Deuterium Nuclear Magnetic Resonance Spectroscopy

1—Larmor Frequency Ratio, Referencing and Chemical Shift

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Precise values for the ratio of the Larmor frequencies, $w_{^1H}/w_{^2H}$, were measured at constant field for various organic compounds. The values of the Larmor frequency ratio depend on carbon–hydrogen bond hybridization. The best ratio for the ghost referencing of ^{2}H NMR spectra was then determined (6.514399862). This value enables an accurate ghost reference for any ^{2}H NMR spectrum to be derived from the observed ^{1}H NMR frequency of the normal internal reference. Deuterium and proton chemical shifts measured from internal, partially deuteriated TMS under the same conditions are shown to be the same.

INTRODUCTION

The first detailed high resolution study by ^{2}H NMR was reported 16 years ago.[1] Despite this early excellent account of the chemical applications of ^{2}H NMR spectroscopy there was very little activity in this field until recently.[2]

Deuterium NMR spectroscopy is undoubtedly the best method for locating the position(s) of this nucleus in deuteriated compounds and the relative extent of labelling.[3] ^{2}H NMR Chemical shifts provide a means of assigning complicated ^{1}H NMR spectra.[4] Deuterium NMR spectroscopy can also be used to study reaction mechanisms,[5] stereochemical applications[6] and the mechanism of biochemical synthesis or degradation.[7] The aim of the present work is to establish a reference standard for the ^{2}H NMR spectra of labelled compounds and to find the effect of *sp* hybridization on the ratio of Larmor frequencies, $w_{^2H}/w_{^1H}$. The relationship between the proton and deuterium chemical shift is verified.

RESULTS AND DISCUSSION

Ratio of Larmor frequencies

By definition, the condition for resonance of any nucleus X at constant field B_0 is given by Eqn (1).

$$\nu_X = \gamma_X B_0(1-\sigma_X) \tag{1}$$

The conditions for resonance of protium and deuterium are therefore given by Eqns (2) and (3), respectively.

$$\nu_{^1H} = \gamma_{^1H} B_0(1-\sigma_{^1H}) \tag{2}$$

$$\nu_{^2H} = \gamma_{^2H} B_0(1-\sigma_{^2H}) \tag{3}$$

If the nuclear screening constants, $\sigma_{^1H}$ and $\sigma_{^2H}$, are mainly functions of the local molecular environment, which for a single isotopic replacement is virtually unchanged, then the ratio of the Larmor frequencies, $w_{^1H}/w_{^2H}$, for any site at constant applied field should be virtually constant. Measurements of NMR line frequencies made on a selection of deuteriated organic compounds (Table 1) show this to be the case and provide a mean value of 6.5143997 ($+4\times10^{-7}$) for the ratio. Of the previous measurements for this Larmor frequency ratio the most accurate are those of Wimmett,[12] which agree with our results. No clear primary isotopic effect on the Larmor frequency ratio was observed (or they were similar in magnitude to the experimental error, Table 1). In fact, very similar values were found for all sp^3 hybridized[4] compounds, regardless of whether they are monodeuteriated (**1–3**), dideuteriated (**4**, **5**) or trideuteriated (**6–10**). However, inspection of the ratios in Table 1 show that the values fall into three groups. sp^3 Hybridized compounds (**1–10**) gave a mean value of 6.51439982 ($\pm9\times10^{-8}$), sp^2 hybridized compounds (**11** and **12**) gave a mean value of 6.51439944 ($\pm7\times10^{-8}$), while that for *sp* hybridized compounds (**13** and **14**) was 6.51439975 ($\pm5\times10^{-8}$). It is thus evident that these values depend upon carbon–hydrogen hybridization[8] and show a similar dependence pattern to that of the $w_{^1H}/w_{^3H}$ ratio on carbon–hydrogen hybridization.[9] Evidently, the ratio of the isotopic screenings is not constant but varies detectably with bond type.

Referencing of ^{2}H NMR spectra

Natural abundance TMS has been used as the internal reference for natural abundance ^{2}H NMR spectra,[11] while d_4-methanol[4] and $CDCl_3$[13] have been used as the internal reference for the ^{2}H NMR of deuteriated compounds. d_4-Methanol, d_1-chloroform, D_2O,d_6-acetone or other deuteriated compounds can be used as the internal reference for the ^{2}H NMR of enriched compounds. However, it should be mentioned that

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Table 1. Measurement of the ratio of ^{2}H and ^{1}H Larmor frequencies

No.	Compound (position of deuteration)		Observed relative frequencies[a] Hz $\nu_{^1H}$ followed by $\nu_{^2H}$	$w_{^1H}/w_{^2H}$
1	Chloroform	CH	90025538.125	6.51439974
		CD	13819467.901	
2	Acetophenone	CH_3	90025187.968	
		CH_2D	13819414.046	6.51439979
3	Diethyl malonate	CH_2	90025278.987	
		CHD	13819428.048	6.51439978
4	Dichloromethane	CH_2	90025422.510	
		CD_2	13819450.169	6.51439973
5	Dioxane	CH_2	90025334.877	
		CD_2	13819436.394	6.51439989
6	Acetone	CH_3	90025205.113	
		CD_3	13819416.611	6.51439982
7	Acetonitrile	CH_3	90025225.923	
		CD_3	13819419.835	6.51439982
8	Nitromethane	CH_3	90025462.119	
		CD_3	13819455.964	6.51439988
9	Dimethyl sulphoxide	CH_3	90025184.979	
		CD_3	13819413.509	6.51439984
10	*N*,*N*-Dimethylformamide	CH_3	90025279.704	
		CD_3	13819427.968	6.51439988
				sp^3 mean value $= 6.51439982 \pm 9 \times 10^{-8}$
11	Benzene	CH	90025575.028	6.51439951
		CD	13819474.056	
12	Benzothiazole(2)	CH	90025658.068	
		CD	13819487.10	6.51439937
				sp^2 mean value $= 6.51439944 \pm 7 \times 10^{-8}$
13	Acetylene	≡CH	90025267.077	
		≡CD	13819426.191	6.51439979
14	Phenylacetylene	≡CH	90025123.839	
		≡CD	13819404.394	6.51439970
				sp mean value $= 6.51439975 \pm 5 \times 10^{-8}$
15	Water	HOD	90025602.381	
		DOD	13819477.426	6.51439990

[a] The error is ±1 channel which is precisely ±0.1465 Hz.

Table 2. Proton and deuterium chemical shifts (ppm) from internal TMS and monodeuteriated TMS, respectively, using hexafluorobenzene as a solvent

No.	Compound		$\delta_{^1H}$ followed by $\delta_{^2H}$	$\delta_{^1H}/\delta_{^2H}$
1	Chloroform	CH	7.32	1.0
		CD	7.3	
2	Acetophenone	CH_3	2.41	1.02
		CH_2D	2.38	
3	Diethyl malonate	CH_2	3.26	0.98
		CHD	3.32	
4	Dichloromethane	CH_2	5.33	1.01
		CD_2	5.3	
5	Dioxane	CH_2	3.53	1.01
		CD_2	3.49	
6	Acetone	CH_3	2.06	1.02
		CD_3	2.02	
7	Acetonitrile	CH_3	1.98	1.02
		CD_3	1.93	
8	Nitromethane	CH_3	4.37	1.01
		CD_3	4.34	
9	Dimethyl sulphoxide	CH_3	2.57	0.98
		CD_3	2.64	
10	*N*,*N*-dimethylformamide	CH_3	2.95 *trans*	1.02
			2.90 *trans*	1.02
		CD_3	2.77 *cis*	
			2.72 *cis*	
11	Benzene	CH	7.126	1.00
		CD	7.15	
12	Benzothiazole	CH	8.86	1.00
		CD	8.89	

these compounds have inherent disadvantages (e.g. solvent–solute interaction, magnetic susceptibility etc.). Tetramethylsilane (TMS) is accepted as a universal reference for proton,[14] tritium[15] and ^{13}C[16] NMR spectra, and we state that monodeuteriated TMS can be used as a suitable internal reference for the ^{2}H NMR spectra of labelled compounds.

It is not feasible to prepare monodeuteriated TMS by simple exchange methods; furthermore, using lithium metal with trimethylchloromethylsilane[9] gave a very low yield and is a tedious preparation scheme. We prepared monodeuteriated TMS by the following route.[10]

$$Me_3SiCH_2Cl \xrightarrow{LiAlD_4} Me_3SiCH_2D$$

Proton and deuterium chemical shifts were measured on the same sample in the same probe head, using a fluorine locking signal for both ^{1}H and ^{2}H NMR spectra on selected organic compounds, and using TMS and monodeuteriated TMS, respectively, as internal reference (Table 2). The experimental results show that deuterium and proton chemical shifts are identical, the mean value for the ratio $\delta_{^1H}/\delta_{^2H}$ being 1.01 and a plot of $\delta_{^1H}$ against $\delta_{^2H}$ giving a straight line with a slope of unity and zero intercept. Mono-, di- and tri-isotopic replacement of ^{2}H for ^{1}H in a molecule will not appreciably alter the shielding at the replacement position[1,17] (or it is close in magnitude to the experimental error). Hence $\delta_{^1H}/\delta_{^2H}$ was unity for compounds **1**–**3**, **11** and **12** (monodeuterium isotopic replacement), **4**, **5** (di-isotopic replacement) and **6**–**10** (tri-isotopic replacement).

Protonated TMS can also be used as an internal reference for ^{2}H NMR. To achieve this, the Larmor frequency ratio for protonated and monodeuteriated TMS was determined. From three sets of very similar measurements on ^{2}H TMS and protonated TMS in hexafluorobenzene (Table 3) the ratio of the Larmor

Table 3. Measurement of $w_{^1H}/w_{^2H}$ for partially monodeuteriated TMS at 25 °C in hexafluorobenzene

Observed line frequencies (Hz) $w_{^1H}$ followed by $w_{^2H}$	$w_{^1H}/w_{^2H}$
90025039.946	6.514399862
13819391.173	
90025039.946	6.514399862
13819391.173	
90025039.946	6.514399862
13819391.173	

Table 4. Correlation between the frequency observed for ^{2}H TMS and that calculated from ^{1}H TMS measured under the same conditions

Compound[a]	^{1}H of TMS (Hz)	Observed ^{2}H for monodeuteriated TMS	Calculated[b] ^{2}H for monodeuteriated TMS	Difference[c] Hz	Difference[d] (ppm)
1	90024879.21	13819366.64	13819366.50	0.14	0.010
2	90024956.096	13819378.52	13819378.30	0.22	0.016
3	90024988.37	13819383.57	13819383.26	0.31	0.022
4	90024933.06	13819374.33	13819374.76	−0.43	−0.03
5	90024992.55	13819384.93	13819383.90	1.03	0.075
6	90025004.21	13819385.62	13819385.69	−0.07	−0.005
7	90025031.56	13819390.32	13819389.88	0.56	0.040
8	90025042.95	13819391.17	13819391.63	−0.46	0.033
9	90024911.92	13819371.18	13819371.52	−0.34	−0.025
10	90025008.03	13819386.47	13819386.27	0.20	0.014
11	90024908.85	13819371.26	13819371.05	0.21	0.015
12	90024861.09	13819363.99	13819363.72	0.27	0.019
16[e]	90024994.68	13819384.34	13819384.22	0.12	0.009

[a] See Table 1.

[b] Calculated ^{2}H = ^{1}H/6.514399862

[c] The difference in Hz = ^{2}H observed − ^{2}H calculated

[d] The difference in ppm = difference in Hz/13.82

[e] Propionitrile

frequencies for TMS was found to be 6.514399862. This value is very close to the mean value of sp^3 hybridized compounds (Table 1) and is now being used for the ghost referencing[9] of ^{2}H NMR spectra from ordinary internal TMS or DSS. Good agreement was found between the observed frequency for monodeuteriated TMS and the calculated value from ordinary TMS using the Larmor frequency ratio of 6.514399862, and Table 4 shows that their differences in ppm for different sample systems are very small (±0.1 ppm). Ghost referencing in ^{2}H NMR should be carried out on the same sample using the same locking signal for ^{1}H and ^{2}H NMR measurements.

EXPERIMENTAL

Compounds

Chloroform-d_1, dichloromethane-d_2, dioxane-d_8, acetone-d_6, acetonitrile-d_3, nitromethane-d_3, DMSO-d_6, *N,N*-dimethylformamide-d_7, water-d_2 and deuteriated benzene were commercially available and were used with no further purification.

d_1-Acetophenone, d_1-diethyl malonate,[18] d_1-propionitrile,[18] d_1-benzothiazole[15] and d_1-phenylacetylene[9] were prepared according to reported methods.

d_2-Acetylene was prepared from the dropwise addition of D_2O on to calcium carbide. The acetylene gas was dried by passing through anhydrous $CaCl_2$ and was then bubbled through hexafluorobenzene at low temperature (≈15 °C) to allow NMR measurements.

Monodeuteriated TMS[10] was prepared by suspending lithium aluminium deuteride (1 g, 2 mol) in very dry tetrahydrofuran; trimethylchloromethylsilane (6.1 g, 1 mol) was then added dropwise at 50 °C. Monodeuteriated TMS, which distilled between 39–40 °C, was trapped at 10 °C with a yield of 65–70%.

NMR Measurements

^{2}H and ^{1}H NMR spectra were recorded at 13.8 and 90 MHz (nominal), respectively, on a Bruker WH90DS Fourier transform NMR spectrometer equipped with quadrature detection, Aspect 2000, 32 K computer and disc storage. The frequencies for the above measurements were locked to a master 5 MHz clock to which the field is also locked via a ^{19}F signal derived from the sample. The measurement of the resonance frequency (Tables 1–4) was carried out in a 10 mm Wilmad NMR tube by dissolving the deuteriated compound (with a few drops of the undeuteriated compound) in hexafluorobenzene (50/50 v/v) as a locking signal. External lock was used in the case of D_2O measurement. A flip angle of 45° was always used for the ^{2}H NMR spectra in the above measurements. The free induction decay was accumulated in 8 K and the frequency domain was obtained in 4 K data points. An acquisition time of 13.7 s, with a sweep width of 300 Hz was used, with 32 transitions. Broad band proton-decoupled ^{2}H spectra were obtained using two filters. The first filter (band-stop) is connected to the output of the lock signal and is designed to stop 90 MHz and pass 84.67 MHz. The second filter is connected to the output of the decoupler and is designed to pass 90 MHz and stop 84.67 MHz.

^{1}H NMR spectra were measured on the same sample in the same probe using the decoupler coil (leaving the filters connected as mentioned above).

The absolute frequency for ^{2}H and ^{1}H spectra were obtained using the computer output.

The chemical shifts in the ^{2}H and ^{1}H spectra were measured in a manner similar to that of the absolute frequency on the same sample by adding a few drops of TMS and monodeuteriated TMS. Sweep widths of 300 Hz and 600 Hz were used for the ^{2}H and ^{1}H spectra, respectively.

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