, London, 1958 and 1965.
41 J. M. Risley, S. A. DeFrees, and R. L. Van Etten, *Org. Magn. Reson.*, 1983, **21**, 28.
42 J. R. Everett, *Org. Magn. Reson.*, 1982, **19**, 169.
43 R. Aydin and H. Günther, *J. Am. Chem. Soc.*, 1981, **103**, 1301.
44 Y. K. Griskin, N. M. Sergeyev, and Y. A. Ustynyuk, *Mol. Phys.*, 1971, **22**, 711.

Received 7th July 1983; *Paper* 3/1165