

Second-order NMR spectra at high field of common organic functional groups†

Paul J. Stevenson*

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The proton NMR spectra of aryl *n*-propyl sulfides gave rise to what may appear to be first-order proton NMR spectra. Upon oxidation to the corresponding sulfone, the spectra changed appearance dramatically and were clearly second-order. A detailed analysis of these second-order spectra, in the sulfone series, provided vicinal coupling constants which indicated that these compounds had a moderate preference for the *anti*-conformer, reflecting the much greater size of the sulfone over the sulfide. It also emerged, from this study, that the criterion for observing large second-order effects in the proton NMR spectra of 1,2-disubstituted ethanes was that the difference in vicinal coupling constants must be large and the difference in geminal coupling constants must be small. *n*-Propyl triphenylphosphonium bromide and 2-trimethylsilylethanesulfonyl chloride, and derivatives thereof, also exhibited second-order spectra, again due to the bulky substituents. Since these spectra are second-order due to magnetic nonequivalence of the nuclei in question, not chemical shifts, the proton spectra are perpetually second-order and can never be rendered first-order by using higher field NMR spectrometers.

Introduction

Signals in NMR spectroscopy in which the contributions from the coupling constant and chemical shift terms cannot be treated independently are generally known as second-order.¹ Such multiplets have been known since the genesis of NMR spectroscopy and were instrumental in devising the detailed theoretical basis of the subject. When the difference in chemical shift between two nuclei is of the same order of magnitude, or less, than the coupling constant between the multiplets then second-order behaviour is observed. This normally results in a dramatic increase in complexity of the signals and renders analysis, and annotation, of the spectra much more difficult. Since the chemical shift, in Hertz, is directly proportional to the magnetic field strength at which the NMR spectrometer operates, the advent of high field NMR spectrometers has greatly diminished the occurrence of second-order multiplets as most chemically non-equivalent nuclei have different chemical shifts.

However, it is possible for two nuclei to be chemically equivalent *i.e.* have the same chemical shift, but to be magnetically non-equivalent. The criterion for magnetic non-equivalence, in such cases, is that the coupling constant to a third nucleus must

be different. However, though the two chemically equivalent, magnetically non-equivalent nuclei have the same chemical shifts, the NMR spectra that result are second-order. In practice, the difference in the two coupling constants must be substantial for second-order behaviour to be observed. This phenomenon is most widely observed in rigid, or symmetrical molecules such as substituted benzenes, with *ortho*-dichlorobenzene, an NMR standard, being the best known example.

Second-order behaviour in the NMR spectra of achiral 1,2-disubstituted ethanes has been known since the dawn of NMR spectroscopy using low field spectrometers. For example AA'BB' spin systems are observed in the aliphatic region of the proton NMR spectra of 1-chloro-2-phenylethane,² and 3-bromopropionitrile³ when run at low field. On increasing the magnetic field to 300 MHz 1-chloro-2-phenylethane and 3-bromopropionitrile became AA'XX' spin systems and essentially looked like first-order triplets with a little roofing.⁴ 1-Chloro-2-bromoethane,⁵ 3,3-dimethylbutyl chloride,⁶ 3-chloropropyl trimethoxysilane⁷ and chloroethyltrimethyl silane⁸ are all AA'XX' spin systems, at high field, and in all these molecules the *anti*-conformer is favoured for steric or electronic reasons. This leads to measurable differences in average coupling constants, J_{AX} and $J_{AX'}$, making nuclei A and A' magnetically nonequivalent and results in complex second-order NMR spectra. Molecules such as acetyl choline,⁹ and analogues,¹⁰ as well as 1,2-difluoroalkanes¹¹ show a marked preference for the *gauche* conformer and again this leads to second-order spectra. The detailed analysis of such spin systems has been reviewed¹² in the early 1970's and is now included in many standard, older NMR textbooks.¹³⁻¹⁵

School of Chemistry and Chemical Engineering, Queens University of Belfast, Belfast, UK, BT9 5AG; Fax: +44 2890974426

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However, because these studies were carried out a very long time ago, using mostly low-field NMR spectrometers, there is now a common, incorrect, perception that strong second-order spectra are not observed on high field NMR spectrometers. Consequently, for all achiral 1,2-disubstituted ethanes, which exhibit second-order behaviour, due to differences in vicinal coupling constants, the use of higher magnetic fields is *never* going to make the proton NMR spectra first-order as the chemical shift of A and A' will always be identical regardless of field strength! In essence, the proton NMR spectra of these molecules are perpetually second-order and nothing can ever be done to mitigate this complicating effect.

A preliminary search of the chemical literature revealed that although AA'XX' spin systems are still commonly encountered and reported in the inorganic chemistry literature,^{16–18} these are rarely identified in the recent organic chemistry literature.^{19,20}

Results and discussion

The Julia–Lythgoe reaction has emerged as the method of choice for preparing *trans*-alkenes from aldehydes.^{21–23} Modification of the original procedure, firstly by Julia,^{24–26} and then by Kocienski,^{27–29} using heterocyclic sulfones derived from benzothiazole and phenyltetrazole respectively, enable the reaction to be carried out as a one-pot operation increasing the versatility and utility of the procedure.

During recent synthetic endeavours, directed towards the synthesis of the indolizidine piclavine alkaloids,³⁰ the modified Julia–Lythgoe reaction was investigated. Sulfide **1**, Fig. 1, was prepared by a literature procedure³¹ and initial examination of the proton NMR spectrum indicated that the methylene group adjacent to the sulfur was a triplet. Upon closer inspection this signal was not quite a proper triplet as the central line was very broad at the bottom, Fig. 2. On oxidation of the sulfide to the sulfone **2**, the signal for the low field methylene group took on a most unusual appearance, as illustrated in Fig. 2.

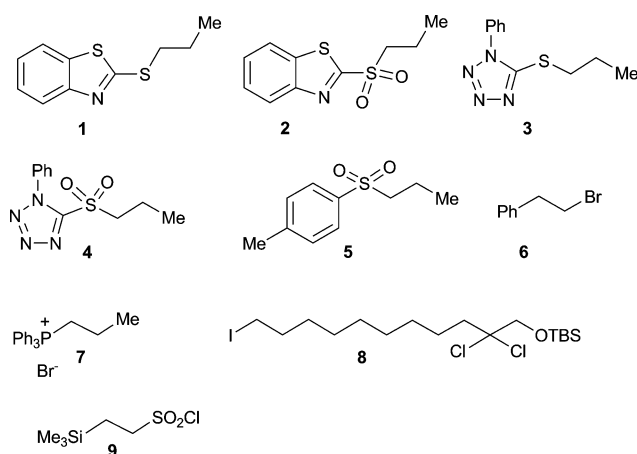


Fig. 1 Series of 1,2-disubstituted ethanes, seven of which display second-order spectra at high field.

At first glance the multiplet for the sulfone **2** looked like a triplet but with the middle line L4 diminished in intensity, by about a factor of two. On expansion it became clear that the gross structure of this multiplet was three main lines, of about equal

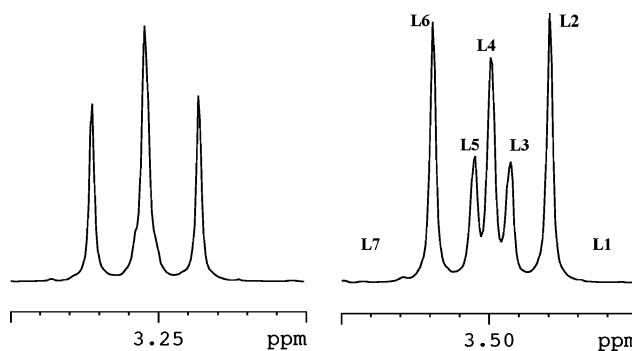


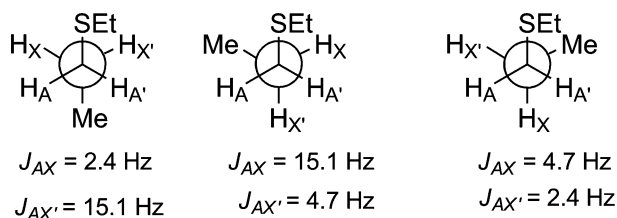
Fig. 2 NMR spectra depicting methylene signals adjacent to sulfur for sulfide **1** and sulfone **2**.

intensity (L2, L4 and L6), but that the central line was flanked by two additional peaks (L3 and L5). In addition, the main multiplet was flanked by two very low intensity peaks (L1 and L7), at about the intensity level of ¹³C satellites and were only apparent on very close scrutiny. The NMR spectra of sulfide **3** and sulfone **4** showed analogous behaviour. Upon inspection of the literature of proton NMR spectra of achiral aryl *n*-alkyl sulfone containing α -methylene signals, these signals were generally interpreted as multiplets.^{32–35} In journals which published actual spectra in the supplementary material,^{36,37} it was clear that the shape of the multiplet adjacent to the sulfone was identical to the multiplet that was observed for compounds **2** and **4**. However, to date no attempt has been made to rationalise or analyse this most unusual multiplet in the sulfone series, or to offer any explanation as to why the spectra of the sulfones are so radically different from those of the sulfides from which they were derived.

It was previously known that hindered rotation about aryl sulfur bonds was possible,^{38,39} and when the two *ortho*-positions had different substituents this could render hydrogens within methylene groups chemically nonequivalent. Since the heterocyclic sulfones in question, **2** and **4**, had different *ortho*-substituents this was initially believed to be the most plausible source of the complexity within the proton NMR spectra of these compounds. However, heating the sample to 50 °C or cooling to –30 °C had no noticeable effect on the multiplet, making a dynamic process seem less plausible. *p*-Tolyl propyl sulfone **5** was prepared by a literature procedure,⁴⁰ and the methylene protons adjacent to the sulfone had an identical splitting pattern to that of the heterocyclic sulfones **2** and **4**, ruling out any effects due to asymmetry in the aromatic ring. Furthermore, the proton NMR spectrum for dibutylsulfone showed a similar pattern for the signal of the methylene group next to sulfur.⁴

It was eventually realised that the multiplet for the sulfone **2** at δ 3.50 ppm was the classic pattern for a second-order AA'XX' spin system.¹² The perplexing question was, why was the multiplicity of the methylene signal adjacent to the sulfone in compounds **2** and **4** so different to the sulfides **1** and **3** from which they were derived?

In Fig. 3, it was clear that for any particular conformer, the two vicinal coupling constants J_{AX} and $J_{AX'}$ are different. The consequence of this is to render the chemically equivalent nuclei H_A and $H_{A'}$ as well as H_X and $H_{X'}$ magnetically nonequivalent. In principle the chemical shifts of protons H_A and $H_{A'}$ are dissimilar in the *gauche* conformations, but these differences average to zero due to rapid inter-conversion of these conformers. Consequently,



Couplings constants were empirically evaluated by the Gandour method, which is the Karplus equation with the electronegativity of the substituents factored in.

$$J_{AX} (\text{average}) = 2.4\rho + (15.1 + 4.7)1/2(1-\rho)$$

$$J_{AX'} (\text{average}) = 15.1\rho + (4.7 + 2.4)1/2(1-\rho)$$

$$\rho = \text{mol fraction of conformer in which EtS and Me are anti}$$

Fig. 3 Staggered conformations of ethylthiopropyl ether, together with empirically evaluated coupling constants for each conformation. This allows for the calculation of average coupling constants values, which are ultimately what are observed for J_{AX} and $J_{AX'}$.

when the difference in vicinal coupling constants ($J_{AX} - J_{AX'}$), averaged over all conformations has a non-zero value, then the spectra became second-order. Furthermore, when the difference in vicinal coupling constants ($J_{AX} - J_{AX'}$) was large, the manifestation of second-order behaviour may be very perceptible.

The observed vicinal coupling constants, are the average values of J_{AX} and $J_{AX'}$ over all of the different discrete conformations, weighted by the population of molecules in those particular conformations.^{41,42} Clearly, in a 1,2-disubstituted ethane, the most highly populated conformations are going to be the three staggered conformations depicted in Fig. 3. For illustrative purposes only, it was instructive to examine how the observed coupling constants would differ as the relative ratio of the three staggered conformers varied. To do this calculation it was necessary to have values for J_{AX} and $J_{AX'}$ in the three staggered conformations. Although these values cannot be measured directly from the spectra, they can be estimated using the Gandour method,⁴³ which takes account of both the electronegativity of the substituents and the dihedral angle. Unfortunately, there were no empirical values available for aryl sulfides or sulfones so for the illustration in Fig. 3, the vicinal coupling constants were evaluated for an ethyl sulfide, for which empirical values were available. Using this approach, values for J_{AX} and $J_{AX'}$ were evaluated for each of the discrete staggered conformers shown in Fig. 3 and these values are tabulated below the relevant conformers. Since the two *gauche* conformers have the same energy, they are equally populated. Therefore, it was possible to evaluate the percentage of all three staggered conformers when the mole fraction ρ , of the *anti* conformer was varied from 0–100%. Using these population distributions, column 1, Table 1, and the empirically derived angle dependent vicinal coupling constants, for each discrete staggered conformer, it was possible to crudely gauge how the weighted average value of the vicinal coupling constants would vary with conformational preference, Table 1, columns 2 and 3. The final column in Table 1 tabulates the difference in average vicinal coupling constants, which was an important parameter in determining magnetic non-equivalence between protons A and A'.

It was clear from Table 1 that there was a range of conformational distributions in which the difference in the vicinal coupling constants were small. When all three conformers were equally

Table 1 Variation of the value of the vicinal coupling constants J_{AX} and $J_{AX'}$, averaged over three staggered conformations, and weighted for the population density of each conformer uniquely defined by ρ

ρ mol fraction <i>anti</i> %	Average J_{AX} Hz	Average $J_{AX'}$ Hz	$J_{AX} - J_{AX'}$ Hz
0	9.9	3.6	6.3
10	9.2	4.7	4.5
20	8.4	5.9	2.5
23	8.2 ^b	6.2	2.0
30	7.7 ^b	7	0.7
33	7.4 ^a	7.4	0
40	6.9 ^b	8.2	-1.3
44	6.6 ^b	8.6	-2.0
50	6.2	9.3	-3.1
60	5.4	10.5	-5.1
70	4.7	11.6	-6.9
80	3.9	12.8	-8.9
90	3.2	13.9	-10.7
100	2.4	15.1	-12.7

^a Both coupling constants are the same so the multiplet is a true first-order triplet. ^b Both coupling constants are different but multiplet still looks like a first-order triplet and is best described as an 'apparent triplet'.

populated both J_{AX} and $J_{AX'}$ were equal in value giving rise to a true first order triplet. Using the g-NMR software simulation package, for a linewidth of 1 Hz, and a coupling constant difference of 2 Hz it was just about possible to see additional lines L3 and L5 as shoulders, with a substantial broadening to the central line L4. Therefore, for sulfides **1** and **3** it was tempting to speculate that the mol fraction of *anti* conformer was somewhere between 23% and 44%, a maximum deviation of $\pm 10\%$ from its statistical value of 33%. However, as will be articulated later, the difference in geminal coupling constants is also important and one must be very wary of using vicinal coupling constant information, that was not measured, only inferred, to deduce a conformational preference.

For sulfones **2**, **4** and **5**, due to the strong second-order nature of the spectra, it was possible to measure the two vicinal coupling constants J_{AX} and $J_{AX'}$ and the two geminal coupling constants $J_{AA'}$ and $J_{XX'}$. The four coupling constants defining the multiplets were extracted using the g-NMR software package and these are tabulated in Table 2. Using the Becker¹⁵ or Gunther¹² analysis, L1 minus L7 gave twice the sum of the geminal coupling constants $J_{AA'}$ and $J_{XX'}$ and the average value of these was used as a starting point in the subsequent iteration. L2 minus L6 gave the sum of the vicinal coupling constants, and since we believed that the difference of these values had to be greater than 2 Hz to observe splitting of lines L3 and L5, this gave a sensible starting point for the subsequent iteration.

Fig. 4 shows the expanded region of the proton NMR spectrum of sulfone **2** depicting the signal due to H_A and H_{A'} together with a simulated spectrum generated using the g-NMR software package with a 1 Hz line width. There was a good match of intensity and frequencies between experimental and calculated

Table 2 Chemical shifts and coupling constants extracted from second-order multiplets for sulfones **2**, **4** and **5**

Sulfone	δ CH ₂ S ppm	J_{AX} Hz	$J_{AX'}$ Hz	$J_{AA'}$ Hz	$J_{XX'}$ Hz
2	3.5	5.5	10.3	-14.0	-14.0
4	3.72	5.8	10.0	-14.0	-14.0
5	3.08	5.0	11.5	-13.9	-13.9

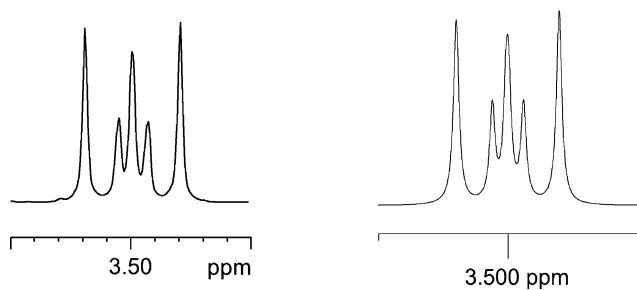


Fig. 4 Experimental and simulated spectra of sulfone 2.

spectra. The initial guess for the geminal coupling constants, was also correct to within the error of the experimental measurement. Indeed, when the geminal coupling constants $J_{AA'}$ and $J_{XX'}$ were different this led to lines L3 and L5 being further split in the simulation. Although, there was indeed some broadening in these lines, they failed to split, indicating that the values for the geminal coupling constants were very similar.

Equating the measured values of J_{AX} and $J_{AX'}$ to Table 1, and assuming there is no *gauche* effect, indicates that the *anti* conformer was present at greater than 60%, for the three sulfones investigated. This comparison is extremely crude as it assumes that the coupling constants in the sulfones are the same as in the ethyl thiopropylsulfide ethers. The distinct preference for the *anti*-conformer, in those cases, may well reflect the larger size of a sulfone, which has an *A*-value of 2.5 for the phenyl series.⁴⁴ By comparison, the *A*-value for a phenyl sulfide was only 0.8. Clearly a conformational preference for the *anti* conformer was strongly contributing to making the spectra second-order for the sulfones 2, 4 and 5.

It is instructive to investigate how the appearance of the spectra vary as vicinal and geminal coupling constants change. The spin physics of an AA'XX' system is well understood with the secular determinant factorising giving rise to three separate distinct sub-spectra, labelled A to C, Fig. 5, comprising ten lines in total. These arguments are essentially an extension of the Becker analysis.¹⁵ The position of, and intensity of all lines can be explicitly defined. Sub-spectrum A provides information primarily on the geminal coupling constants. When the sum of the geminal

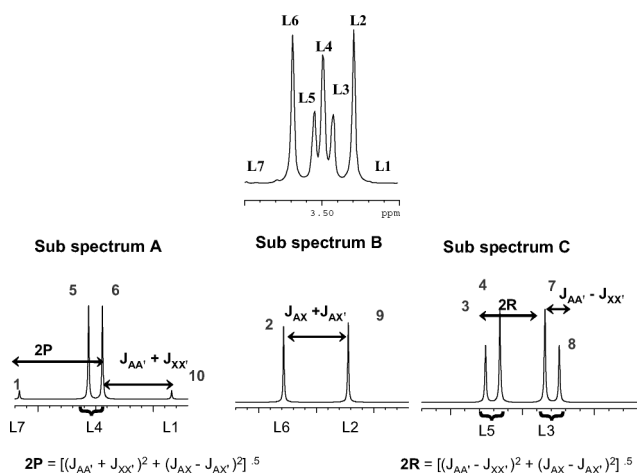


Fig. 5 Breakdown of an AA'XX' spectrum into its three constituent subspectra with equations relating line positions to coupling constants.

coupling constants is large compared to the difference in the vicinal coupling constants then lines 5 and 6 overlap to give L4 in the experimental spectrum. Lines 1 and 10 correspond to L1 and L7 in the experimental spectrum and if these can be located they give useful information on the values of the geminal coupling constants. In the first-order limit, *i.e.* $J_{AX} = J_{AX'}$ then lines 5 and 6 perfectly overlap, to give 50% of the intensity of the middle line of a first-order triplet, with lines 1 and 10 having zero intensity. Sub-spectrum B does not contain any transitions to mixed states and as such the intensity of lines 2 and 9 are completely independent of value the coupling constants and correspond to lines L6 and L2 in the experimental spectrum. The difference between L6 and L2 is equal to the sum of the vicinal coupling constants and these lines are the outer lines of the triplet in the limit when the system approaches and then becomes first-order.

Sub-spectrum C provides information on both the geminal and vicinal coupling constants. When the two geminal coupling constants are equal then lines (3, 4) and (7, 8) overlap giving lines L5 and L3 in the sulfone experimental spectrum. In this special case it is clear from the value of 2P that the difference between lines L5 and L3 is the difference in vicinal coupling constants. When Δ_{geminal} is large compared to Δ_{vicinal} then lines 4 and 7 move towards each other and in the first-order limit *i.e.* $J_{AX} = J_{AX'}$ lines 4 and 7 perfectly overlap, to give 50% of the intensity of the middle line of a first-order triplet. In the general case where the two geminal coupling constants are different, when lines 4 and 7 overlap lines 3 and 8 have zero intensity as they are the outer lines in an AB spin system.

The value for 2R is dependent on both the difference in vicinal and geminal coupling constants. When the difference in geminal coupling constants is large this brings lines 4 and 7 closer together and offsets the effect from vicinal coupling constant differences on the *appearance* of the spectra. As lines 3 and 8 move further apart their intensity decreases and they can easily be concealed under the larger peaks in the multiplet. This effect is simulated in Fig. 6 with typical values of vicinal coupling constants and allowing the difference in geminal coupling constants to vary. When the difference in geminal coupling constant is close in value to the difference in vicinal coupling constant then the multiplet essentially looks like a triplet with outer lines 3 and 8 being concealed under lines 2 and 9 with lines 4 and 7 constrained from moving apart. In this regard sulfones 2, 4 and 5, which have identical geminal coupling constants, are ideal substrates for giving rise to complex second-order spectra. As the geminal coupling constant becomes larger still then lines 3 and 8 resolve from lines 4 and 7 but their intensity is so low they can be easily overlooked, Fig. 6, $\Delta_{\text{geminal}} = 10$ Hz. When $\Delta_{\text{geminal}} = 16$ Hz these outer lines can no longer be detected and all their intensity is transferred into the middle line. The resulting multiplet now looks like a binomial triplet even though the two vicinal coupling constants are very different! This multiplet could be accurately described as an 'apparent triplet' as it looks like a triplet, but a first order analysis does not return the two vicinal coupling constants of 5.5 and 15.5 Hz, only their average value of 10.5 Hz!

Although specialist NMR software was initially used to analyse the multiplets, it is clear from the above arguments that extraction of the coupling constants from these complex multiplets is trivial when the two geminal coupling constants $J_{AA'}$ and $J_{XX'}$ are, to within the error of the linewidth, identical. The mechanics for

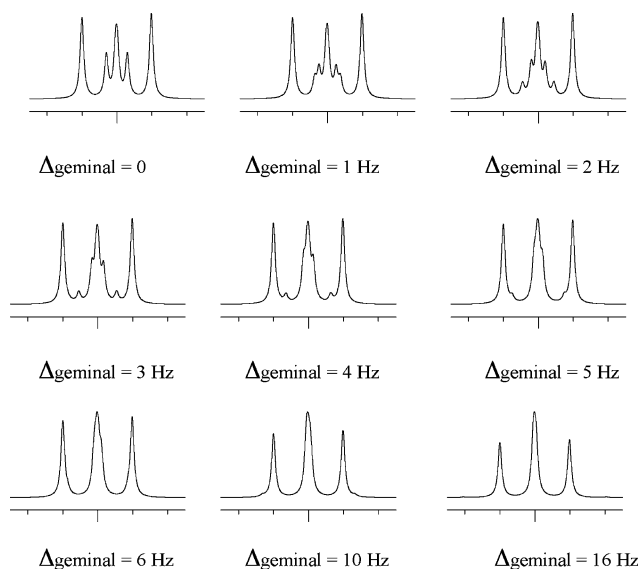


Fig. 6 Effect of varying the difference in geminal coupling constants for a fixed vicinal coupling constant difference of 5.5 Hz and sum of 15.5 Hz with a linewidth of 1 Hz.

doing this are outlined in Table 3. Since the sum and difference of the vicinal coupling constants were easily extracted, then J_{AX} and $J_{AX'}$ were readily evaluated.

It was clear from Table 3, column 3, that when the two vicinal coupling constants became close in value, then lines L3 and L5 may no longer be resolved and the multiplet takes on a first-order appearance. The intensities of the outer low intensity lines L1 and L7 were also highly dependent on this vicinal coupling constant difference and went to zero when J_{AX} was equal to $J_{AX'}$.

1,2-Disubstituted ethanes are ubiquitous in organic chemistry, whilst second-order AA'XX' spectra for these molecules are relatively rarely reported. Why should this be so? Is it simply down to the size of the substituents favouring a conformation which extenuates the differences in vicinal coupling constants? Although the A -value for a sulfone is relatively large at 2.5, it was still less than that of the more commonly encountered phenyl group with an A -value of 2.7. The proton NMR spectrum of propyl benzene⁴ showed a triplet for the benzylic methylene group, with the central line much broader than the outer lines, but it failed to resolve in the same way as the sulfone **5** did. Spectral simulation and examination of the relevant equations reveals that the appearance of the spectra were highly dependant on the differences of vicinal and geminal coupling constants $J_{AX} - J_{AX'}$ and $J_{AA} - J_{XX'}$ respectively. When the two geminal coupling constants are different this led to a further splitting in lines L3 and L5, which became an AB-type quartet. The result of this was to push the stronger inner lines towards L4 and the lower intensity outer lines towards lines L2 and L6. This gave the multiplet the resemblance of a first-order

Table 3 Manual extraction of coupling constants when $J_{AA} = J_{XX'}$

L1–L7	L2–L6	L3–L5
$4 J_{AA}$	$J_{AX} + J_{AX'}$	$J_{AX} - J_{AX'}$

triplet by broadening the middle line L4. In essence, the criterion for observing complex second-order spectra in 1,2-disubstituted ethanes is that the difference in vicinal coupling constants must be large and the difference in geminal constants must be small, as illustrated in Fig. 6. In practice these conditions are rarely met and apparent triplets are thus the norm.

Fig. 7 shows the proton NMR spectrum of 2-bromoethyl benzene for the methylene pair adjacent to the bromide, which looks essentially first-order. However, on careful inspection, the two weaker outer lines, corresponding to the splitting of lines L3 and L5, are clearly visible. In this case the difference in geminal coupling can be estimated to be a maximum value of 4.2 Hz. With this difference in the geminal coupling constant, spectral simulation reveals that a difference of 3 Hz in vicinal coupling constants would not be resolvable, though the central line does become quite broad. Again it is this large difference in geminal coupling constant, along with the small difference in vicinal coupling that renders the spectrum to appear first-order. Another salient point worth noting is that the line shape in modern NMR spectrometers is routinely very much better than that of high field instruments from only ten years ago. In the 300 MHz NMR spectrum for 2-bromoethyl benzene, published in the Aldrich Catalogue of NMR Spectra,⁴ the small peaks due to the second-order behaviour were not resolved, evidently due to the mediocre quality of the lineshape.

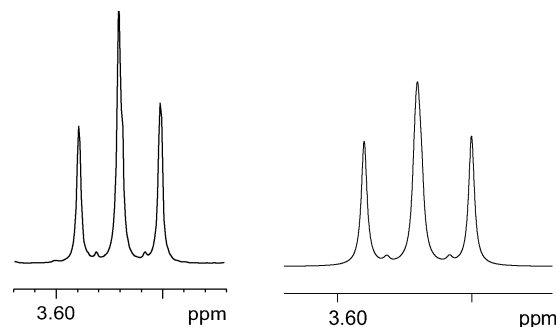


Fig. 7 Proton NMR spectrum of 2-bromoethyl benzene **6** displaying additional small peaks due to second-order behaviour. Simulated spectrum with $\Delta_{\text{geminal}} = 4.2$ Hz and $\Delta_{\text{vicinal}} = 3$ Hz.

Alkyl triphenylphosphonium salts are complementary to sulfones in organic synthesis as they give rise to *cis*-alkenes *via* Wittig reaction. Since the triphenyl phosphonium group is extremely large, it seemed a likely candidate to give rise to strong second-order spectra. *n*-Propyl triphenylphosphonium bromide **7** was prepared by a literature procedure,⁴⁵ and the methylene multiplet next to the phosphorus is displayed in Fig. 8 along with simulated spectra with and without phosphorus coupling.

This multiplet which is clearly second-order, was again an AA'XX' spin system with additional complexity coming from the phosphorus coupling as well as the non-zero value for the difference in geminal coupling constants. Using the g-NMR software package, the coupling constants were evaluated as $J_{AX} = 4.6$ Hz, $J_{AX'} = 11.5$ Hz and $\Delta J_{\text{geminal}} = 2.5$ Hz. Unfortunately, the lower intensity outer lines, containing information on the sum of the geminal coupling constants could not be located making it impossible to reliably evaluate the exact value of the geminal

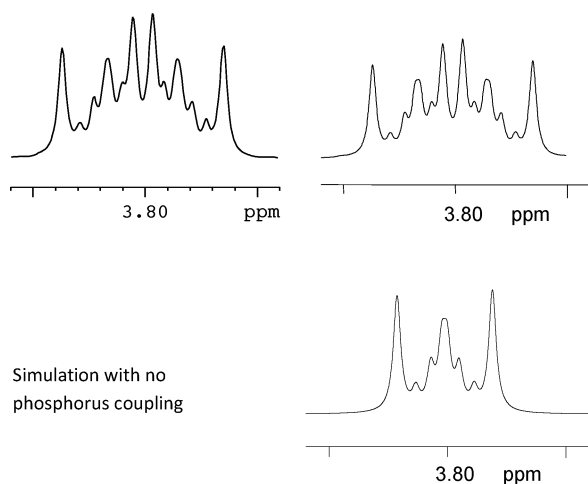


Fig. 8 Proton NMR spectrum of *n*-propyl triphenylphosphonium bromide **7** along with simulated spectra with and without phosphorus coupling with a linewidth of 1.5 Hz.

coupling constants. When the phosphorus coupling, 12.5 Hz, was excluded from the simulation it became clear that spectrum resembled those shown in Fig. 8.

Recently, an excellent example of an AA'XX' spin system was observed for compound **8** on route to the marine natural product Malhamensilipin A, Fig. 9.⁴⁶ Clearly, the heavy substitution of two chlorines and a methylene group containing a TBS protected alcohol, are favouring the *anti* conformation, thus giving rise to the observed second-order spectra. Interestingly, the methylene group containing the iodide is essentially first-order, probably reflecting the low *A*-value of 0.46 for this substituent.

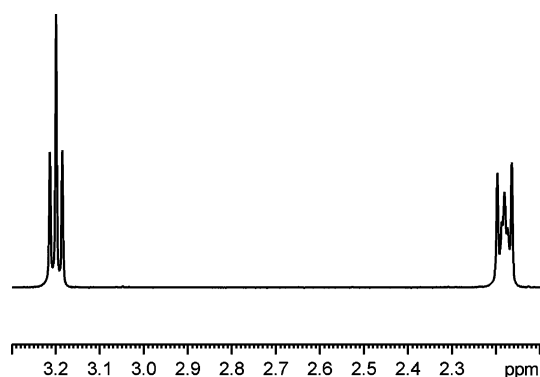


Fig. 9 Proton NMR spectrum of compound **8**, run at 600 MHz, clearly showed the second-order behaviour of the methylene group adjacent to the dichloromethylene group. The methylene group attached to the iodide is essentially first-order.⁴⁷

A screen of published spectra revealed that 2-trimethylsilyl-ethanesulfonyl chloride **9**,⁴⁸ the precursor for the commonly used SES protecting group, and the corresponding *N*-SES derivatives both display second-order AA'XX' spectra.⁴⁹ Clearly, the large sulfonyl combined with the large trimethylsilyl groups are favouring the *anti*-conformers and attenuating the differences in vicinal coupling constants leading to strong second-order behaviour.

It is prudent to comment on the nomenclature employed for describing multiplets. The terms 'deceptively simple spectra' and 'apparent multiplet' can both be used to describe multiplets. The

former term is rigorously defined,⁵⁰ was developed over fifty years ago to describe second-order spectra which had fewer lines than were initially anticipated, and is rarely used these days. However, the latter term, 'apparent multiplet', which has become part of the NMR lexicon, has to my knowledge, never been explicitly defined in the primary literature. An 'apparent multiplet' may be defined as 'a multiplet which looks like a first order multiplet but is not.'⁵¹ There are two reasons why the aforementioned multiplet may not be a first order multiplet, namely intensity anomalies and that a first order analysis does not return the true values of all the coupling constants. Intensity anomalies occur when the difference in coupling constants, from at least two contributing chemically different nuclei, is non zero but is less than the linewidth. This leads to a broadening of the signal, as the two lines do not exactly overlap, which leads to a subsequent reduction in intensity, although its integration is more or less correct. Therefore a double doublet with two similar, but not *identical* coupling constants, can be described as an 'apparent triplet'. Rapid visual inspection of intensities, and broadening of some peaks, is a good indicator that the multiplet is 'apparent.' Clearly, the difference in frequency between consecutive lines in this apparent triplet cannot provide both coupling constants as they are not resolved. Based on this, a formal definition of the term apparent multiplet, which makes it distinctive may be: 'A multiplet which looks like a first order multiplet, but that the difference in frequency between the first line and all the other lines does not return the true values of *all* the coupling constants defining the multiplet.'

For apparent multiplets, in the first-order case, the coupling constants of the nuclei contributing to the coupling are similar but their chemical shifts are very different. In the second-order case the opposite is true, the chemical shifts are similar, even identical, but the coupling constants may be very different. As a word of caution, it is clear that the term 'apparent' as applied to multiplets, cannot, in a general sense, be equated to near equality of contributing coupling constants. For example an AA'X spin system will give an 'apparent triplet' for signal X, probably flanked by two very low intensity combination lines depending on the magnitude of the coupling constants J_{AX} and $J_{AX'}$. The difference in frequency between any two consecutive triplet lines, in this multiplet, will only provide the average value of the two potentially very different coupling constants J_{AX} and $J_{AX'}$. Likewise, the X signal of the second-order ABX spin system could be described an 'apparent triplet' if the difference in coupling constants was large but the chemical shift difference between A and B was very small. Interestingly, if an ABX spin system was comprised of four double doublets these could be described as 'apparent double doublets' *i.e.* they resembles first order double doublets but the differences in frequency between the lines 1 and 2 and lines 1 and 3 in each multiplet does not return the true values of *all* the coupling constants! That would greatly aid annotation as ABX spin systems are still very common, and extraction of true coupling constants from this multiplet is not a trivial task for the majority of non-spectroscopists who routinely employ NMR spectroscopy for structure elucidation. Of course if these coupling constants were going to be further employed to establish stereochemistry, or conformational preference, then they would have to be evaluated correctly. Similarly the spectrum of sulfide **1** which is showing substantial broadening of the central line could be described as an 'apparent triplet' as the difference in value between consecutive

lines in the triplet only returns the average value for the two different vicinal coupling constants. The multiplet in Fig. 7 could be described as an apparent triplet as the additional peaks, due to second order behaviour, have very low intensity. However, it would not be appropriate to describe the multiplet in Fig. 2, for the sulfones **2**, as an 'apparent triplet,' as it contains five distinct lines. This multiplet is best described as 'AA'XX' and then provide the four coupling constants defining the multiplet.'

Conclusions

In conclusion, second-order proton NMR spectra in 1,2-disubstituted ethanes of commonly encountered organic functional groups for example sulfones, phosphonium salts, and SES protecting groups are much more common than what has been acknowledged in the recent chemical literature. Because these spectra arise due to magnetic non-equivalence of chemically equivalent nuclei, due to a preference for particular conformer, the use of higher magnetic field NMR instruments is *never* going to make these spectra become first-order. These spectra are essentially perpetually second-order. Second-order proton NMR spectra are here to stay and furthermore these spectra are not restricted to esoteric structures, but occur in common functional groups with which the average synthetic organic chemist commonly encounters. It was shown that aryl *n*-propyl sulfones and *n*-propyl triphenylphosphonium bromide gave rise to proton NMR spectra which were perpetually second-order. This was due to these molecules adopting an *anti*-conformation which extenuated the difference in vicinal coupling constants and having substituents which diminished the difference in geminal coupling constants. When the two geminal coupling constants were close in value, as was the case with the sulfones, then extraction of the vicinal coupling constants from the second-order multiplet was trivial. For *n*-propyl triphenylphosphonium bromide the difference in geminal coupling constants was small, 2.5 Hz, in comparison with the difference in vicinal coupling constants of 6.9 Hz. This contributed significantly to the observed second-order nature of this multiplet.

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