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Chapter 1

THE DYNAMIC AND ELECTRONIC FACTORS IN ISOTOPE EFFECTS ON NMR PARAMETERS

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CONTENTS

INTRODUCTION

The other chapters in this volume involve observation of the NMR nucleus (such as ^2H, ^3H, or ^{13}C) which itself is the isotopic label. In this chapter we consider the mass effects of the isotopic label on the chemical shifts and coupling constants of the neighboring resonant nuclei, a secondary isotope effect. We also consider the mass effect on the reduced coupling constants when one of the coupled nuclei is the isotopic label, a primary isotope effect.

The physical picture is a simple one: When a heavier isotope replaces an atom in a molecule its effects are felt by every resonant NMR nucleus in the molecule because the changed mass causes changes in the rovibrational averaging of all electronic properties of the molecule. In particular, the chemical shift of each resonant nucleus and the spin-spin coupling between it and other nuclei are affected to a larger or smaller extent dependent on its location in the molecule relative to the site of the perturbation (mass change). What this means in a practical sense is that we can use the isotope effects on these electronic quantities as a way of arriving at the location (structure-wise) of the mass-label. All resonant nuclei linked to the label site by some efficient electronic transmission path will report on its location, providing a multiplicity of useful information. There are obvious applications of this to the determination of mechanisms of reactions.

There are two important factors affecting the magnitudes and signs of these isotope effects. One, the dynamic factor, has to do with the slight change in the rovibrationally-averaged geometry of the molecule upon substitution of an atom by a heavier isotope; the dynamic average bond lengths tend to become shorter. The other, an electronic factor, has to do with the sensitivity of the chemical shift or of the coupling constant to a change in molecular geometry. The dynamic factor depends on the potential energy surface of the molecule. Anharmonic bond stretching plays an important role in the mass-dependence of the mean bond length. On the other hand, the electronic factor depends on the chemical shift range of the resonant nucleus, which itself is a measure of the sensitivity of the nuclear magnetic shielding to molecular structure. The electronic factor depends on the electronic transmission pathway leading from the site of the isotopic substitution to the site of the resonant nucleus.

II. ISOTOPE EFFECTS ON CHEMICAL SHIFTS

NMR isotope shifts are useful in that, where an isotopic label is introduced, every neighboring resonant nucleus experiences a slight chemical shift. If labeling is less than 100%, the resonant nuclei in both the labeled and the unlabeled molecules are observed, with intensities according to statistical distribution, and positions dependent on the electronic and dynamic factors. The magnitude of the shift depends on the fractional change in mass at the substitution site, on the remoteness of the resonant nucleus from the substitution site and on the sensitivity of the nuclear magnetic shielding to bond lengthening at the substitution site. Every resonant nucleus in the isotopically labeled molecule experiences this isotope shift but the shift is only observable under favorable conditions such as when it is larger than the half-width of the peaks.

We consider in the following sections the intrinsic isotope shifts. That is, except for Sect. IIF, we limit our discussions to those observations in which the distinct isotopomers are intact molecules, non-exchanging, or at least the exchange (of ^{2}D for ^{1}H for example) is slow compared to the characteristic NMR time, the reciprocal of the isotope shift in Hertz. The shifts are observed in the same sample rather than two samples containing isotopically different solvents. Charged molecular species, in which the isotopomers have slightly different first sphere and second sphere solvation cages or form intramolecular or intermolecular hydrogen bonds, may have solvent effects which could obscure the true nature of the intrinsic isotope shifts when the latter are small. H_2O and D_2O have slightly different liquid structures due to differential hydrogen-bonding strengths. The isotopic solvent effect could be important when the observed nucleus is in a charged molecular species.

Isotope shifts depend on molecular structure since both the dynamic and electronic factors are dependent on structure. This observable is a convolution of electronic and dynamic terms of various orders of magnitude, all of which are specific to the molecule. Viewed in this light the quantitative interpretation or prediction of isotope shifts is molecule-specific and becomes extremely difficult for large molecules. However, there are several empirical trends which provide interesting insights into the separation of the electronic and dynamic factors.[1,2]

(A) General trends and some examples

The large body of data on isotope shifts have been collected and reviewed.[3-6] There are several general observations which have been made about magnitudes and signs of isotope shifts:

(1) Upon substitution with a heavier isotope the NMR signal of the nearby nucleus usually shifts towards lower frequencies (higher shielding). An example is shown in FIGURE 1. This trend is fairly general, although there are exceptions.

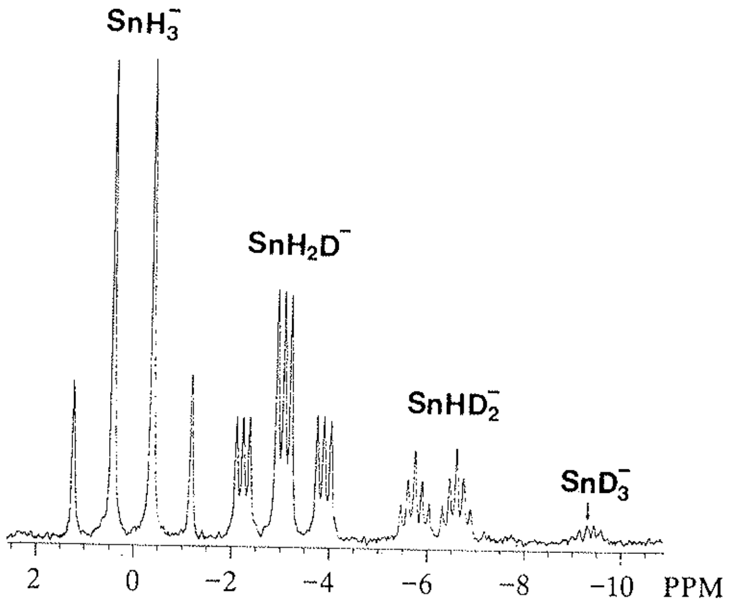
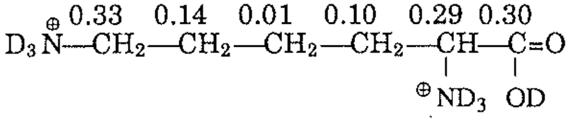


Fig. 1. Tin-119 NMR spectrum of $SnH_{3-n}D_n^-$ at -50°C in liquid ammonia, reproduced with permission from R.E. Wasylishen and N. Burford, *Can. J. Chem.*, 65 (1987) 2707.[7]

Among one-bond shifts, ^{13}C-induced ^{113}Cd and ^{199}Hg shifts in $M(CH_3)_2$,[8] and in fact all known ^{199} Hg isotope shifts, are of unusual sign.[9] Among 2-bond shifts the D-induced ^{13}C isotope shifts in the H-C-^{13}C⊕, H-C-^{13}C=O, H-C-^{13}C=S fragments are of unusual sign. So are the 3-bond D-induced ^{19}F shifts in the  $\text{H—}\overset{\overset{\text{F}}{|}}{\text{C}}\text{—C=O}$ fragment and the ^{17}O shift in the H-C-C=^{17}O fragment. Longer-range isotope shifts can be of unusual sign, and in some cases a continuum of values negative through positive have been observed in related molecules,[10] as shown in the examples in FIGURE 2.

(2) The magnitude of the isotope shift is dependent on how remote the isotopic substitution is from the observed nucleus. Although there are exceptions, one-bond isotope shifts are larger than two-bond or three-bond isotope shifts. An example is shown below [11]



$$\mathrm{D_3\overset{\oplus}{N}-\overset{0.33}{CH_2}-\overset{0.14}{CH_2}-\overset{0.01}{CH_2}-\overset{0.10}{CH_2}-\underset{{}^{\oplus}ND_3}{\overset{0.29}{CH}}-\underset{OD}{\overset{0.30}{C}}=O}$$

where the magnitudes of the D-induced ^{13}C shifts (in ppm) are indicated over each observed carbon. In para-difluorobenzene the ^{13}C- induced ^{19}F shifts are -0.090, -0.026, -0.005, and -0.005 ppm for ^{13}C substitution, one, two, 3, and 4 bonds away from the observed ^{19}F.[12]

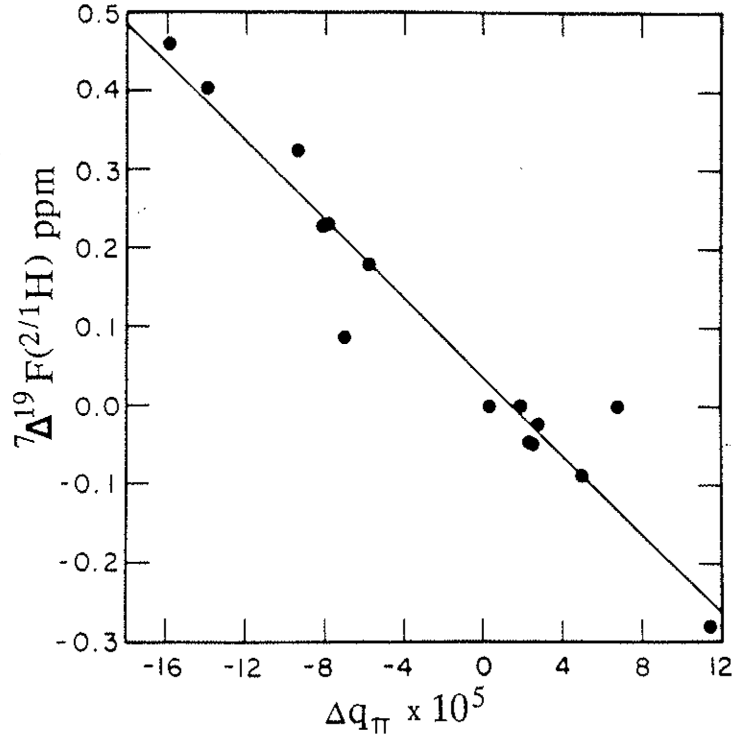


Fig. 2. The D-induced ^{19}F shift $^7\Delta^{19}F(^{2/1}H)$ in 4-fluorophenyl species vs. the change in pi electron density at fluorine induced by C-H bond shortening in MNDO calculations, reproduced with permission from D. A. Forsyth and J. R. Yang, *J. Am. Chem. Soc.*, 108 (1986) 2151.[10] Copyright 1986 American Chemical Society.

(3) The magnitude of the shift is a function of the observed nucleus and reflects its chemical shift range. In analogous molecules the isotope shifts very roughly scale as the chemical shift ranges of the observed nucleus: e.g., ^{31}P in PH_3 (-0.85 ppm per D) [13] compared to ^{15}N in NH_3 (-0.623 ppm per D) [14], ^{77}Se in H_2Se (-7.04 ppm per D) [15]

compared to ^{17}O in H_2O (-1.55 ppm per D) [14], and even in the case of the ^{13}C- induced ^{199}Hg and ^{113}Cd shifts in Me_2Hg (+0.4 ppm per ^{13}C) and Me_2Cd (+0.14 ppm per ^{13}C) [8] where the isotope shifts are of unusual sign.

(4) The magnitude of the shift is related to the fractional change in mass upon isotopic substitution. For a given resonant nucleus the largest shifts are induced by D or T substitution for H. For example, the one-bond ^{51}V shifts induced by $^{2/1}H$ and $^{13/12}C$ substitution in the $[CpVH(CO)_3]^-$ ion are respectively -4.7 ppm per D and -0.51 ppm per ^{13}C.[16]

(5) The magnitude of the shift is approximately proportional to the number of equivalent atoms which have been substituted by isotopes. In other words, isotope shifts exhibit additivity. This is quite evident in FIGURE 1. In $[Co(NH_3)_6]^{3+}$ complex ion in a H_2O-D_2O solvent, each of the 18 replaceable hydrogens in the complex can be H or D. Each of the 19 isotopomers (H_{18}, $H_{17}D$, ..., D_{18}) which gives rise to one ^{59}Co resonance signal can be observed in the spectra obtained in solvents of varying H : D ratios (FIGURE 3). The ^{59}Co shift relative to the H_{18} isotopomer is proportional to

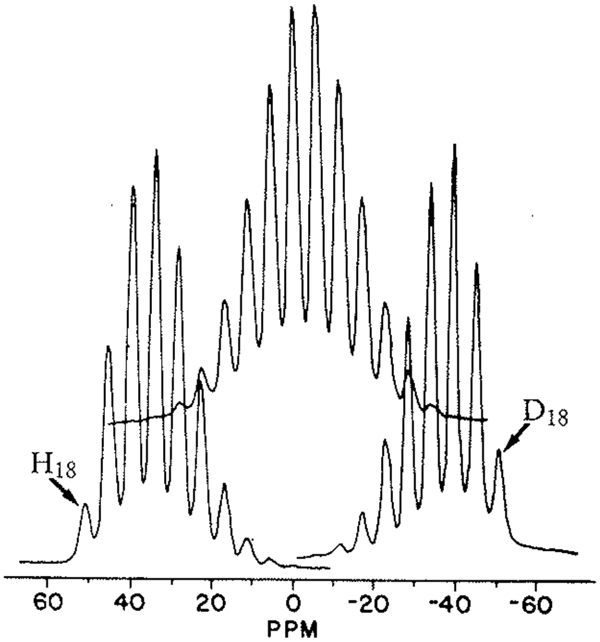


Fig. 3. The ^{59}Co NMR spectrum of $[Co(NH_3)_6]^{3+}$ ion in D_2O/H_2O solvent. The spectra, from left to right, are for 15%, 50%, 85% D_2O samples, reproduced with permission from J.G. Russell and R.G. Bryant, *Anal. Chim. Acta,* 151 (1983) 227.[17]

the number of H atoms replaced by D, so there are 19 peaks equally spaced.

These general trends have been explained by a theory based on rovibrational averaging [1,2,18] which we outline briefly in the next section. The interpretation of isotope shifts involves a consideration of the vibrational and rotational averaging of nuclear shielding. For this reason the isotope shift is intimately related to the observed temperature dependence of nuclear shielding in the gas phase in the zero-pressure limit. These two measurable properties share the same electronic factors - the change in shielding with bond extension or bond angle deformation.

(B) Rovibrational theory of isotope shifts

Nuclear magnetic shielding σ is dependent on the geometry of the molecule, and we are particularly interested in the geometries very close to the equilibrium geometry since vibration of the molecule involves only very small displacements away from this geometry. The average shielding can then be expressed as follows

$$\langle\sigma\rangle = \sigma_e + \sum_i \left(\frac{\partial\sigma}{\partial r_i}\right)_e \langle\Delta r_i\rangle + \sum_{ij} \left(\frac{\partial^2\sigma}{\partial r_i \partial r_j}\right)_e \langle\Delta r_i \Delta r_j\rangle + \sum_{ij} \left(\frac{\partial\sigma}{\partial\alpha_{ij}}\right)_e \langle\Delta\alpha_{ij}\rangle + \ldots \tag{1}$$

Isotopic substitution changes all the dynamic averages $\langle\Delta r_i\rangle$, $\langle\Delta r_i^2\rangle$, $\langle\Delta\alpha_{ij}\rangle$, etc., with the largest changes occurring in the bond displacements directly involving the substituted atom. The measured isotope shift is denoted by a symbol $^n\Delta A\ (^{m'/m}X)$ and is usually in units of ppm per $^{m'}X$ substitution, for the chemical shift of nucleus A in the isotopomer with the heavier isotope $^{m'}X$, relative to the isotopomer containing the lighter ^mX at a site n bonds away. This measured value, the isotopic chemical shift or the "isotope shift", is the difference $\langle\sigma\rangle - \langle\sigma\rangle^*$ where the * denotes the heavier isotopomer. For a one-bond isotope shift involving a group AX_n where the A-X bond in question is denoted by r_1

$$\begin{aligned}\langle\sigma\rangle - \langle\sigma^*\rangle = &\left(\frac{\partial\sigma}{\partial r_1}\right)_e [\langle\Delta r_1\rangle - \langle\Delta r_1\rangle^*] + \left(\frac{\partial^2\sigma}{\partial r_1^2}\right)_e [\langle(\Delta r_1)^2\rangle - (\Delta r_1)^2\rangle^*] \\ &+ \left(\frac{\partial\sigma}{\partial\alpha_{12}}\right)_e [\langle\Delta\alpha_{12}\rangle - \langle\Delta\alpha_{12}\rangle^*] + \ldots + \sum_{j\neq 1}\left(\frac{\partial\sigma}{\partial r_j}\right)_e [\langle\Delta r_j\rangle - \Delta r_j\rangle^*] + \ldots\end{aligned} \tag{2}$$

Δr_1 is the bond displacement at the substitution site and Δr_j are the other bond displacements. Thus, there is a primary dynamic effect which we shall denote by

$$\Delta = [\langle\Delta r_1\rangle - \langle\Delta r_1\rangle^*], \tag{3}$$

a change in the mean bond displacement at the site of substitution of ^mX by $^{m'}X$.The terms involving $\Delta\alpha_{12}$, the bond angle deformation at the substitution site, turns out to be unimportant in many cases where calculations have been carried out.[19,20] There are much smaller changes (secondary dynamic effect) in the bond lengths at sites remote from the substitution site; let us represent these smaller changes to be of magnitude δ,

$$\delta \approx [\langle\Delta r_j\rangle - \langle\Delta r_j\rangle^*] . \qquad (4)$$

A one-bond isotope shift is observed when the resonant nucleus is directly bonded to the substituted atom. In this case one type of term is much larger than the others because the nuclear magnetic shielding changes nearly linearly with bond extension at bond lengths close to the equilibrium geometry.[21-26]

$$\langle\sigma\rangle - \langle\sigma\rangle^* = (\partial\sigma/\partial r_1)_e \bullet \Delta \quad + \quad \text{smaller terms} \qquad (5)$$

The smaller terms include terms in the second and higher derivatives of nuclear shielding, terms involving bond angle deformations and derivatives of the shielding with respect to the bond angle, as well as the much smaller terms such as $(\partial\sigma/\partial r_j)\ [\langle\Delta r_j\rangle - \langle\Delta r_j\rangle^*]$, involving the shielding change due to the small secondary changes in bond length elsewhere in the molecule.

The factor $(\partial\sigma/\partial r_1)_e$ is the sensitivity of the shielding of the resonant nucleus to the lengthening of a bond to it (a primary electronic effect). The factor $(\partial\sigma/\partial r_j)_e$ may be exactly the same as $(\partial\sigma/\partial r_1)_e$, such as for ^{13}C shielding in CH_4. On the other hand, $(\partial\sigma/\partial r_j)_e$ could well be much smaller, as for ^{17}O in $^{17}O{=}C{=}^{16}O$ where r_j is the bond length involving the other oxygen. Bond angle deformation might also be important in some cases. Full calculations including the smaller terms have been carried out for diatomic molecules [21], H_2O,[19] and CH_4,[20] using ab initio theoretical values for the derivatives.[21,25,26]

Qualitatively, the mass change accompanying the replacement of ^{m}X by its heavier isotope $^{m'}X$ leads to a shorter average bond length. This happens because the potential energy surface of the molecule is an anharmonic one. Whereas the mean bond displacement, $\langle\Delta r\rangle = \langle r - r_e\rangle$, is zero for a harmonic oscillator, it is a mass-dependent non-zero value for the anharmonic oscillator. The amplitudes of motion of a lighter atom being larger than that of a heavier one, at each vibrational state the heavier isotopomer has a smaller average $\langle\Delta r\rangle$ than the lighter isotopomer. The vibrational frequencies being lower for the heavier isotopomer, the population of higher vibrational states are somewhat greater for the heavier isotopomer. Both effects constitute a mass dependence of the thermal average $\langle \Delta r \rangle$, the former being more important than the latter. Full vibrational calculations are possible for any molecule provided that enough spectroscopic constants are available to determine its potential surface, from which the quantities $\langle \Delta r_1 \rangle$, $\langle \Delta r_j \rangle$, $\langle \Delta \alpha_{12} \rangle$, $\langle (\Delta r_1)^2 \rangle$, etc., can be calculated.[18-20] For a diatomic molecule described by a Morse oscillator these vibrational averages take fairly simple forms

$$\langle \Delta r \rangle = \frac{3a}{2} \langle (\Delta r)^2 \rangle \tag{6}$$

$$\langle (\Delta r)^2 \rangle_v = 2 \left(\frac{B_e}{\omega_e} \right) r_e^2 \left(v + \frac{1}{2} \right) \tag{7}$$

where a is the Morse parameter describing the anharmonicity of the vibration. To obtain the thermal average we need to sum over all the states weighted by their populations.

If we use the harmonic oscillator density of states as an approximation, we find a very simple form for the thermal average

$$\langle v + \frac{1}{2} \rangle^T = \frac{1}{2} \coth \left(hc\omega_e / 2kT \right) \ . \tag{8}$$

Thus, for a diatomic molecule the thermal average bond extension is given by

$$\langle \Delta r \rangle \approx \frac{3a}{2} \left(\frac{B_e}{\omega_e} \right) r_e^2 \coth \left(\frac{hc\omega_e}{2kT} \right) \tag{9}$$

and the thermal average shielding is given by

$$\langle \sigma \rangle \approx \sigma_e + \left[\left(\frac{d\sigma}{dr} \right)_e + \frac{1}{3a} \left(\frac{d^2\sigma}{dr^2} \right)_e \right] \langle \Delta r \rangle \text{ or } \langle \sigma \rangle \approx \sigma_e + \left[\frac{3a}{2} \left(\frac{d\sigma}{dr} \right)_e + \frac{1}{2} \left(\frac{d^2\sigma}{dr^2} \right)_e \right] \langle (\Delta r)^2 \rangle \tag{10}$$

and the isotope shift by

$$\langle \sigma \rangle - \langle \sigma \rangle^* \approx \left[\left(\frac{d\sigma}{dr} \right)_e + \frac{1}{3a} \left(\frac{d^2\sigma}{dr^2} \right)_e \right] \{ \langle \Delta r \rangle - \langle \Delta r \rangle^* \}. \tag{11}$$

In the above expression the first quantity (in square brackets) is a mass-independent purely electronic quantity, the second quantity (in curly brackets) is a mass-dependent dynamic factor.

In polytomic molecules the analogous equation, eq. (2), has a large number of terms even when only up to second derivatives are considered, due to the many types of internal displacements Δr_i, $\Delta\alpha_{ij}$, etc. Nevertheless, the general trends noted in Sect. IIA, which are easily explained by eq. (11) for diatomic molecules, are also found for the very large body of data on polyatomic molecules. The simplicity of eq. (11) can be preserved for one-bond isotope shifts in polyatomic molecules if we consider bond extension as the dominant contributor to isotope shifts. The simple relation (eq. (6)) for Morse anharmonic oscillators permits the discussions of the dynamic factor to be cast in terms of $\langle\Delta r\rangle$ alone and the electronic factor in square brackets in eq. (11) which includes both first and second derivatives will be represented in following discussions entirely by $(\partial\sigma/\partial r)_e$.

(C) The dynamic factors

(1) Mass Dependence

For a diatomic molecule, by making use of the implicit mass dependence of its spectroscopic constants B_e and ω_e in eq. (9), one can express the dynamic factors $[\langle\Delta r\rangle - \langle\Delta r\rangle^*]$ for the v=0 state as follows:

$$\langle \Delta r \rangle - \langle \Delta r \rangle^* = [\, 1 - (\mu/\mu^*)^{1/2}]\, \langle \Delta r \rangle \tag{12}$$

and,

$${}^1\Delta A\, ({}^{m'/m}X) = \langle\sigma\rangle - \langle\sigma\rangle^* = [1 - (\mu/\mu^*)^{1/2}] \bullet \left[\left(\frac{d\sigma}{dr}\right)_e + \frac{1}{3a}\left(\frac{d^2\sigma}{dr^2}\right)_e\right]\langle\Delta r\rangle + \ldots \tag{13}$$

The thermal average isotope shift is nearly the same as above except that coth $(hc\omega_e/2kT)$ is mass-dependent and this can be important when the vibrational frequency is low or the temperature is high, that is, when $(hc\omega_e/2kT)$ is less than about 3 or 4. Thus for several isotopomers, relative to the same parent molecule, the isotope shift is proportional to

$[\, 1 - (\mu/\mu^*)^{1/2}\,]$.

In the hydrogen fluorides this factor is 0.3936 for FT relative to FH and it is 0.2750 for FD relative to FH. In other words we expect

$$\frac{{}^1\Delta\, {}^{19}F\, ({}^{3/1}H)}{{}^1\Delta\, {}^{19}F\, ({}^{2/1}H)} \approx 1.43.$$

It has been shown [1] that upon substitution of heavier nuclei such as ^{13}C for ^{12}C, that is when $(\mu^* - \mu)/\mu^* \ll 1$, the above mass factor can be approximated by

$$(\mu^* - \mu)/2\mu^* \qquad \text{or} \qquad \frac{1}{2}\left(\frac{m' - m}{m'}\right)\left(\frac{m_A}{m_A + m}\right)$$

with an error of about 1% or less. For example, using this formula, we expect

$$\frac{{}^1\Delta\,{}^{31}\mathrm{P}\,({}^{36/32}\mathrm{S})}{{}^1\Delta\,{}^{31}\mathrm{P}\,({}^{34/32}\mathrm{S})} \approx 1.92.$$

It has been shown [27] that even for polyatomic molecules, (m′-m)/m′ appears in the dynamic factors $[\langle\Delta r\rangle - \langle\Delta r\rangle^*]$ and $[\langle(\Delta r)^2\rangle - \langle(\Delta r)^2\rangle^*]$ for the $A^{m'}X$ relative to A^mX. If our interpretation is valid, that the one-bond isotope shift can be considered as being dominated by a single product of an electronic and a dynamic factor, then indeed we should find the following:

(a) Where more than one isotope may be used for substitution we should be able to find a direct proportionality of ${}^1\Delta$ to (m′-m)/m′. Indeed we do. For the atomic masses, m=74, m′=76, 77, 78, 80, 82 of Se in the isotopomers of R_1SeSeR_2 (R_1, R_2=CH_3 and CF_3), the one-bond isotope shifts ${}^1\Delta{}^{77}\mathrm{Se}\,({}^{m'/74}\mathrm{Se})$ show straight lines for each set of R_1 and R_2 in FIGURE 4, reproduced from ref. 18. Similarly, the one-bond Se-induced and Te -induced ${}^{19}\mathrm{F}$ isotope shifts are found to be proportional to (m′-m)/m′.[28] The former are shown in FIGURE 4. There are other examples involving fewer isotopes which also are consistent with this mass factor, as in m′=17 and18, m=16 in ${}^1\Delta{}^{13}\mathrm{C}({}^{m'/16}\mathrm{O})$ in CO molecule [31] and m′=34,36 for S in ${}^1\Delta{}^{31}\mathrm{P}({}^{m'/32}\mathrm{S})$ in thiophosphate anhydrides.[32]

(b) The factor $m_A/(m_A+m)$ is not so easily verified experimentally because this would mean comparing different resonant isotopes (A is the resonant nucleus) and the same set of m′ and m. This factor should lead to an observed isotope shift which is larger for heavier resonant nuclei. A possible candidate is the ${}^{18}\mathrm{O}$- induced shift in ${}^{14}\mathrm{N}$ and ${}^{15}\mathrm{N}$ spectra of NO_3^-, for example. The ${}^1\Delta{}^{15}\mathrm{N}({}^{18/16}\mathrm{O})$ should be larger than the ${}^1\Delta{}^{14}\mathrm{N}({}^{18/16}\mathrm{O})$ by 3.7%. Only the ${}^{15}\mathrm{N}$ data are available so far.[33] The ${}^1\Delta{}^{15}\mathrm{N}({}^{2/1}\mathrm{H})$ and the ${}^1\Delta{}^{14}\mathrm{N}({}^{2/1}\mathrm{H})$ in NH_4^+ ion have been observed. For D-substitution we cannot use the approximate form of the mass factor. The ratio of $[1-(\mu/\mu^*)^{1/2}]$ values in the dynamic factors of ${}^1\Delta{}^{15}\mathrm{N}({}^{2/1}\mathrm{H})$ relative to ${}^1\Delta{}^{14}\mathrm{N}({}^{2/1}\mathrm{H})$ is 1.005. The measured values of ${}^1\Delta{}^{15}\mathrm{N}({}^{2/1}\mathrm{H})$ [34] are indeed slightly greater than the measured values of ${}^1\Delta{}^{14}\mathrm{N}({}^{2/1}\mathrm{H})$ [14] but not by as much; the observed ratio is 1.002.

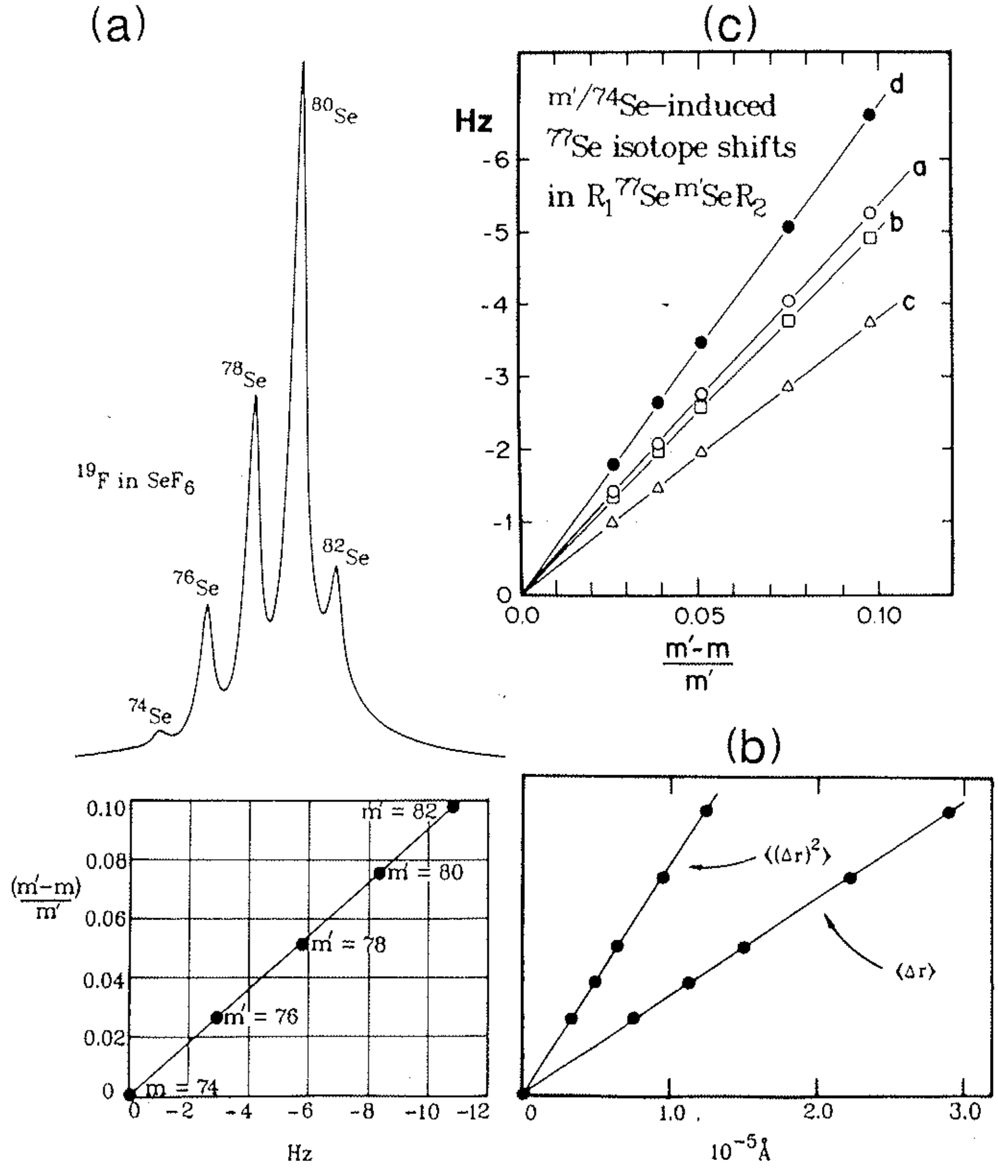


Fig. 4. (a) The effect of selenium isotopes on the ^{19}F nuclear shielding in SeF$_6$, reproduced from C.J. Jameson, A.K. Jameson, and D. Oppusunggu, *J. Chem. Phys.*, 85 (1986) 5480.[28] (b) The calculated mass dependence of the mean bond displacements and mean square amplitudes at 300K of the Se-F bond in SeF$_6$, reproduced from C.J. Jameson and A.K. Jameson, *J. Chem. Phys.*, 85 (1986) 5484.[29] (c) The effect of selenium isotopes on the ^{77}Se nuclear shielding in the diselenides R$_1$ ^{77}Se $^{m'}$SeR$_2$, where R$_1$, R$_2$ = CH$_3$, CF$_3$. Reproduced from C.J. Jameson and H.J. Osten, *J. Chem. Phys.*, 81(1984) 4293,[18] data taken from Ref.30. These illustrate the theoretically predicted mass factor (m′-m)/m′ in polyatomic molecules.

(c) Where several equivalent atoms ${}^{m}X$ may be replaced by the heavier ${}^{m'}X$ in the group AX_n, there will be a large change $(\partial\sigma/\partial r_i)_e\,[\langle\Delta r_i\rangle - \langle\Delta r_i\rangle^*]$ for each replaced atom, leading to the observed additivity of isotope shifts.[18] Even when all the terms in eq.(2) are included and calculated properly, the nearly strict additivity is preserved.[20] Although there are many smaller changes, such as in eq. (4), which are not quite the same as each ${}^{m}X$ is replaced by ${}^{m'}X$, it has been shown that these smaller changes lead to only slight deviations from additivity, which incidentally have been observed just as predicted.[7,18,34]

(d) The dynamic factor can make an important contribution to the differences in isotope effect in analogous molecules, such as in the comparison of ${}^{1}\Delta^{13}C({}^{18/16}O)$ and ${}^{1}\Delta^{13}C({}^{34/32}S)$. The former is -0.019 per ${}^{18}O$ in CO_2[31] and the latter is -0.009 per ${}^{34}S$ in CS_2[35] a ratio of 2.1. The dynamic factors in CO_2 and CS_2 have been calculated

$$\frac{\left[\langle\Delta r\rangle_{{}^{13}C\,{}^{16}O} - \langle\Delta r\rangle_{{}^{13}C\,{}^{18}O}\right]}{\left[\langle\Delta r\rangle_{{}^{13}C\,{}^{32}S} - \langle\Delta r\rangle_{{}^{13}C\,{}^{34}S}\right]} = 3.15.$$

Thus, a large part of the observed difference between the isotope shifts ${}^{1}\Delta^{13}C({}^{18/16}O)$ and ${}^{1}\Delta^{13}C({}^{34/32}S)$ is in the dynamic factors.

(2) Mean bond displacement depends on r_e

It has been shown that for ground state diatomic molecules the vibrational part of $\langle\Delta r\rangle$ can be described fairly well for closed or open shell molecules, for all types of bonds, electron deficient, single, double, triple bonds, between any two elements in the periodic table, by the relationship[27]

$$\langle \Delta r \rangle \approx \left(\frac{3h}{8\pi}\right) \mu^{-1/2}\, 10^{-D} \qquad (14)$$

where $$D \equiv \frac{r_e - a_3}{b_3} - \frac{3(r_e - a_2)}{2b_2} \qquad (15)$$

in which a_2, b_2, a_3, b_3 are the empirical parameters of Herschbach and Laurie characterizing any two rows of the periodic table.[36] The factor of fundamental constants $(3h/8\pi)$ is 19.35×10^{-3}. Similarly, in the same analysis

$$\langle (\Delta r)^2 \rangle \approx \left(\frac{h}{4\pi}\right) \mu^{-1/2}\, 10^{+d} \qquad (16)$$

where $$d \equiv \frac{r_e - a_2}{2b_2} \quad . \qquad (17)$$

For a given bonded pair of atoms, $\langle \Delta r \rangle$ increases with increasing r_e. These are zeropoint vibrational averages. The temperature dependence of $\langle \Delta r \rangle$ and $\langle (\Delta r)^2 \rangle$ are discussed elsewhere.[37] It has been shown that these equations can be used as well to estimate the dynamic parts for polyatomic molecules, except that the factor 19.35×10^{-3} is replaced by 22×10^{-3}. In comparing the dynamic parts for different bonding situations, it may be noted that the explicit r_e dependence in eq. (14-17) may play a role as r_e in turn depends on bond order, axial vs equatorial positions, and so on. However, as we shall see in the following sections, this is not as significant as the accompanying changes in the electronic factor.

The magnitude of the shift is a function of the observed nucleus and reflects its chemical shift range. Only a small part of this is due to the dynamic factor. For D-substitution in ^{13}C-H, ^{51}V-H, and ^{93}Nb-H bonds for example, the factor $[1-(\mu/\mu^*)^{1/2}]\langle \Delta r \rangle$ is 5.65, 5.54, and 5.05 respectively for bond lengths r_e=1.0871Å, 1.54Å, and 1.66Å, respectively. On the other hand the observed D-induced shifts in Me_3CH, $CpVH(CO)_3$, and $CpNbH(CO)_3$ are -0.472 [38] , -4.7 [16] , and -6 ppm [39]. The dynamic factors are in the opposite order compared to the observed isotope shifts, which confirms that the electronic factors are overwhelmingly larger for ^{93}Nb and ^{51}V compared to ^{13}C. This seems to indicate that the electronic factor in each case depends to a great extent on the general sensitivity of the nuclear magnetic shielding of each nucleus to changes in electronic environment, which sensitivity is indicated by its chemical shift range, which are roughly 680, 6000, and 5000 ppm respectively for ^{13}C, ^{51}V, and ^{93}Nb.

(D) Further trends in one-bond isotope shifts

We have noted the general trends in Sect. IIA. There are further correlations with indices of the chemical bond which have been observed in favorable cases to apply to related molecules. With other quantities more or less being equal, these correlations reveal important characteristics of the electronic factor, which is after all the chemical part of isotope shifts. Our ability to calculate the dynamic factor or at least determine a semi-quantitative estimate, allows us to extract from the measured isotope shift that part which reveals the sensitivity of the nuclear shielding to minor changes in the molecular geometry.

(1) Correlation with absolute shielding

In closely related compounds the least shielded nucleus exhibits the largest isotope shift. Of course this trend only becomes apparent when the dynamic terms are very similar. Examples are ${}^{1}\Delta^{13}C({}^{18/16}O)$ in acetophenones [40] , ${}^{1}\Delta^{19}F({}^{13/12}C)$ in fluoromethanes [41] ,${}^{1}\Delta^{13}C({}^{2/1}H)$ in 1-D, 4-X- substituted benzenes.[42] This behavior is also observed for ${}^{7}\Delta F({}^{2/1}H)$ in 4-fluorophenyl systems in FIGURE 2,[43] and two-bond isotope shifts ${}^{2}\Delta^{13}C({}^{2/1}H)$ in H_3C ${}^{13}C$ R=X.[44] The last is shown in FIGURE 5.

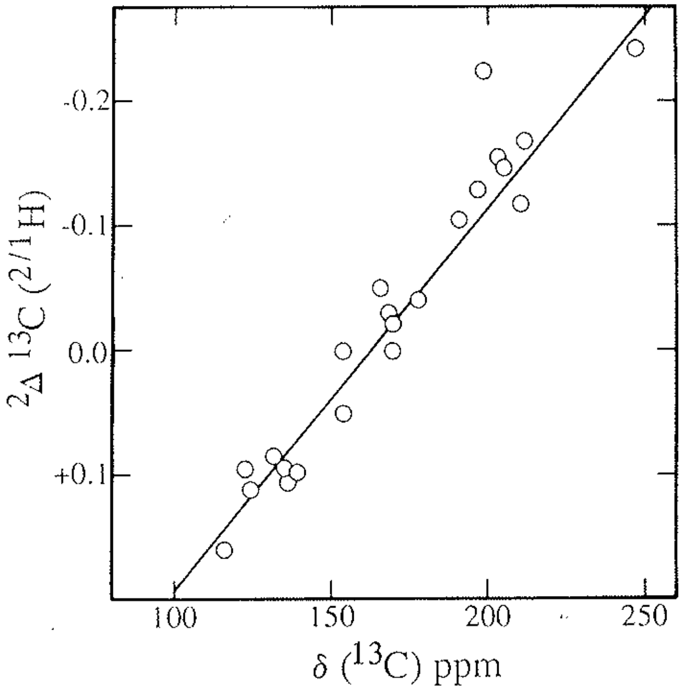


Fig. 5. The 2-bond deuterium isotope effects on a trigonal carbon vs. the ${}^{13}C$ chemical shift of the latter. Values plotted are ${}^{2}\Delta^{13}C({}^{2/1}H)$ for replacement of CH_3 by CD_3, from C.H. Arrowsmith and A.J. Kresge, *J. Am. Chem. Soc.*, 108 (1986) 7918.[44] The largest negative isotope shifts are for the least shielded carbons.

This trend is consistent with the correlation discovered in studies of temperature-dependent chemical shifts, that the derivative of nuclear shielding with respect to bond extension is largely dependent on the paramagnetic term [28,45] . The larger the paramagnetic term the less shielded the nucleus, the greater the magnitude of the derivative, the greater the temperature dependence. Exactly the same electronic factors appear in both the temperature-dependent chemical shifts and the mass-dependent chemical shifts; only the dynamic factors are different.[2,37,46] Two examples are shown in FIGURE 6.

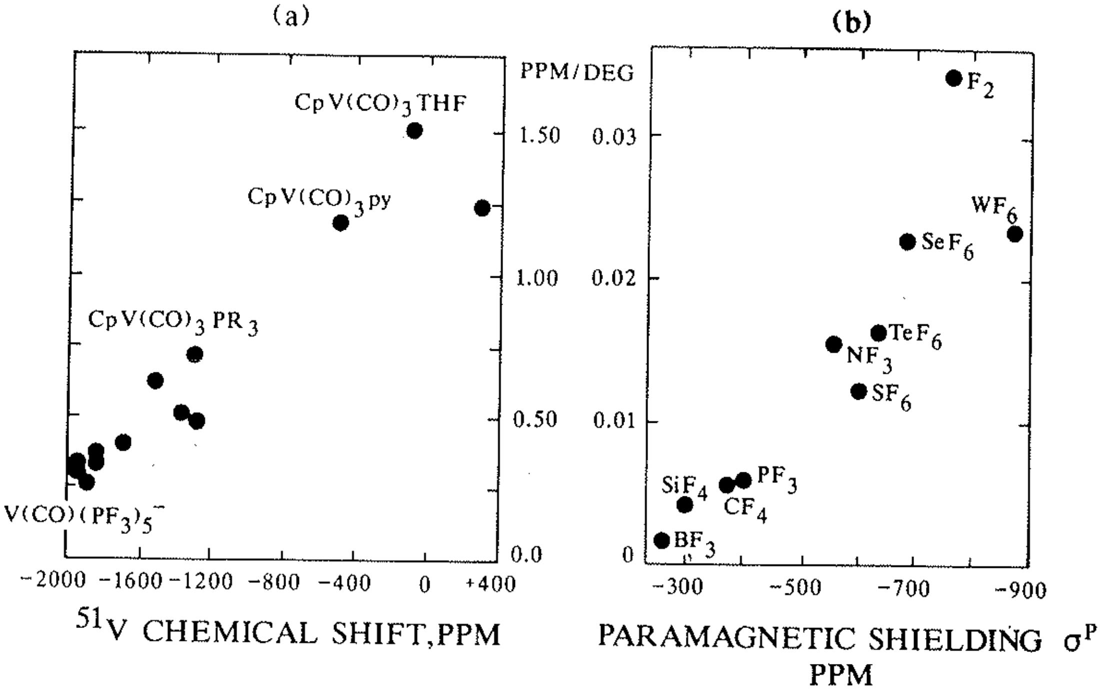


Fig. 6. Temperature coefficients of chemical shifts correlate with paramagnetic shielding (a) for ^{51}V in vanadium carbonyl complexes, and (b) for ^{19}F in binary fluorides, from C.J. Jameson, D. Rehder, and M. Hoch, *J. Am. Chem. Soc.*, 109 (1987) 2589,[47] and C.J. Jameson, A.K. Jameson and D. Oppusunggu, *J. Chem. Phys.*, 85 (1986) 5480.[28] The largest temperature coefficients are for the least shielded nuclei.

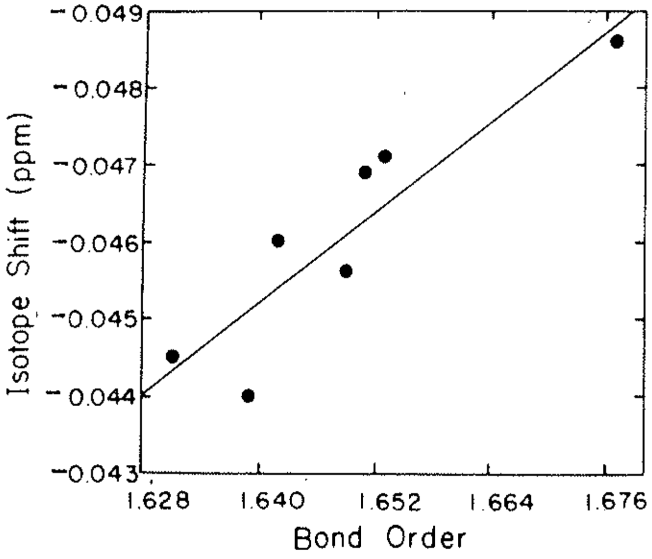


Fig. 7. The ^{18}O-induced ^{13}C shifts, $^1\Delta^{13}$C($^{18/16}$O) of carbonyl carbons in para-substituted acetophenones as a function of the carbonyl bond order, reproduced by permission of John Wiley & Sons, Ltd. from J. M. Risley, S. A. Defrees, and R. L. van Etten, *Org. Magn. Reson.*, 21 (1983) 28,[50]

(2) Bond order

The dependence of isotopic shifts on bond order was first noted in ^{18}O- induced ^{31}P shifts.[48] The nominal bond orders are shown to be in a monotonic correlation with $^{1}\Delta$.[49] Risley et al [50] found that the isotope shifts $^{1}\Delta C(^{18/16}O) = -0.0440$ to -0.04856 and the calculated bond orders in acetophenones give a linear plot shown in FIGURE 7.

The correlations indicate that we should expect to find theoretical derivatives of nuclear shielding to be greater upon stretch of a triple bond than upon stretch of a double bond. Indeed there are examples which indicate just this:

	empirical $(\partial\sigma^C/\partial r_{CO})_e$ ppm $\mathring{A}^{-1}$ [31]
CO	-456±15
O=C=O	-214±17
	theoretical $(\partial\sigma^C/\partial r_{CO})_e$ [51]
CO	-573.9
$H_2C=O$	-406.6

Is there an underlying physical reason for this ? This is a very interesting question that can perhaps be answered by theoretical calculations such as by the IGLO method, in which the individual MO contributions to the shielding derivative can be examined. Unfortunately it has been found that theoretical calculations on nuclei involved in multiple bonds give less satisfactory agreement with experimental shielding. Answers to this question may require calculations including electron correlation.

(3) Effects of the net charge

It has been observed by Wasylishen and coworkers [7,53], that the magnitude of the isotope shift decreases with a net positive charge on the molecule and increases with a net negative charge on the molecule. An example is shown below [53]

	$^{1}\Delta^{119}Sn(^{2/1}H)$ ppm per D	$(\partial\sigma/\partial r)_e$ ppm $\mathring{A}^{-1}$
^{119}Sn in SnH_4	-0.403	-92
^{119}Sn in SnH_3^+	-0.05 ± 0.03	-10

There are no lone pairs involved in the above. The empirical electronic factors shown above were deduced by Leighton and Wasylishen (using eq. (1) and the methods of estimation of $\langle\Delta r\rangle$ described in the preceding sections). The trend is that the derivative increases algebraically with algebraically increasing net charge. This was also found in the theoretical ab initio studies by Chesnut and Foley.[22] Examples are shown below.

	$(\partial\sigma/\partial r)_e$ ppm Å^{-1} [22]
^{11}B in BH_3	-3.5
^{11}B in BH_4^-	-27.
^{27}Al in AlH_3	+84.2
^{27}Al in AlH_4^-	+11.6

It appears that in a molecule with a net negative charge the nuclear shielding is more drastically affected by a bond stretch. Except for the diamagnetic part, nuclear shielding and local charge density are not directly related. However, a net negative charge on the molecule will mean that, upon bond extension, there will be more electron density to follow or not follow the nucleus as it moves out. A net positive charge will have the opposite effect. The dependence of the shielding derivative on the net charge is clear in the comparison of theoretical and empirical derivatives in HCN versus CN^- :

	$(\partial\sigma/\partial r)_e$ ppm Å^{-1}		
^{13}C in HCN	-263	theor,[51]	
^{13}C in CN^-	-538.7	theor,[51]	-473 emp.[54]
^{15}N in HCN	-675.4	theor,[51]	
^{15}N in CN^-	-892.2	theor,[51]	-872 emp.[54]

There are other data which could be used as examples to illustrate the above trends of isotope shifts and net charge. However, they also involve the presence or absence of lone pairs on the resonant nucleus, which we now consider.

(4) Lone pair effects

It had been predicted that the presence of a lone pair gives a larger negative isotope shift.[55] This was later demonstrated experimentally by Wasylishen et al. in the comparisons of related systems in TABLE 1. One possible explanation is that the observed differences are partly due to dynamic factors, i. e., there may be significant $\langle\Delta\alpha\rangle$ terms in the bent and pyramidal molecules where the resonant nucleus bears a lone pair or two. Full calculations on H_2O molecule show that the $^1\Delta^{17}O(^{2/1}H)$ is largely due to the $\langle\Delta r\rangle$ term although there are smaller other terms.[19] Thus, the differences between molecules with and without lone pairs likely comes from the electronic factor being a larger negative number when lone pairs are present. These are indeed found to be the case, as shown in TABLE 2.

TABLE 1

One-bond isotope shifts in small molecules with and without lone pairs

	number of lone pairs	Average $^1\Delta$ ppm per D	Ref
^{15}N in NH_3	1	- 0.623	34
NH_4^+	0	- 0.293	34
^{31}P in PH_2^-	2	- 0.2760	7
PH_3	1	- 0.846	7
PH_4^+	0	very small	7
^{119}Sn in SnH_3^-	1	- 3.281	56
SnH_4	0	- 0.403	53
SnH_3^+	0	- 0.05 ± 0.03	53
^{15}N in NO_2^-	1	- 0.138	33,57
NO_3^-	0	- 0.056	33
^{17}O in H_2O	2	- 3.090	34
H_3O^+	1	- 0.3	58

TABLE 2

The electronic factors $\dfrac{(\partial\sigma/\partial r)_e}{\text{ppm } \mathring{A}^{-1}}$

	Ab initio	theoretical	From expt
N in NH_3	- 130.3 [22]	-144 (-70 from LP) [24]	-124[34]
NH_4^+	- 67.9 [22]		-60[34], -65[27]
P in PH_2^-			-585 [7]
PH_3	- 150.8 [22]	- 154 (-47 from LP) [24]	-180 [7]
PH_4^+	- 52.9 [22]		very small [7]
Sn in SnH_3^-			- 750 [56]
SnH_4			- 92 [53]
SnH_3^+			- 10 [53]

Theoretical calculations too show that the change in shielding with bond extension is greater for the systems with one or more lone pairs. In comparing NH_3 with NH_4^+ there is a factor of roughly 2 in the electronic factors (-130.3 vs -67.9 ppm $\mathring{A}^{-1}$) and also in the observed isotope shifts (-0.623 ppm vs. -0.293 ppm).

In particular, calculations by Fleischer and Kutzelnigg [24] for NH_3 and PH_3

provide separately the lone pair contributions (shown in parentheses in the second column of numbers in TABLE 2). Roughly 1/2 and 1/3 of the change in shielding upon bond extension in these molecules come from lone pair molecular orbitals. It would thus be predicted that with a lone pair centered on the resonant nucleus, larger isotope shifts may be expected, all other things being roughly similar. The nitrogen in NO_2^- has a lone pair that NO_3^- does not have, so $^1\Delta N(^{18/16}O)$ should be larger for NO_2^- than for NO_3^-, and it is (-0.138 compared to -0.056 ppm per ^{18}O).[33,57] Similarly for aniline, $^1\Delta N(^{2/1}H)$ = -0.714 ppm per D (neat)[34] while for anilinium + ion, $^1\Delta N(^{2/1}H)$ = -0.40 ppm per D.[59] In the above examples and those in TABLE 1 and 2 the lone pair and the net charge effects cannot be separately considered; those effects are in the same direction, exaggerating the observed differences.

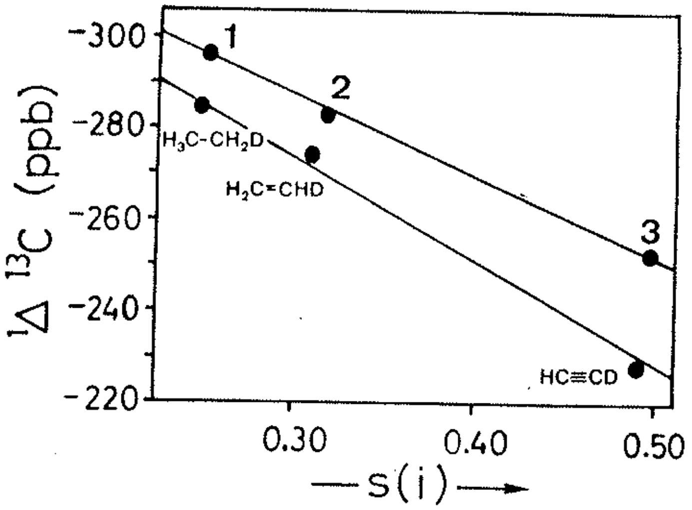


Fig. 8. Correlation between $^1\Delta^{13}C(^{2/1}H)$ and $^1J(CD)$ in H_3C-CH_2D, $H_2C=CHD$, and $HC\equiv CD$ and also for $Ph-CH_2-CH_2D$ (1), E isomer of $PhHC=CHD$ (2), and $PhC\equiv CD$ (3). $^1J(CD)$ are plotted in terms of the fractional s characters s(i) derived directly from the observed $^1J(CD)$. Reproduced with permission from J.R. Wesener, D. Moskau, and H. Gunther, *J. Am. Chem. Soc.*, 107 (1985) 7307.[38] Copyright (1985) American Chemical Society.

(5) Correlation with spin-spin coupling

Since the one-bond coupling constant is a purely electronic quantity, it must be the electronic factors in the one-bond isotope shifts which allow linear correlations with the coupling constant to become apparent. This was most clearly observed for $^1\Delta^{31}P(^{18/16}O)$ vs. $^1J(P^{17}O)$[60], for $^1\Delta^{19}F(^{13/12}C)$ vs. $^1J(CF)$ in fluoromethanes[41], and for $^1\Delta^{119}Sn(^{13/12}C)$ vs. $^1J(SnC)$ in $R_{4-n}Sn(C\equiv CH)_n$ (R=Me, Et, n=0-4)[61] and similarly for

$Me_{4-n}Sn(CH{=}CH_2)_n$.[61] In each case the magnitude of the isotope shifts increase with increasing magnitude of the coupling constant. Wesener et al. expressed the correlation of the isotope shift with the hybridization of the resonant carbon derived directly from the observed $^1J(CH)$ [38] in FIGURE 8.

(6) Increments due to substituents

An interesting incremental effect observed in isotope shifts can be attributed to the electronic factor. The successive replacement of H by CH_3 or by Ph substituents at the observed nucleus leads to incremental changes in the isotope shift.[38] The effect of phenyl substitution is dramatic. Examples are shown below.

			$^1\Delta$ ppm per D	Ref
^{15}N	in	NH_3	- 0.623	34
	in	$PhNH_2$	- 0.715	34
^{31}P	in	PH_3	- 0.846	13
	in	$PhPH_2$	- 1.21	62
^{13}C	in	CH_4	- 0.192	63
	in	$PhCH_3$	- 0.28	64
^{77}Se	in	SeH_2	-7.02	15
	in	PhSeH	-7.96	65

Successive substitution shows the increments are nearly additive. For example, (to avoid confusion the replaced ^1H is written as a D in the following)

			$^1\Delta^{13}C(^{2/1}H)$ ppm per D	Ref
^{13}C	in	CH_3D	- 0.187	38,63
	in	$PhCH_2D$	- 0.2755	38
	in	$(Ph)_2CHD$	- 0.342	38
	in	$(Ph)_3CD$	- 0.4377	38

that is, an increment of about -0.081 ppm per Ph, more clearly shown in FIGURE 9. A somewhat larger increment is observed for CH_3 (about -0.095 ppm per CH_3) as shown below:

		$^1\Delta^{13}C(^{2/1}H)$ ppm per D
^{13}C	in CH_3D	- 0.187
	in H_3CCH_2D	- 0.284
	in $(H_3C)_2CHD$	- 0.3759
	in $(H_3C)_3CD$	- 0.4722

There is a factor of 2.5 in the magnitude of the isotope shift in $(CH_3)_3CD$ compared to CH_3D. There are no data on Bu_3CD compared to H_3CD but the $^1\Delta^{13}C(^{2/1}H)$ in BuH_2CD is -0.301 [38], an increment of -0.114 ppm per Bu. If Bu substitution does follow an incremental pattern as CH_3 substitution does, Bu_3CD would have an isotope shift of -0.529 ppm, i.e., a factor of 2.8 in going from H_3CD to Bu_3CD. The large increase of ${}^1\Delta{}^{119}Sn({}^{2/1}H)$ in going from H_3SnD (-0.463 ppm [53]) to Bu_3SnD (-1.62 ppm [66]), a factor of 4.0, is therefore not unexpected.

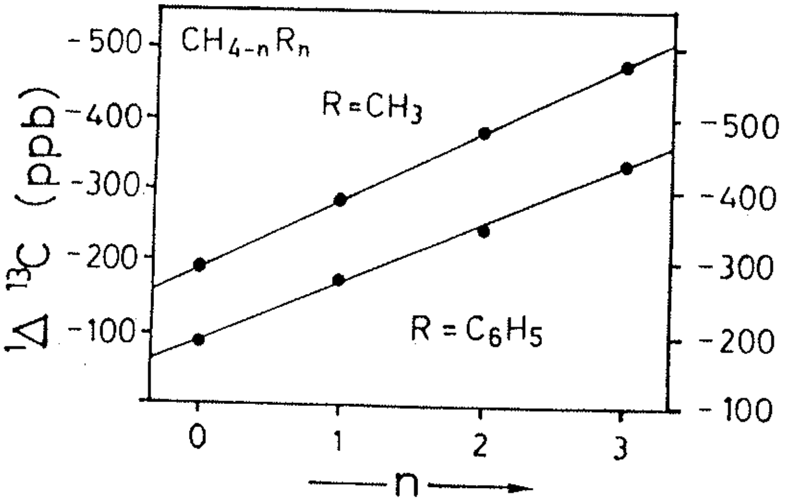


Fig. 9. Incremental effects of CH_3 substitution and of phenyl substitution on ${}^1\Delta{}^{13}C({}^{2/1}H)$, reproduced with permission from J.R. Wesener, D. Moskau, and H. Günther, *J. Am. Chem. Soc.*, 107 (1985) 7307.[38] Copyright (1985) American Chemical Society.

It can be supposed that part of these observed increments may be due to incremental changes in $[\langle \Delta r_{CH} \rangle - \langle \Delta r_{CD} \rangle]$ upon substitution at C. It has been found that $\langle \Delta r \rangle$ is related to bond length in a general way as shown in eq. (14)-(15) in Sect. IIC2, which provides a general relationship for fairly broad comparisons. Although we do not expect very accurate predictions from this, the form of the relationship leads to larger Δr for longer r_e. Therefore, electronic factors being equal, a larger dynamic term for a longer r_e would lead to a larger isotope shift for longer bonds. It is well known that substitutions have an incremental effect on r_e of CH [67] and therefore also on $[\langle \Delta r_{CH} \rangle - \langle \Delta r_{CD} \rangle]$. For example, from Table 2 of Ref 67 we have

H_3C-H	$r_{C\text{-}H}$ = 1.081Å
MeH_2C-H	1.083
Me_2HC-H	1.085
Me_3C-H	1.087

These small increments (~ 2×10^{-3}Å) in r_e correspond to even smaller increments in $\langle \Delta r \rangle$ which are much too small (~2×10^{-5} Å) to account for the observed increments in isotope shifts, even though the changes are in the right direction. Therefore, the electronic factor clearly must be responsible for these increments. Once again, in view of the well-known incremental substituent effects on nuclear shielding, it is not surprising that there appear to be incremental substituent effects on shielding derivatives.

(7) Bond length

An interesting trend is the effect of chain prolongation in the isotope shift of a terminal $^{13}CH_2D$ as shown in FIGURE 10a. This is entirely parallel to the change in r_e for the terminal CH, as seen in FIGURE 10b, the sharp rise in going from methane to ethane, the flattening out at pentane and longer, even including the slight dip at butane. These values of r_e are the ab initio calculated bond lengths which have been found to have a clearly established excellent correlation with the reported isolated C-H stretching frequencies.[67,69] The latter were found to have excellent correlation with spectroscopically determined r_0 values for a wide range of organic compounds: [67]

$r_0^{expt}(CH)/\text{Å} = 1.3982 - 1.023\text{x}10^{-4}(\nu_{CH}^{iso}/cm^{-1})$

in which differences in length of 0.0005Å could be distinguished. The correlation with calculated r_e is [69]

$r_e^{calc}(CH)/\text{Å} = 1.2719 - 0.639\text{x}10^{-4}(\nu_{CH}^{iso}/cm^{-1})$

in which differences in length of 0.0001Å could be distinguished. The measured r_e are known to be longer by ~ 0.01Å than calculated by ab initio SCF methods, and the slope is known to be larger than calculated by nearly a factor of two. Snyder et al.[69] have found a simple relation between the above and the local structure in the immediate vicinity of the C-H bond, such that the isolated C-H frequency or the C-H bond length is not significantly influenced by structure beyond the next nearest neighbors of the carbon of a given $\overset{*}{C}$-$\overset{*}{H}$ bond, and can be predicted from simple additivity relations that reflect local structure, i.e.,can be predicted by how many atoms (H or C) are trans or gauche to the $\overset{*}{H}$ across the $\overset{*}{C}$-C bond.[69] Here again, the r_e(C-H) differences are very small, $3.2\text{x}10^{-3}$Å over-all, so the slight changes in $\langle\Delta r\rangle$ with chain length can not possibly account for the observed increments in isotope shifts. Therefore, the electronic factor must be changing precisely as shown in FIGURE 10a or 10b. The parallel behavior of r_e and $^1\Delta$ with increasing chain length almost surely indicates an electronic factor that reflects the r_e behavior, since r_e is after all a purely

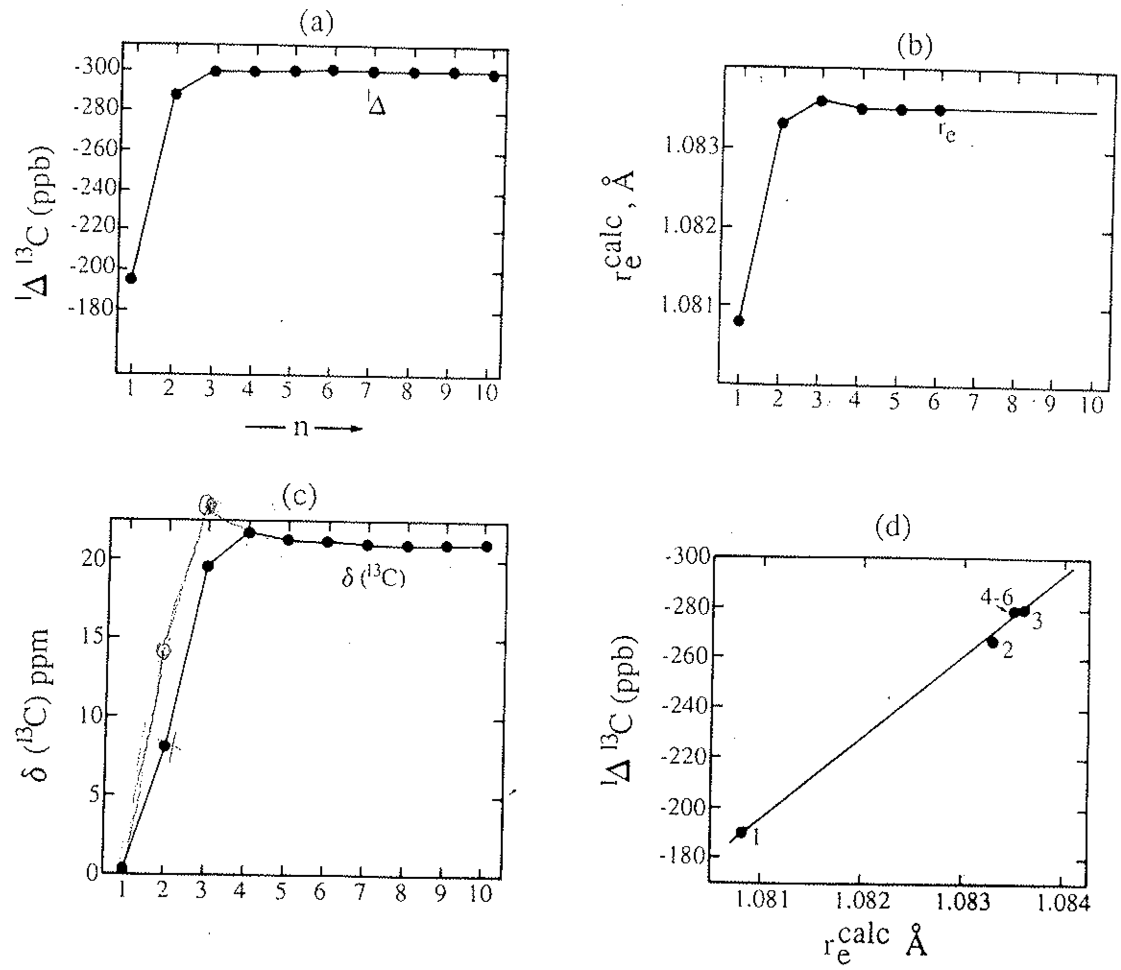


Fig. 10. Chain prolongation effects. (a) The $^1\Delta^{13}C(^{2/1}H)$ in the terminal -CH_2D group varies with number of carbons in the normal alkanes, with permission from J.R. Wesener, D. Moskau, and H. Günther, *J. Am. Chem. Soc.*, 107 (1985) 7307.[38] (b) r_e in the terminal -CH_3 group varies with number of carbons in the normal alkanes. (c) ^{13}C chemical shift of the terminal-CH_3 group. Data taken from Ref. 68. (d) The one-bond isotope shift for the terminal -CH_3 in the normal alkanes correlate with the r_e (CH).

electronic phenomenon. There are smaller known contributions to $^1\Delta^{13}C(^{2/1}H)$ in CH_4 from second order and second derivative terms.[18,20] It is just simpler to think of such an electronic factor as $(\partial\sigma^C/\partial r_{CH})_e$ rather than some composite including second-order and second derivative contributions. These molecule-specific smaller contributions may change in going from CH_4 to n-decane, but it is difficult to see how these contributions could be responsible for the precise similarities in shape of FIGURE 10a and 10b. Finally a comparison of FIGURE 10a, 10b and 10c gives convincing proof that the electronic factors are responsible for the changes in FIGURE 10a. The observations in FIGURE 10c have been described in terms of increments due to "α-, β-, and γ- effects" of methyl substitution on ^{13}C- chemical shifts in alkanes, where γ- effects lead to shielding and α-, β- effects lead to deshielding.[68,70] Comparison of FIGURE 10c with 10a offers convincing evidence that the well-known incremental α-, β-, γ- effects which apply to the ^{13}C shielding also apply to its derivatives with respect to bond extension. A plot of $^1\Delta$ vs r_e from FIGURE 10a and 10b is shown in FIGURE 10d. This is probably the simplest relation between $^1\Delta$ and bond length. In these homologous compounds there are no accompanying changes in hybridization or bond order which could be modifying both the bond length and $^1\Delta$. What we find is that the magnitude of the isotope shift increases with increasing bond length. In cyclohexane the comparison of $^1\Delta^{13}C(^{2/1}H_{ax}) = -0.445$ ppm and $^1\Delta^{13}C(^{2/1}H_{eq}) = -0.395$ ppm [38] is consistent with the bond length for the axial CH being longer than the equatorial by 0.0017Å.

In contrast, the dependence of one-bond isotope shifts on bond length which have been noted in the literature have been in the opposite direction to that just discussed. That is, shorter bond lengths have been associated with larger isotope shifts. FIGURE 11 shows the linear dependence of $^1\Delta F(^{34/32}S)$ on the SF bond length in a wide variety of compounds.[71] Further examples are the $^1\Delta^{31}P(^{18/16}O)$ in oxyphosphoranes [32,72], and $^1\Delta P(^{15/14}N)$ in phosphorinanes [73], and $^1\Delta Se(^{13/12}C)$ in a variety of organoselenium compounds.[74] In each of these examples the electronic environments are drastically different for the compounds being compared, in particular, the bond orders are different. What is apparently an increase of isotope shift with decreasing bond length is actually more appropriately attributed to an increase in isotope shift with increasing bond order. Again, this can not be interpreted primarily in terms of the dynamic factors. First of all, as already discussed, the dependence of the dynamic factor on the bond length is in the opposite direction. Secondly, it is far too small to account for the observed changes in the isotope shift in any of these systems. Therefore, we can only attribute these correlations to changes in the electronic factor accompanying these bond order changes which incidentally are also reflected by bond length changes. The dependence of the shielding derivative on bond order has already been discussed in Sect. II D2 for cases in which the bond order is fairly well defined and it was found that theoretical carbon shielding derivatives with respect to C-O stretch were indeed larger for CO than CO_2, for CO than H_2CO. Therefore, there is theoretical support for the concluson that the correlations such as shown in FIGURE 11 provide relations between two purely electronic quantities: $(\partial\sigma/\partial r)_e$ and r_e in these molecules.

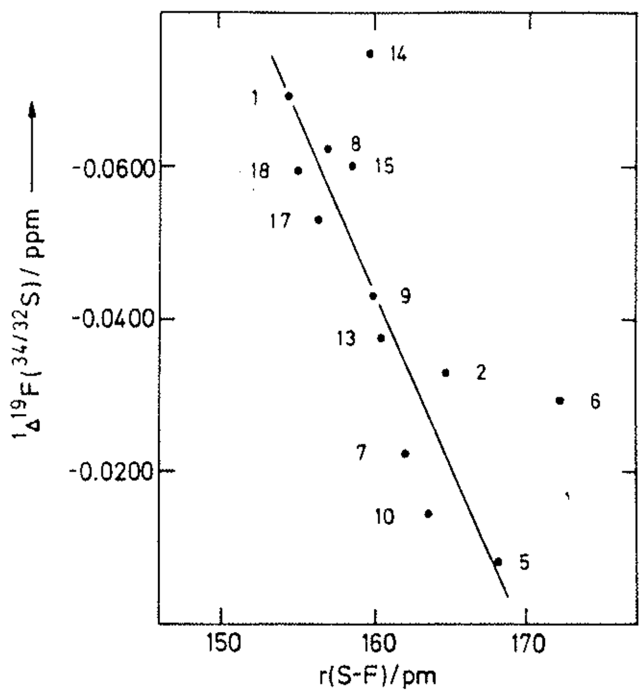


Fig. 11. Correlation of the ^{34}S-induced ^{19}F shifts with the S-F bond length in a wide variety of compounds such as FSSF (10), SF_4(eq.) (1), and SO_2ClF (18), reproduced with permission from W. Gombler, *Z. Naturforsch.* B, 40 (1985) 782.[71]

(E) Long-range isotope shifts

These are generally smaller than one-bond shifts; nevertheless a large number of them have been observed, some over a distance of seven bonds. The question is, what information is contained in these long range shifts? What we propose to show here is that these long-range shifts are a property of the electronic transmission path from the site of substitution up to the resonant nucleus.

(1) Dominance of the secondary derivative

When the observed isotope shift is over a distance of 2 or more bonds then the magnitudes can only be explained if terms beyond the primary ones are included in the discussion [75]. For one-bond shifts, both the electronic and the dynamic factors are the primary terms: the change in the mean bond length when the mass of one of the atoms in the bond is changed, and the response of the nuclear shielding to a stretch of a bond directed to the resonant nucleus. Since 2-bond shifts involve a remote bond (i.e., an atom is substituted at a bond remote from the resonant nucleus), then secondary factors have to be considered, that is, the response of the shielding to a stretch of a remote bond, or else the change in the mean bond length when the mass of an atom in a remote bond is changed.

For example, for the resonant A nucleus in A-Y-X, the primary dynamic factor is of course the change (call it Δ) in the Y-X bond upon substitution of ^{m}X by $^{m'}$X. The primary electronic factor is $(\partial\sigma^{A}/\partial r_{AY})_{e}$. The secondary electronic factor is $(\partial\sigma^{A}/\partial r_{YX})_{e}$ and the secondary dynamic factor is the much smaller change (call it δ) in the A-Y bond upon substitution of ^{m}X by $^{m'}$X.

The secondary dynamic factor can be thought of in terms of interactions between local vibrational modes. Take as local modes the Y-X stretch and the A-Y stretch. The small change δ in the bond length A-Y upon isotopic substitution of X is dependent on the coupling between the Y-X and the A-Y stretches. In short, the leading terms in a 2-bond isotope shift can be written in the form

$$(\partial\sigma^{A}/\partial r_{AY})_{e}\,\delta + (\partial\sigma^{A}/\partial r_{YX})_{e}\,\Delta + \dots \tag{18}$$

where

$$\delta \equiv \langle r_{AY}\rangle_{AY^{m'}X} - \langle r_{AY}\rangle_{AY^{m}X} \tag{19}$$

$$\Delta \equiv \langle r_{YX}\rangle_{AY^{m'}X} - \langle r_{YX}\rangle_{AY^{m}X} \tag{20}$$

For example, the ^{17}O isotope shift due to ^{18}O substitution in CO_2 is the ^{17}O shielding difference between $^{17}O_1{-}^{12}C{-}^{16}O_2$ and $^{17}O_1{-}^{12}C{-}^{18}O_2$, which can be written approximately as

$$\langle\sigma^{O} - \langle\sigma^{O}\rangle^{*} \approx \left(\frac{\partial\sigma^{O_1}}{\partial r_{CO_1}}\right)_{e}\delta \quad + \quad \left(\frac{\partial\sigma^{O_1}}{\partial r_{CO_2}}\right)_{e}\Delta \tag{21}$$

Note that $(\partial\sigma^{O_1}/\partial r_{CO_2})_{e}$, is a measure of the change in the ^{17}O shielding upon a change in the length of the remote CO bond, a secondary electronic factor which depends on the transmission of the electronic information along the O-C-O path. Δ is of course the $\langle \Delta r\rangle - \langle \Delta r\rangle^*$ that we have been able to easily estimate as discussed in Sect. IIC, whereas δ is a much smaller long-range dynamic factor, a molecule-specific quantity dependent on the over-all potential energy surface of the molecule. There are indications that even in long-range isotope shifts the terms of the order of Δ are dominant compared to the terms in δ.

We have stated that the signs and magnitudes of isotope shifts across 2 or more bonds reflect the signs and magnitudes of the secondary derivatives.[75,76] What is the evidence for secondary derivatives being important for isotope shifts over 2 bonds and longer paths? The observed additivity of long-range isotope shifts is completely consistent with this. Isotope shifts from equivalent substitution sites such as a remote CH_3 group involve the same secondary derivative and one Δ term for each C-D replacing a C-H. There are other clues. One is that the mass dependence of the 2-bond isotope shift is the same as the 1-bond. Vibrational calculations showed [75] that

$$\frac{\langle \Delta r_{CH}\rangle_{CH_4} - \langle \Delta r_{CT}\rangle_{CT_4}}{\langle \Delta r_{CH}\rangle_{CH_4} - \langle \Delta r_{CD}\rangle_{CD_4}} = 1.426.$$

In the one-bond isotope shift, we have seen in Sect. IIB that the leading term is

$$\left(\frac{\partial\sigma}{\partial r}\right)_e [\, \langle \Delta r_{CH}\rangle - \langle \Delta r_{CD}\rangle \,] \quad \text{for deuterium substitution and}$$

$$\left(\frac{\partial\sigma}{\partial r}\right)_e [\, \langle \Delta r_{CH}\rangle - \langle \Delta r_{CT}\rangle \,] \quad \text{for tritium substitution.}$$

The observed ratio of tritium and deuterium one-bond isotope shifts in ${}^{13}CH_3C(O)CH_3$ is [77]

$$\frac{{}^{1}\Delta^{13}C\,({}^{3/1}H)}{{}^{2}\Delta^{13}C\,({}^{2/1}H)} = 1.424 \pm 0.025$$

That this ratio is indistinguishable from 1.426 serves to reassure us that the leading term is dominant in one-bond shifts. The two-bond isotope shifts have also been observed in $CH_3{}^{13}C(O)CH_3$, and these have the ratio

$$\frac{{}^{2}\Delta^{13}C\,({}^{3/1}H)}{{}^{2}\Delta^{13}C\,({}^{2/1}H)} = 1.41 \pm 0.12.$$

This ratio too is indistinguishable from 1.426, which indicates that in the leading terms the dominant contribution is

$$\left(\frac{\partial\sigma^{C(O)}}{\partial r_{CH}}\right)_e [\, \langle \Delta r_{CH}\rangle - \langle \Delta r_{CT}\rangle \,] \quad \text{for tritium substitution and}$$

$\left(\frac{\partial\sigma^{C(O)}}{\partial r_{CH}}\right)_e$ [$\langle\Delta r_{CH}\rangle - \langle\Delta r_{CD}\rangle$] for deuterium substitution.
The minor changes in the C-C and C=O bond lengths upon deuterium substitution are apparently not important although the electronic factors associated with them may be large.

Another clue is that the long-range isotope shifts correlate with indicators of electronic transmission paths:

(1) dihedral angle dependence of 3-bond shifts

(2) stereospecificity (cis vs. trans vs. gauche) of isotope shifts parallel to that of spin-spin coupling

(3) correlation of long-range isotope shifts with electron-withdrawing / donating ability of substituents, even across a path traversing 7 bonds.

The negative one-bond isotope shift ${}^1\Delta^{13}C\,({}^{2/1}H)$ in $(CH_3)_2C{=}O$ means that $(\partial\sigma^{C(H)}/\partial r_{CH})_e$ is negative (the usual sign). Incidentally, $(\partial\sigma^{C(O)}/\partial r_{CO})_e$ is also negative, as observed in the ${}^1\Delta^{13}C({}^{18/16}O) = -0.050$ ppm [78] in this molecule. What about the sign of the secondary derivative $(\partial\sigma^{C(O)}/\partial r_{CH})_e$? C-H bond lengthening increases the gross atomic charge at ${}^{13}C(=O)$ in $(CH_3)_2C{=}O$ and at ${}^{13}C\oplus$ in $(CH_3)_2C\oplus$, according to theoretical self-consistent field (STO-3G level) calculations.[79] Since an increase in gross atomic charge usually (though not always) means an increase in nuclear shielding, the $(\partial\sigma^{C(O)}/\partial r_{CH})_e$ is probably positive. Indeed, in both $(CH_3)_2{}^{13}CO$ and $(CH_3)_2{}^{13}C\oplus$ the 2-bond ${}^{13}C$ shift upon deuteration is positive, + 0.054 [77,79-81] and + 0.133 ppm per D [82] respectively. Thus, the important term must be

$$(\partial\sigma^{C(O)}/\partial r_{CH})_e \bullet \Delta$$

and not

$$(\partial\sigma^{C(O)}/\partial r_{CO})_e \bullet \delta.$$

This is very encouraging because the secondary dynamic factor δ is so dependent on the entire molecular framework and potential energy surface in which vibrations take place that it is difficult to estimate. On the other hand Δ has a very straightforward dependence on the r_e and masses in the local fragment and can be estimated,[27] as discussed in Sect. IIC2. This means that if the δ terms are unimportant, the sign and magnitude of the long-range isotope shifts are a direct measure of the sign and magnitude of $(\partial\sigma/\partial r_{remote})_e$. This derivative is stereospecific, dependent on electron-withdrawing / donating abilities of substituents, and has the usual electronic-transmission-path-dependence of various observables such as long range spin-spin coupling, substituent effects on chemical shifts, etc.

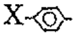
How well are these ideas supported by calculations of secondary derivatives? Unfortunately the shielding derivatives $(\partial\sigma^C/\partial r_{CH})_e$ across the fragments H-C-^{13}C⊕ have not been calculated. On the other hand the following are known: [51]

path	$(\partial\sigma^C/\partial r_{CH})$ / ppm Å^{-1}
H-C≡^{13}C in HC≡CH	+12.5
H-C=^{13}C in $H_2C=CH_2$	+5.3
H-C-^{13}C in H_3C-CH_3	-12.4

and for H-C-^{17}O in $H_2C=O$, $(\partial\sigma^O/\partial r_{CH})_e$=+94.0 ppm Å.[51] So indeed, both + and - signs are possible for these secondary derivatives.

In $CH_3C(O)X$ too, the observed $^2\Delta^{13}CO(^{2/1}H)$ is positive and the magnitude appears to be related to the electron withdrawing / donating ability of X, as shown in the examples below.

X in $CH_3{}^{13}C(O)X$	$^2\Delta^{13}CO(^{2/1}H)$, ppm per D [83]
CH_3COO	+0.008
CH_3O	+0.010
OH	+0.013
F	+0.014
Ph	+0.039
CH_3	+0.054
H	+0.072

Long-range isotope shifts are usually large enough to be observed only when the electronic transmission pathway involves a pi system.[84] For example, the D-induced ^{19}F isotope shifts in 4-fluorophenyl systems correlate linearly with the calculated changes in pi electron density at the F atom upon a C-H bond shortening, as shown in FIGURE 2. It appears that the electronic transmission across the ring determines the sign of the effectively 7-bond isotope shift, and that $(\partial\sigma^F/\partial r_{CH})_e$ is determined largely by changes in the pi charge density at the F atom, $(\partial q_\pi/\partial r_{CH})_e$. The change in the pi charge densities at F atom upon shortening the C-H bond in the X group in X--F calculated by MNDO range from +11.4 x 10^{-5} (electron-donating X) to -15.9 x 10^{-5} (electron-withdrawing X) [10] and correlate with the isotope shift

${}^{7}\Delta^{19}F\ ({}^{2/1}H)$ of -0.28 ppm to +0.461 ppm.[10,43] The signs of the observed isotope shifts imply that the long-range derivative $(\partial\sigma^{F}/\partial r_{CH})_{e}$ is positive when X is an electron-withdrawing group in $X=\overset{\oplus}{C}\text{-}(CD_3)_2$, and negative when X is an electron-donating group as in $X=\overset{\oplus}{C}\text{-}(CHD_2)(CD_3)$.

Although charge densities do not tell the whole story about nuclear shielding, in these specific examples the shielding changes are mimicked by the changes (upon remote bond extension) of the pi charge densities or the gross atomic charges centered at the resonant nucleus. In FIGURE 2 the signs and relative magnitudes are mimicked well enough that in these cases we may assume that the secondary derivative is directly related to the observed long-range isotope shift.

(2) Stereospecificity

Once we accept the notion that isotope shifts across 2 or more bonds reflect secondary (long-range) electronic factors and primary (local) dynamic factors, then the dependence of 3-bond shifts on dihedral angle is not surprising. For example, there is a quantitative correlation of vicinal isotope effects with dihedral angles ϕ of the bonding pathway ${}^{13}C\text{-}C\text{-}C\text{-}D$ in the isotopomers of norbornane.[85] A Karplus-type relationship like that for the vicinal spin-spin coupling constant and ϕ fits the data well. This is also observed in exo-1,6 trimethylene norbornan-3-one and the related alcohol,[86] as well as for ${}^{119}Sn$ isotope shifts.[66] An explanation which is consistent with our previous analysis (Sect. E1) is that the isotope shift is determined primarily by a shortened average bond length at the D-substitution site combined with a long-range derivative which describes the change in shielding at ${}^{13}C$ upon a remote bond stretching. This derivative describes the change in shielding along the same electron-transmission pathway as for vicinal coupling constants. Thus, it is expected that,

as $|{}^{3}J_{trans,cis}| > |{}^{3}J_{gauche}|$

so do $|{}^{3}\Delta^{13}C({}^{2/1}H)_{trans,cis}| > |{}^{3}\Delta^{13}C({}^{2/1}H)_{gauche}|$

and as ${}^{3}J = a+b\cos\phi + c\cos 2\phi$

so do ${}^{3}\Delta A({}^{2/1}H) = a_0 + a_1\cos\phi + a_2\cos 2\phi$ where ϕ is the dihedral angle.

This is indeed found to be the case for ${}^{3}\Delta^{13}C$ in adamantane [87], proadamantanes [88], and ${}^{3}\Delta^{19}F$ in deuterated acetyl and propionyl fluorides,[83] and for ${}^{3}\Delta^{19}F$ in deuterated fluorocyclohexane and bicyclo [2.2.1] heptane [89]. Similarly, there is a general correlation of ${}^{2,3}\Delta^{19}F(^{2/1}H)$ with ${}^{2,3}J(HF)$ coupling in fluoroethenes.[76] Unlike ${}^{3}J$ however, a detailed angle dependence for isotope shifts that includes all known examples cannot be formulated using the same set of a_0, a_1, and a_2. Nevertheless, there is a clear angular dependence in each class of related examples. The stereospecificity of long-range isotope shifts confirm the dominance of the long-range electronic factor rather than the long-range dynamic factor, a fortunate occurrence since the former is far more interesting and useful than the latter.

(F) Isotope exchange equilibria

A common means of preparing partly deuterated chemical species in solution is by dissolving a solute in water of known deuterium / hydrogen ratio and waiting until the sample has come to equilibrium with respect to D/H exchange. Examples are shown in FIGURE 3 for solutions with 0.15, 0.50, and 0.85 D isotopic fraction.[17] Depending on the solvent isotope composition (call the deuterium fraction *d*, the proton fraction *(1-d)*, the relative intensities of the ^{59}Co peaks of the various

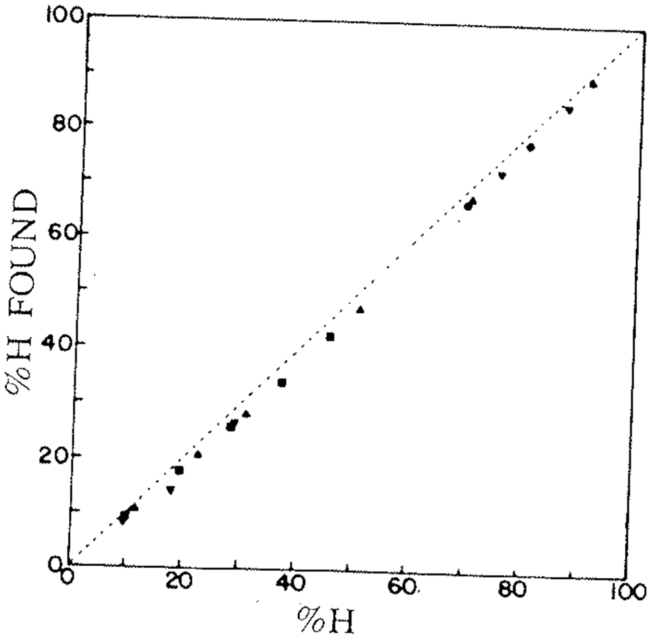


Fig. 12. The proton fraction found from analysis of intensities in Fig. 3 as a function of the D_2O/H_2O solvent composition. The deviations from the dotted line are due to isotope effects on the chemical equilibria involving H/D exchange between the hexammine sites and the water sites. This is a plot of *(1-f)* on the ordinate and *(1-d)* on the abcissa. Reproduced with permission from J.G. Russell and R.G. Bryant, *Anal. Chim. Acta*, 151 (1983) 227.[18]

isotopomers H_{18}, H_pD_{18-p}, through D_{18} will be given strictly by the statistical formula,

$$I = [\ 18! / p!\ (18-p)!\ ]\ (1-d)^p\ d^{18-p}$$

provided that there are no isotope effects on the chemical equilibrium . Indeed, in this particular case the found fraction *f* of deuterated species slightly differs from *d* as shown in FIGURE 12. This figure shows explicitly the proton fraction *(1-f)* expressed in percent, found by fitting intensities of the several peaks in the spectrum of each prepared solvent composition *(1-d)* expressed in percent. The precision and accuracy of the data are sufficient to clearly indicate that there are isotope effects on the exchange equilibria. In this case, the so-called isotopic fractionation factor for H-D exchange in aqueous solution is larger than 1.0, that is the D prefers to attach to the N in the hexammine complex rather than the O in water.

Isotope effects on chemical equilibria have been studied since 1933 (H.C. Urey).[90-93] NMR spectroscopy has provided quantitative experimental information.[94-96] In this section we will discuss only the use of isotope shifts to determine the isotopic fractionation factors in OH, NH, SH, etc... groups exchanging hydrogen and deuterium with hydroxylic solvents, H_2O/D_2O in particular.[97,98] Many of the systems studied involve multiple equilibria. Nevertheless, each of the many equilibrium constants involved can be expressed in the same form. Let us consider a ^{15}N site (such as aniline) with two exchangeable protons as an example and for the purpose of this illustration, limit the chemical species to the following:

$$RNH_2 + D_2O \overset{K_1}{\rightleftharpoons} RNHD + HDO \qquad (22)$$

$$RNHD + HDO \overset{K_2}{\rightleftharpoons} RND_2 + H_2O \qquad (23)$$

$$RNHD + D_2O \overset{K_3}{\rightleftharpoons} RND_2 + HDO \qquad (24)$$

$$RNH_2 + HDO \overset{K_4}{\rightleftharpoons} RNHD + H_2O \qquad (25)$$

$$H_2O + D_2O \overset{K_w}{\rightleftharpoons} 2HDO \qquad (26)$$

$$RNH_2 + RND_2 \overset{K_{self}}{\rightleftharpoons} 2RNHD$$

Let f_1 = fraction present as RNHD

f_2 = fraction present as RND_2

f_0 = fraction present as RNH_2

such that $f_1 + f_2 + f_0 = 1$. Ordinarily the individual fractions f_1, f_2, and f_0 can be observed directly from the spectrum as in aniline and aniline derivatives [99]. The spectra appear as in the example of FIGURE 1 for ^{119}Sn in $SnH_{3-n}D_n^-$ when the isotope exchange is slow relative to the NMR time scale, that is, when the rate of exchange is less than the isotope shifts in hertz. The equilibrium constants can then be expressed as:

$$K_1 = \frac{f_1}{f_0}\frac{(HDO)}{(D_2O)} \qquad K_2 = \frac{f_2}{f_1}\frac{(H_2O)}{(HDO)} \tag{27}$$

$$K_3 = \frac{f_2}{f_1}\frac{(HDO)}{(D_2O)} \qquad K_4 = \frac{f_1}{f_0}\frac{(H_2O)}{(HDO)} \qquad K_w = \frac{(HDO)^2}{(H_2O)(D_2O)}$$

K_w is known theoretically as 3.85 at 298 K. the experimental value is about 3% lower.[92] From this K_w the ratios of (HDO) : (H_2O) : (D_2O) can be calculated at each solvent composition *d*. Even when the isotopic exchange is fast, resulting in only an average resonance signal, it is still possible to obtain the fractionation factor in the method proposed by Jarrett and Saunders [97,98]. The frequency of the average resonance signal of the probe nucleus is measured in a D_2O/H_2O mixture of known isotopic composition D/H = *d/(1-d)*. The shift is measured relative to a separate H_2O solution. The measured chemical shift between the probe nucleus in the H_2O solution and in the separate D_2O solution includes the intrinsic isotope shift and solvent isotope shifts. For example the D-induced intrinsic ^{19}F isotope shift in HF is -2.5±0.5 ppm [100] whereas the measured shift between HF in H_2O and DF in D_2O was around -6 ppm [91]. In the case of $^{19}F^-$ ion in KF solutions or of $^{37}Cl^-$ ion, the entire shift observed is the solvent isotope shift. The experimental quantity *f* is then obtained as

$$f = \frac{\nu_{ave} - \nu_{in\ H_2O}}{\nu_{in\ D_2O} - \nu_{in\ H_2O}} \tag{28}$$

In the particular example of two equivalent exchangeable protons, *f* can be related to the fractions of the individual isotopomers if the isotope shifts are taken to be strictly additive (which is a very good approximation in most cases) and if the self exchange is strictly statistical. Thus, in the above example,

$$f = \frac{1}{2} f_1 + f_2 \qquad \text{and} \quad 1 - f = \frac{1}{2} f_1 + f_0 \tag{29}$$

Thus, we can write

$$K_1 = \frac{2f}{1-f}\frac{(HDO)}{(D_2O)} \qquad K_2 = \frac{1}{2}\frac{f}{1-f}\frac{(H_2O)}{(HDO)}$$
$$K_3 = \frac{1}{2}\frac{f}{1-f}\frac{(HDO)}{(D_2O)} \qquad K_4 = 2\frac{f}{1-f}\frac{(H_2O)}{(HDO)} \tag{30}$$

It turns out that

$$\frac{(HDO)}{(D_2O)} \approx \frac{2(1-d)}{d}, \qquad \frac{(H_2O)}{(HDO)} \approx \frac{(1-d)}{2d}, \qquad \text{and} \ \frac{(H_2O)}{(D_2O)} \cong \frac{(1-d)^2}{d^2} \tag{31}$$

The above ratios of water isotopomers are exactly true only if $K_w = 4$ exactly, but for

$K_w = 3.85$ they are close enough. In other words, using the proper $(HDO)/(D_2O)$, etc., ratios calculated from $K_w = 3.85$ change the results only minimally and all changes are a small percent of the experimental error. Thus, each of the above equilibrium constants can be written in the following simple form:

$$K \approx (\text{sym. nos.})\left(\frac{f}{1-f}\right)\left(\frac{1-d}{d}\right) \tag{32}$$

The factors involving the symmetry numbers which accounts for the number of indistinguishable sites (the symmetry number of a molecule is defined as the number of different values of rotational coordinates which correspond to one orientation of the molecule) are respectively 4, 1/4, 1, 1 for K_1 through K_4 respectively (and is 4 for K_w). What this means is that no matter how many equivalent sites are involved, the equilibrium constants are all related to

$$K_{frac} \approx \frac{f}{1-f}\,\frac{1-d}{d} \tag{33}$$

within the approximations already stated above. The individual equilibrium constants will have different factors containing symmetry numbers, of course, and therefore differ by these factors from one another. The studies by Jarrett and Saunders used a wide variety of probe nuclei including ^{31}P, ^{19}F, ^{37}Cl, ^{14}N, ^{13}C, to witness isotope exchange involving O-H, N-H, S-H, and F-H sites in competition with $H_2O/HDO/D_2O$ sites. Their tabulated values of frequencies at various values of d have been used to calculate f for the systems shown in FIGURE 13. The best value of K_{frac} is probably that value around d=0.5 where the observed chemical shifts are largest. They reported an average value of K_{frac} for each system. The method of analysis presented in FIGURE 13 allows an examination of systematic errors in the assumptions or the experiments. Although the experimental scatter is worse in pyrrolidine, the results all show that this empirical measure of isotopic fractionation, $K_{frac} \approx \frac{f}{1-f}\,\frac{1-d}{d}$, tends to decrease with increasing deuterium fraction in the solvent, to an extent which depends on the system, whereas a true thermodynamic equilibrium constant does not. Using the properly calculated $(HDO)/(D_2O)$ ratios from $K_w = 3.85$ makes very slight corrections in the right direction but still well inside experimental error. Activity coefficients will depend on isotopic composition of the solvent but that variation is probably not large enough to account for the systematic trend in FIGURE 13. The latter could well be due to systematic experimental errors.

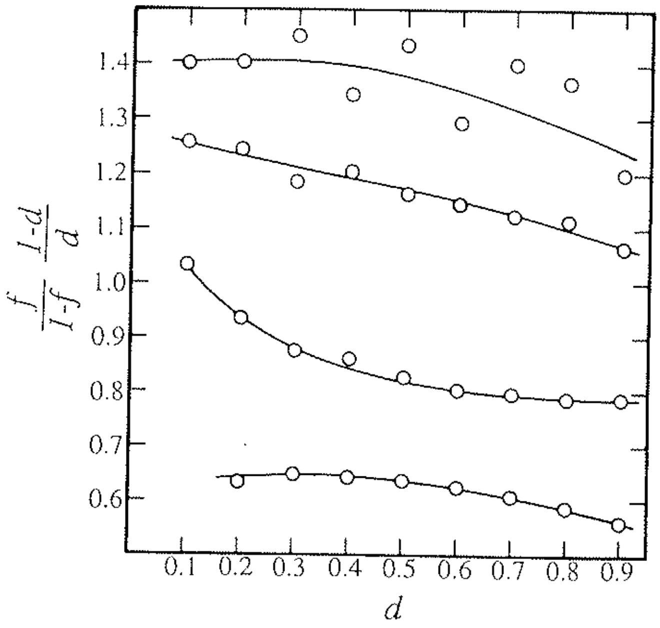


Fig. 13. Isotopic fractionation factor $K_{frac}=[f/(1-f)]\,[(1-d)/d]$ versus d for H/D exchange between the water sites and the N-H site in pyrrolidine, the N-H site in NH_4^+, the O-H site in H_3PO_4, and the S-H in 2-mercaptoethane sulfonic acid Na^+ salt, respectively. Calculated from the experimental data of Ref.97 and 98.

An interesting general result in Jarrett and Saunders's studies which are reflected in these 4 examples (and also, incidentally in Russell and Bryant's example in FIGURE 12) is that N-H sites have $K_{frac} > 1.0$ whereas S-H, and F-H sites have $K_{frac} < 1.0$ in competition with the O-H site in water.

There is a simple theoretical explanation for this. The equilibrium constant for isotopic exchange can be written in terms of the molecular partition functions [90,91]. The potential functions being assumed the same for isotopic molecules (Born-Oppenheimer approximation), the ΔE of the reaction from the zero of energy of reactants to the zero of energy of products is zero in isotopic exchange. The rotational parts are replaced entirely by reciprocals of symmetry numbers and mass factors when the sum over the rotational states is approximated by the classical limit. Since the symmetry numbers have already been separated from K_{frac} all we have to include for a simple exchange such as

$$AH + DB = AD + HB \tag{34}$$

are the following terms:

$$K_{frac} = \frac{\nu_{AD}}{\nu_{DB}} \bullet \frac{\nu_{HB}}{\nu_{AH}} \bullet e^{(\nu_{DB}-\nu_{AD}-\nu_{AH}-\nu_{HB})/2kT} \bullet \frac{(1-e^{-\nu_{AH}/kT})\,(1-e^{-\nu_{DB}/kT})}{(1-e^{-\nu_{AD}/kT})\,(1-e^{-\nu_{HB}/kT})} \tag{35}$$

with $kT = 208.5\ cm^{-1}$ at 300K. In harmonic vibration the first factor is simply

$$\left(\frac{\nu_{AD}\ \nu_{HB}}{\nu_{DB}\ \nu_{AH}}\right)_{harm} = \left[\frac{(m_H + m_B)(m_A + m_D)}{(m_D + m_B)(m_A + m_H)}\right]^{1/2} \tag{36}$$

Right away we can see that in competition with an O-H site, A being lighter than oxygen atom (such as in N-H) will give rise to a factor greater than 1, whereas A being heavier than O (such as in F-H, Cl-H, S-H) will give rise to a factor less than 1. Actually the second factor $e^{(\nu_{DB} - \nu_{AD} + \nu_{AH} - \nu_{HB})/2kT}$ is the most important one. As an example we can put in some typical numbers. Using $\nu_{AH} \approx 3495\ cm^{-1}$, $\nu_{AD} \approx 2491\ cm^{-1}$, $\nu_{HB} \approx 3657\ cm^{-1}$, $\nu_{DB} \approx 2672\ cm^{-1}$, we find

$K_{frac} \approx 1.05$ for NH.

Using $\nu_{AH} \approx 2615\ cm^{-1}$ and $\nu_{AD} \approx 1892\ cm^{-1}$, we find

$K_{frac} \approx 0.53$ for SH.

Of course the use of the harmonic vibrational partition function is not quite correct. Nevertheless, the general comparison between N-H vs O-H on the one hand and S-H vs O-H on the other hand, is well-reproduced. Force constants are in general smaller for the longer A-H bonds involving heavier A, such as sulfur, leading to $K_{frac} < 1$. In general "the heavy isotope tends to concentrate (relative to the light isotope) in that species where it is more tightly bound " (i.e., largest force constants) [92]. That $K_{frac} \neq 1.0$ is indicative of a change of force constant between the two hydrogen sites is probably uninteresting in itself since vibrational spectroscopy is a more direct measure of such changes. However, in solution these isolated molecule partition functions are probably inappropriate so that experimental direct measures of K_{frac} such as provided by the NMR method are necessary. For an O-H site competing with the O-H site in water, the results are more interesting, K_{frac} tends to be < 1 when the hydrogen is involved in strong internal hydrogen bonding and K_{frac} increases with increasing hydrogen bond strength relative to water. The important result is that even when resonance signals from the individual isotopomers are not observable, the NMR isotope shift still provides useful information.

III. ISOTOPE EFFECTS ON COUPLING CONSTANTS

These isotope effects are analogous to the effects on nuclear shielding. A review of available data and the rovibrational theory applied to J has been presented by us [101] and will not be repeated here. These isotope effects are of importance to the fundamental understanding of spin-spin coupling constants as a molecular electronic property. The available experimental and theoretical information on J is not as extensive as for nuclear shielding. There are fewer calculations of the isotropic value of J and even fewer calculations of the components of the J tensor. There is meager experimental information on the J tensor components, largely due to the fact that the traceless direct dipolar coupling tensor D which does not contribute to the isotropic average spin-spin coupling, has components which are usually much larger than the components of J. Since the observed components in oriented molecules are those of (D+J), J tensor components have to be obtained by difference. The D tensor for nuclei N and N′ depends only on geometry, goes roughly as $R^{-3}_{NN'}$, and can explicitly be written in terms of the cartesian positions of the coupled nuclei relative to the external magnetic field. Thus, the J tensor can only be obtained if the rovibrationally averaged nuclear positions can be determined independently with sufficient precision. Experiments which are directly related to isotope effects on an electronic property are the measurements of the temperature-dependence of the property in the absence of intermolecular effects.[102] There are far fewer temperature-dependent studies of J and even fewer studies in the gas in the zero-pressure limit. The indirect spin-spin coupling constant J is a useful index of the chemical bond and isotope effects on it provide information about the sensitivity of J to bond extension. Since the isotope effects on the isotropic average J can be determined more precisely than the individual J tensor components or the anisotropy, the isotope effects can be considered as *the* major source of experimental information for assessing the quality of ab initio theoretical calculations of indirect spin-spin coupling.

The working definitions of the isotope effects on J are: $\Delta_s {}^nJ(AB)[{}^{m'/m}X]$ is the secondary isotope effect on the coupling constant between nucleus A and B due to the substitution of ${}^{m}X$ by the heavier isotope ${}^{m'}X$ somewhere in the molecule.

$$\Delta_s {}^nJ(AB)\,[{}^{m'/m}X] = |{}^nJ(AB)|^* - |{}^nJ(AB)| \qquad (37)$$

$\Delta_p {}^nJ(A^{2/1}H)$ is the primary isotope effect on the coupling constant between nucleus A and H due to the substitution of H by D, the coupled nuclei being separated by n bonds.

$$\Delta_p\, {}^nJ(A^{2/1}H) = |\,{}^nJ(AD)\,|^* \frac{\gamma_H}{\gamma_D} - |\,{}^nJ(AH)\,| \tag{38}$$

where $\gamma_H/\gamma_D = 6.514\ 398\ 04\ (120)$.[103] (39)

Of course if the purely electronic quantities, the reduced coupling constants are compared,

$${}^nK(AH) \equiv 4\pi^2\, {}^nJ(AH)/h\gamma_A\gamma_H \tag{40}$$

then the isotope effect is just a difference:

$$\Delta_p\, {}^nK(A^{2/1}H) = |\,{}^nK(AD)\,|^* - |\,{}^nK(AH)\,|. \tag{41}$$

Only the absolute values are compared, for practical reasons, since the absolute sign of spin-spin coupling constants are not always known. As in isotope shifts the asterisk * denotes the heavier isotopomer. Where both secondary and primary isotope effects are observed, the primary isotope effect should be obtained from J(SnD) in SnH_2D^- and J(SnH) in SnH_3^- for example, rather than J(SnD) and J(SnH) in the same isotopomer SnH_2D^-. The latter difference includes both primary and secondary isotope effects.

Isotope effects on nuclear shielding are usually visually obvious in a high-resolution NMR spectrum since the peaks of the isotopomer are shifted from the parent species. On the other hand, isotope effects on coupling constants are only observed as very slightly different multiplet splittings for each isotopomer (secondary isotope effects) or as a slightly smaller (usually) or larger J(AD) than the expected J(AH) / 6.514 398 04 (primary isotope effects). Because of this factor of 6.514... the isotope effects on J are less precisely determined than the isotope effects on shielding. According to these working definitions a positive isotope effect on J means that the reduced coupling is larger in the deuterated species.

(A) General trends

The general trends and their theoretical explanation have been presented by Jameson and Osten:[101]

(1) The sign of the primary or secondary isotope effect on the coupling constant is not directly related to the absolute sign of the coupling constant. Whether it is related to the absolute sign of the reduced coupling constant is not yet established since one-bond coupling isotope effects are available presently for positive reduced coupling constants only.

(2) Primary isotope effects are negative or positive, the positive signs being

found only in molecules involving one or more lone pairs of the coupled nuclei. For example, primary isotope effects are positive in H_2Se,[15] in PH_2^-,[7] and in PH_3,[13] and in other 3-coordinate phosphorus, but negative in PH_4^+ [7] and in 4- and 5-coordinate phosphorus.[62] It is positive in SnH_3^- (one lone pair) [7] and negative in SnH_4 and SnH_3^+ (no lone pairs) [53].

(3) Secondary isotope effects can have either sign, but are often negative. Positive signs have been observed where triple bonds are involved (as in HC≡CH and HC≡N) but also in some of the same systems with positive primary isotope effects.

(4) Secondary isotope effects are roughly additive upon substitution of several equivalent sites neighboring the coupled nuclei. For example, in NH_4^+ ion, each D substitution decreases $^1J(^{14}NH)$ by 0.05 ± 0.02 Hz,[14] and in PH_3, each D substitution decreases $^1J(PH)$ by 2.5 Hz.[13] Small deviations from additivity have been observed.

(5) The magnitudes of isotope effects are small, the largest primary effect being about 10% of the coupling constant in SnH_3^- and the largest secondary effects being about 3% in SnH_3^-, so that only the effects of deuterium (and tritium) substitution, where the largest fractional changes in mass are involved, have been observed. Some of the larger primary isotope shifts are +11.5 Hz for $\Delta_p\,^1J(PH)$ in PH_3 [13] and +10.5 Hz in SnH_3^-.[7] Secondary isotope shifts as large as -2.0 Hz per D (for $^1J(SiF)$) [104] and +3.0Hz per D (for $^1J(SnH)$) [7] have been observed.

(6) The magnitudes of the isotope effects are roughly proportional to the fractional change in mass, in the very few instances where effects of isotopic substitution of ^1H by ^2H and ^3H have been reported.

(B) Theory and selected examples

Just as in isotope shifts, the isotope effect on J can be written in terms of products of electronic and dynamic factors as follows. For a diatomic molecule,

$$\langle J\rangle^* - \langle J\rangle = (\partial J/\partial r)_e[\langle\Delta r\rangle^* - \langle\Delta r\rangle] + \frac{1}{2}(\partial^2 J/\partial r^2)_e[\langle(\Delta r)^2\rangle^* - \langle(\Delta r)^2\rangle] + \ldots \qquad (42)$$

The dynamic factors are the same as we have already discussed, (and indeed the same for all rovibrational averaging of any molecular electronic properties).[105] Only the electronic factors need to be discussed here. Of course, γ of some nuclei are negative so we really should compare derivatives of the reduced coupling $\left(\frac{\partial K}{\partial r}\right)_e$ etc..., where

$$\left(\frac{\partial J}{\partial r}\right)_e = \frac{h\gamma_N \gamma_{N'}}{4\pi^2}\left(\frac{\partial K}{\partial r}\right)_e \tag{43}$$

One important difference between J and σ is that the latter is a one-center property whereas J is a two-center property. In polyatomic molecules there are usually several electronic factors of comparable size which contribute to the isotope effects on J.

For polyatomic molecules, if ^1J is most sensitive to the bond length, the one-bond shifts can also be written in the same way as for diatomic molecules, the terms such as $(\partial J/\partial\alpha)_e \bullet [\langle\Delta\alpha\rangle^* - \langle\Delta\alpha\rangle] + \ldots$ being less important. Let us consider SnH_4 as an example of a polyatomic molecule. If we consider only the terms in the first derivatives as the leading terms in the spin-spin coupling then,

$$\langle K\rangle_{\text{bond 1}} \approx K_e + \left(\frac{\partial K}{\partial r}\right)_e \Delta r_1 + \left(\frac{\partial K}{\partial r'}\right)_e (\Delta r_2 + \Delta r_3 + \Delta r_4) + \ldots \tag{44}$$

If we further neglect the secondary effects on an Sn-H bond length due to substitution of a remote H by D, then we may represent $\langle\Delta r_{SnH}\rangle$ in all the isotopomers by d and all $\langle\Delta r_{SnD}\rangle$ by (d-Δ) since the average length of the Sn-D bond is shorter than the SnH bond. Then we may write the reduced coupling constants in the following simple forms:

$$SnH_4: \quad K(SnH) \approx K_e + \left[\left(\frac{\partial K}{\partial r}\right)_e + 3\left(\frac{\partial K}{\partial r'}\right)_e\right] d + \ldots \tag{45}$$

$$SnH_3D: \quad K(SnH) \approx K_e + \left(\frac{\partial K}{\partial r}\right)_e d + \left(\frac{\partial K}{\partial r'}\right)_e [2d + d - \Delta] + \ldots$$

$$K(SnD) \approx K_e + \left(\frac{\partial K}{\partial r}\right)_e (d-\Delta) + 3\left(\frac{\partial K}{\partial r'}\right)_e d + \ldots$$

$$SnH_2D_2: \quad K(SnH) \approx K_e + \left(\frac{\partial K}{\partial r}\right)_e d + \left(\frac{\partial K}{\partial r'}\right)_e [d + 2(d-\Delta)] + \ldots$$

$$K(SnD) \approx K_e + \left(\frac{\partial K}{\partial r}\right)_e (d-\Delta) + \left(\frac{\partial K}{\partial r'}\right)_e [(d-\Delta) + 2d] + \ldots$$

$$SnHD_3: \quad K(SnH) \approx K_e + \left(\frac{\partial K}{\partial r}\right)_e d + \left(\frac{\partial K}{\partial r'}\right)_e [3(d-\Delta)] + \ldots$$

$$K(SnD) \approx K_e + \left(\frac{\partial K}{\partial r}\right)_e (d-\Delta) + \left(\frac{\partial K}{\partial r'}\right)_e [2(d-\Delta) + d] + \ldots$$

$$SnD_4: \quad K(SnD) \approx K_e + \left[\left(\frac{\partial K}{\partial r}\right)_e + 3\left(\frac{\partial K}{\partial r'}\right)_e\right] (d-\Delta) + \ldots$$

We can further estimate Δ which is literally

$[\langle \Delta r_{SnH}\rangle - \langle \Delta r_{SnD}\rangle]$ as $\{1-(\mu/\mu^*)^{1/2}\}\langle \Delta r_{SnH}\rangle$ or $0.290\,\langle \Delta r_{SnH}\rangle$.

Estimating $\langle \Delta r_{SnH}\rangle$ by the approximate method used in isotope shifts,[27] using $r_e \approx 1.70\text{Å}$, we get

$\langle \Delta r_{SnH}\rangle \approx 17.80\times10^{-3}$ Å or $\Delta = 5.161\times10^{-3}$ Å.

The observed coupling constants can be converted to the reduced coupling constants

$K = (4\pi^2/h\, \gamma_{Sn}\, \gamma_{H\text{ or }D})\, J$

in reduced units of $10^{19}J^{-1}T^2$. Thus converted, the experimental data are shown below:

	Expt[53]		Calc	
	K(SnH)	K(SnD)	K(SnH)	K(SnD)
SnH_4	429.19±.02		429.20	
SnH_3D	428.81±.02	428.21±.14	428.81	428.16
SnH_2D_2	428.43±.02	427.78±.14	428.42	427.77
$SnHD_3$	428.08±.04	427.49±.14	428.04	427.39
SnD_4		426.91±.29		427.02

Using the parameters

$$\left(\frac{\partial K}{\partial r}\right)_e \approx 200 \text{ reduced units per Å}, \qquad \left(\frac{\partial K}{\partial r'}\right) \approx 75 \text{ reduced units per Å},$$

the leading terms in the vibrational correction for K(SnH) in SnH_4 is +7.565 reduced units so that $K_e \approx 421.63$ reduced units. Using these parameters we are able fit all 8 experimental numbers to within experimental error, as shown in the right side of the above table.

An analogous treatment of SnH_3^- leads to the estimates

$$\left(\frac{\partial K}{\partial r}\right)_e \approx -580 \text{ reduced units per Å} \qquad \left(\frac{\partial K}{\partial r'}\right)_e \approx -130 \text{ reduced units per Å}.$$

These provide a rough vibrational correction of -14.95 reduced units for K(SnH) in SnH_3^- so that K_e is estimated as 39.04 reduced units. Comparisons of the calculated and experimental values are shown below:

	Expt[7]		Calc	
	K(SnH)	K(SnD)	K(SnH)	K(SnD)
SnH_3^-	24.09±0.01		24.09	
SnH_2D^-	24.76±0.02	27.09±0.14	24.76	27.08
$SnHD_2^-$	25.40±0.03	27.72±0.22	25.43	27.75
SnD_3^-		28.53±0.43		28.42

The agreement with the 6 experimental numbers is very good. We have neglected differential intermolecular effects on the coupling constants of the isotopomers of SnH_3^-, which could be significant. These quantities can be translated back to Hz Å^{-1}

	SnH_4	SnH_3^-
$\left(\frac{\partial J(SnH)}{\partial r}\right)_e$	-900 Hz Å^{-1}	+2600 Hz Å^{-1}
$\left(\frac{\partial J(SnH)}{\partial r'}\right)_e$	-340 Hz Å^{-1}	+580 Hz Å^{-1}
$\langle J(SnH)\rangle - J_e$	-34.1 Hz	+67.3 Hz
J_e	-1899.3 Hz	-175.8 Hz

It is interesting that although the magnitude of the SnH coupling constant is about one order of magnitude smaller in SnH_3^- compared to SnH_4, the sensitivity of the spin-spin coupling to bond extension is almost 3 times as great. The lone pair (on Sn in SnH_3^-) is known to be responsible for negative contributions to the reduced coupling,[106,107] leading to a much smaller magnitude of the spin spin coupling. Apparently it is also the lone pair which is responsible for the greater sensitivity to bond extension. By similar procedures, the change in the reduced coupling constant with extension of the bond $(\partial K/\partial r)_e$, or of an adjacent bond $(\partial K/\partial r')_e$, can be estimated in other systems such as SnH_3^+, PH_4^+, PH_3, PH_2^-, and SeH_2 from experimental values of J(AH) and J(AD) combined with values of the dynamic factor calculated by methods described here. These values are compared in TABLE 3 with some published theoretical values. Since all are expressed as γ-free reduced coupling constants these are purely electronic quantities which can be directly compared with each other in sign and magnitude. Theory has shown that the Fermi contact term is most sensitive to bond stretch.[108,109] Thus,it is not surprising that the magnitude of the empirical derivatives in TABLE 3 increase with increasing spin density at the nucleus just as the reduced coupling constants are known to do.[106] The earlier prediction by Jameson and Osten that $(\partial K(AH)/\partial r)_e$ will generally be negative when A has lone pairs but will be positive otherwise [101] appears to be correct. Other interesting trends which also emerge in TABLE 3 are that the dependence of the coupling on the extension of a neighboring bond $(\partial K/\partial r')_e$, is usually smaller, and usually depends on whether A has a lone pair or not (PH_3 is an exception , however). The values in TABLE 3 for molecular ions should be considered with caution for there may be differential intermolecular effects for the isotopomers, which we have ignored.

In summary, theory supports the following general behavior: where no lone pairs are involved on atom A, the magnitude of the AD coupling is smaller than expected from the observed AH coupling. Further, the magnitude of the AH coupling becomes smaller with increasing mass of neighboring atoms. Where there is one or more lone pairs on A, the magnitude of the AD coupling is larger than expected from the observed AH coupling. The magnitude of the AH coupling (except for PH_3) becomes larger with increasing mass of neighboring atoms.

TABLE 3

Changes in reduced spin-spin coupling upon extension of the bond r and upon extension of a neighboring bond r′

Molecule	$(\partial K/\partial r)_e$[a]	$(\partial K/\partial r')_e$[a]	Ref(expt)	Ref(theor)
Without lone pairs				
HD	+149.79			108
CH_4	+ 41.175	+26.8 [b]		110
CH_4	$[(\partial K/\partial r)_e + 3(\partial K/\partial r')_e] = 121.8$		102	
PH_4^+	+104±20	+7.5±2	7	
$H_2P(O)OH$	+50			101
SnH_4	+200±30	+75±7	53	
SnH_3^+	+600±400	~0	7	
With lone pairs				
$^{13}C^{17}O$	negative			109
$^{14}N^{15}N$	negative			109
HF	-51.56			111
PH_3	-230			101
PH_3	-422	+46.5	13	
PH_2^-	-125	-26	7	
SeH_2	-190±60	-71±9	15	
SnH_3^-	-580±40	-130±10	7	

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[a] Error estimates are based only on the quoted errors in experimental values of J and do not include errors associated with rovibrational averaging or failure to take into account intermolecular effects and second and higher derivatives.

[b] From the observed temperature dependence of J(CH) in CH_4.

IV. CONCLUSIONS

The isotope effects on nuclear shielding and on spin-spin coupling can be measured with precision and are found to have many useful applications. The very large collection of these observations have been systematically discussed here in terms of general trends and specific dependences on the chemist's usual concepts (net charge on the molecule, presence or absence of lone pairs, bond order, hybridization, etc...).

We have found that the observed isotope effects on shielding and on the spin-spin coupling can be interpreted with a theoretical model within the Born-Oppenheimer approximation. The observed isotope effect is therefore, by its nature, a convolution of electronic and dynamic parts which can be individually calculated by ab initio theoretical methods and combined in the way described by eq. 2, each term being a product of an electronic factor and a dynamic factor, up to second derivatives or even up to sixth derivatives, as desired. In the very few cases in which this full calculation has been done (H_2O, CH_4, and a few diatomic molecules), it has been found that beyond the largest single term there are other smaller but significant terms. Therefore, in accurate work it is obviously necessary to do the complete calculations. On the other hand, short of doing such complete calculations, we have seen that important information , albeit semi-quantitative, can be obtained from the measured isotope effects.

The trends which emerge from the measured isotope effects become apparent when one of the terms in the above equation dominates. In particular, for one-bond shifts we considered cases in which the dominant term is

$$^{1}\Delta A\,(^{m'/m}X) \approx \left(\frac{\partial\sigma^{A}}{\partial r_{AX}}\right)_{e} \left[\, \langle \Delta r_{A^{m}X} \rangle - \langle \Delta r_{A^{m'}X} \rangle \,\right] \tag{46}$$

and in long-range isotope shifts we considered cases in which the dominant term is

$$^{n}\Delta A\,(^{m'/m}X) \approx \left(\frac{\partial\sigma^{A}}{\partial r_{YX}}\right)_{e} \left[\, \langle \Delta r_{Y^{m}X} \rangle - \langle \Delta r_{Y^{m'}X} \rangle \,\right] \tag{47}$$

where the Y-X bond is n bonds away from resonant nucleus A.

We have shown the mass-dependence of the dynamic term in the square brackets, and elicited the $[(m'-m)/m'] [m_A/(m_A+m)]$ factors in it by using a diatomic model. We have also shown the dependence of $\langle \Delta r \rangle$ itself on the bond length r_e at the equilibrium geometry, on reduced mass, and on the general constants which characterize the harmonic and anharmonic force constants and which largely depend only on the rows in the periodic table to which the bonded atoms belong. Those isotope shift observations which exhibit the mass dependence of the dynamic factors do indeed exhibit the mass factors in this particular form. Many trends which have been noted and which provide the means with which the very large body of isotope shift observations can be sorted out have been explained with the rovibrational model.

Our goal was to elicit the electronic part directly from experiment by separating out and calculating or estimating the dynamic part wherever possible. If we can do this then we can examine the electronic part which provides us with direct invaluable information about the shielding of a nucleus in a molecule. Thus, we can view the isotopic substitution at some site as a minor perturbation of the electronic shielding at the site of the resonant nucleus. The electronic transmission path between the substitution site and the nuclear site can thus be probed.

The early questions asked of ab initio calculations were, how well do theoretical methods of calculating shielding reproduce the isotropic chemical shifts (^{13}C relative to some reference environment such as CH_4 for example)? More recently we have asked, how well do the calculations reproduce the shielding tensor components? This is a more stringent test of ab initio theory. In the isotope shift experiments we can pose an even more stringent test, of how well do the calculations reproduce the partial derivatives of shielding with respect to various coordinates, e.g., $(\partial\sigma/\partial r)_e$, $(\partial\sigma/\partial\alpha)_e$, etc...? At the outset we compared theoretical derivatives in very small molecules (where calculations with large basis sets are feasible) to the empirical ones that we have obtained by separately calculating the dynamic part of the isotope shift. This way we checked how well our model holds up. As we found good agreement between the empirical derivatives elicited by our model from experiment and the derivatives calculated by ab initio theoretical methods, we now have confidence in using the model to elicit other empirical derivatives from experiment in larger systems where ab initio calculations are less feasible. In so doing, then the very large collection of isotope shifts can provide insight into the shielding function (a mathematical surface) in terms of its dependence on net charge of the molecule, bond order, presence of lone pairs, hybridization, etc.

The following are our major findings about these shielding derivatives:
The electronic factor in the one-bond shift $(\partial\sigma^A/\partial r_{AX})_e$ has been found to have the fol-

lowing attributes which explain the observed trends.

1. It is nearly always negative. In a linear molecule it is dominated by that component of the shielding tensor perpendicular to the bond.

2. For the same bond in homologous compounds it correlates with r_e, which after all is itself an electronic property.

3. For the same two bonded atoms its magnitude increases with bond order.

4. For the same bond in molecules related by presence or absence of a lone pair on A, $(\partial\sigma/\partial r)_e$ decreases algebraically with the presence of a lone pair.

5. It increases algebraically with net charge on the molecule.

6. It is easily visualized in terms of depletion of electron density in the immediate vicinity of nucleus A as nucleus A is moved away from X, but this is a simplistic view.

7. For the same nucleus, it correlates with the paramagnetic part of shielding as in comparisons of $(\partial\sigma^F/\partial r_{MX})_e$ in various MX_n, M being B, C, N, S, Se, Te, W, etc. atoms.

8. For various nuclei, it correlates with the chemical shift range, that is, $(\partial\sigma_A/\partial r)_e$ correlates with $\langle r^{-3} \rangle$ for atomic A. This is a consequence of the paramagnetic part of the shielding being more sensitive to bond stretching than the diamagnetic part.

The electronic factor in the long-range isotope shifts $(\partial\sigma^A/\partial r_{YX})_e$ is found to have the following attributes:

(1) The magnitude decreases (usually) as the Y-X bond becomes more remote from nucleus A.

(2) It is stereospecific. For n=3, cis, trans ⟩ gauche, and in some cases the dihedral angle dependence has been clearly observed and it is not unlike the Karplus relation of 3-bond spin-spin coupling with angle ϕ. This stereospecificity is purely electronic in nature.

(3) It correlates with other purely electronic quantities which are dependent on the same electronic transmission path such as substituent effects on chemical shifts by electron-withdrawing or donating groups.

(4) It is easily visualized in terms of the easily calculated change in electron density (gross atomic charge, pi electron density, etc.) at A upon extension of the

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