

## Analytical Applications of NMR Spectra in the Gas Phase

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**Abstract:** Gas-phase multinuclear magnetic resonance (MR) spectra allow the total elimination of intermolecular effects from magnetic shielding in molecules. Consequently, the resonance frequencies of isolated atoms and molecules are also available for reading from MR spectra. Following the connectivity between nuclear magnetic moments, resonance frequencies of two different nuclei in the same MR experiment and the shielding of helium-3, it is demonstrated that the direct shielding measurement is available on a nuclear MR spectrometer. As shown, the shielding parameters can completely replace the chemical shifts of numerous nuclei. The new method has also many additional advantages; as it allows for example the direct comparison of experimental and theoretical shielding constants and makes possible the determination of the first order isotope effect in shielding, which was not available in nuclear MR spectroscopy before.

**Keywords:** Chemical shifts, gas-phase experiments, intermolecular interactions, localized MRI, multinuclear magnetic resonance, shielding measurements.

### INTRODUCTION

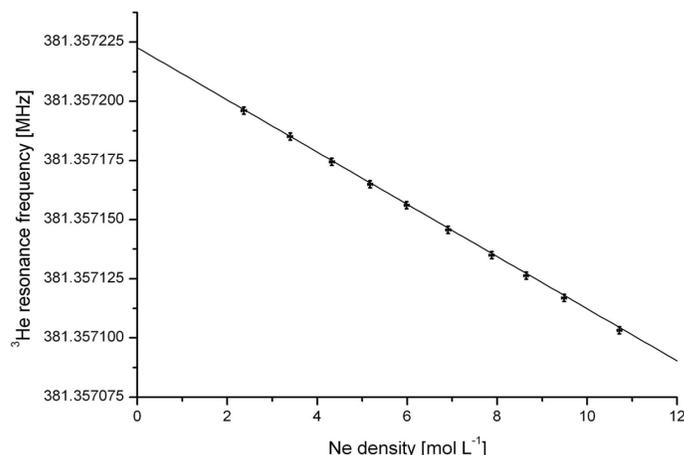
Nuclear magnetic resonance (MR) spectroscopy is a powerful tool for the determination of structure of chemical compounds and a character of intra- and intermolecular interactions and is widely used for searching information on molecular structure in chemistry, biology and pharmacy. High-resolution nuclear MR experiments are mostly applied to liquids and they are also present in medicine as the localized magnetic resonance imaging (MRI) studies [1]. More difficult problems arise when molecules are fixed and their reorientation is hindered. However, there is also a possibility of observing high-resolution MR spectra for solids when the technique of magic angle spinning (MAS) is applied [2]. Nuclear MR studies in the gas phase are as easy as for liquids but the preparation of gaseous samples is not trivial and requires special laboratory methods. That is why gaseous MR spectra are mostly used for the improvement of this kind of spectroscopy which is further explored for the improved investigations of liquids and solids. First, let us consider only one important problem in nuclear MR spectroscopy. From a theoretical view point it is obvious that any MR measurement performed for a macroscopic sample is disturbed by intermolecular interactions and temperature [3]. It occurs for solids, liquids and gases as well though these effects are considerably smaller in the gas phase than in solids or liquids. Nuclear MR analysis may contain serious errors if the final conclusions are based on uncertain MR parameters. Fortunately it is possible to avoid such mistakes if the magnetic shielding and spin-spin coupling values are obtained for isolated molecules. Such unique nuclear MR parameters are available from the gas-phase

measurements performed as the function of density and with the further extrapolation of experimental points to zero density.

Modern nuclear MR spectrometers equipped in superconducting magnets permit the precise investigations of extremely weak MR signals. Generally the most popular nuclei like  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$ ,  $^{29}\text{Si}$  or  $^{31}\text{P}$  (all with the spin number  $I = \frac{1}{2}$ ) give relatively strong MR signals. Many other nuclei have low natural abundance and their MR spectra are difficult for observation and require the application of enriched isotopomers. In our laboratory we use such isotopomers and additionally explore gaseous solutions which allow the observation of other magnetic nuclei in the gas phase. The above method was used for the studies of numerous molecules which are engaged in strong intermolecular interactions being liquids at room temperature e.g. sevoflurane (2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether), an efficient agent for induction of anesthesia [4]. When a small amount of investigated compound is dispersed in a gaseous solvent, then the measurements are performed changing the density of this solvent, cf. for example also our  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{15}\text{N}$  one- and two-dimensional MR spectra of acetonitrile [5].

Finally MR experiments in the gas phase help us to develop the method of shielding measurements which can be applied on any nuclear MR spectrometer. It is based on the calculated value of shielding in an isolated helium-3 atom [6] and our own observation of resonance frequencies in a constant magnetic field [7]. As shown, the chemical shifts can be successfully replaced by the shielding parameters for numerous nuclei, which was not possible in nuclear MR spectroscopy before. The chemical shifts certainly remain the important parameter of MR spectra whenever the measurement of shielding is not easily available. Let us only note that the direct reading of shielding has numerous distinct advantages which are discussed in this paper.

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**Fig. (1).** Density-dependent helium-3 MR frequency in a gaseous neon solution. According to Eq. (4) the  $\nu_0^{\text{He}}$  value can be precisely determined from this experiment. The plot presents helium-3 measurements explored up to high pressure ( $\sim 300$  bar) [8].

## EXPERIMENTAL METHOD

Gas samples are prepared by the condensation of gases from the calibrated part of vacuum line to glass ampoules and sealed. The sealed gas sample is placed into the standard 5 mm o.d. NMR tube with liquid deuterated solvent in the annular space. This method is good for the observation of MR signals when the pressure of gases does not exceed 50 bar. For higher pressure we use the zirconia tube equipped with a metal valve for gas filling, which was delivered to us by Daedalus Innovations (USA) [8]. Applying the above experimental methods we have studied numerous chemical compounds containing various magnetic nuclei, including  $^1\text{H}$ ,  $^2\text{H}$ ,  $^3\text{He}$ ,  $^{10}\text{B}$ ,  $^{11}\text{B}$ ,  $^{13}\text{C}$ ,  $^{14}\text{N}$ ,  $^{15}\text{N}$ ,  $^{17}\text{O}$ ,  $^{19}\text{F}$ ,  $^{29}\text{Si}$ ,  $^{31}\text{P}$ ,  $^{73}\text{Ge}$ ,  $^{77}\text{Se}$  and all three magnetic isotopes of tin:  $^{115}\text{Sn}$ ,  $^{117}\text{Sn}$  and  $^{119}\text{Sn}$ .

In a gas of low density, the nuclear magnetic shielding ( $\sigma$ ) of a given nucleus (X) can be written as an expansion in powers of density ( $\rho$ ):

$$\sigma(X) = \sigma_0(X) + \sigma_1(X)\rho + \sigma_2(X)\rho^2 + \dots \quad (1)$$

where  $\sigma_0(X)$  is the shielding for an isolated molecule and  $\sigma_1(X)$ ,  $\sigma_2(X)$  are the coefficients of the intermolecular terms. It is worth noting that the higher-order terms, starting from  $\sigma_2(X)\rho^2$ , are usually very small and negligible for low-density samples. In such a case the dependence of shielding on density is linear and the two parameters ( $\sigma_0(X)$  and  $\sigma_1(X)$ ) are precisely determined from nuclear MR experiment. The above description is widely used for investigations of pure gaseous compounds. Following Eq. (1), the extrapolation of gas-phase measurements to the zero-density limit gives the  $\sigma_0(X)$  value free from intermolecular interactions, which is equivalent to the shielding of an observed nucleus in an isolated molecule. This parameter is very important as it permits us to learn the total effect of intermolecular interactions in shielding when the same compound is also monitored in the condensed state.

It is interesting that the  $\sigma_0(X)$  shielding values can be determined also for chemicals with low vapor pressure at room temperature. This can be done if the MR signal of a

sample is strong and can be observed at low concentration in another solvent gas. Molecules enriched in magnetic nuclei are usually required for such investigations. The solvent gas should be chemically inert and stable at higher pressure. It is used to diminish rates of both the spin-spin and spin-lattice relaxation, which makes the observed signal more intensive and narrow. Eq. (1) must be modified for gaseous solutions and it is changed as follows. For a mixture of gas A and B, where A contains the nucleus X whose shielding  $\sigma(X)$  is measured, and B is the gas solvent, one can write it as:

$$\sigma(X) = \sigma_0(X) + \sigma_{AA}(X)\rho_A + \sigma_{AB}(X)\rho_B + \dots \quad (2)$$

In Eq. (2) the  $\rho_A$  and  $\rho_B$  parameters describe the densities of A and B while  $\sigma_0(X)$  is the shielding at the zero-density limit. The coefficients  $\sigma_{AA}(X)$  and  $\sigma_{AB}(X)$  define the intermolecular effects for the collisions of A-A and A-B molecules. When the density of the solute compound is small ( $\rho_A$ ) than also the  $\sigma_{AA}(X)\rho_A$  term is small and usually can be neglected. As the shielding parameters in Eqs. (1) and (2) are temperature-dependent, the MR measurements of gases must be carried out at a constant temperature and they are usually performed at 300 K.

Having external magnetic field constant it is possible to rewrite Eqs. (1) and (2) in form of resonance frequencies as follows:

$$\nu(X) = \nu_0(X) + \nu_1(X)\rho \quad (3)$$

$$\nu(X) = \nu_0(X) + \nu_{AB}(X)\rho_B \quad (4)$$

where all frequency parameters ( $\nu$ 's) have similar meanings to those previously described for shielding in Eqs. (1 - 2). As shown, it is possible to determine the resonance frequency free from intermolecular effects ( $\nu_0$ ) which is equivalent to the resonance frequencies of isolated molecules. Fig. (1) illustrates the application of Eq. (4) when a small sample of helium-3 (solute, A) was observed in gaseous neon as the solvent (B). The ideal linear dependence of helium-3 frequency on solvent density is well marked and permits the determination of  $\nu_0$ . In the next section of this review it is shown that the  $\nu_0$  parameter of helium-3 is very important for whole MR spectroscopy.

## MEASUREMENTS OF MAGNETIC SHIELDING

At present nuclear MR analysis is mostly based on the measurements of chemical shifts. The MR chemical shift, discovered in 1950 [9, 10], became the most important parameter of the nuclear MR spectrum. According to the IUPAC conventions [11] the chemical shift ( $\delta_i$ ) is obtained from the difference of resonance frequencies of sample ( $\nu_i$ ) and reference standard ( $\nu_{\text{ref}}$ ):

$$\delta_i = \frac{\nu_i - \nu_{\text{ref}}}{\nu_{\text{ref}}} = \frac{\sigma_{\text{ref}} - \sigma_i}{1 - \sigma_{\text{ref}}} \approx \sigma_{\text{ref}} - \sigma_i \quad (5)$$

where  $\sigma_{\text{ref}}$  and  $\sigma_i$  are the shielding values (in literature also known as shielding constants) of reference and sample, respectively, when the external magnetic field ( $B_0$ ) is constant. The chemical shifts and shielding parameters are small and usually expressed in parts per million [ppm]. At this point let us admit that the application of chemical shifts is rather limited:

- chemical shifts show only the relative measurements of shielding constants,
- usually each magnetic nucleus requires another reference standard,
- every nucleus has its own scale of chemical shifts and it splits nuclear MR spectroscopy for so many different methods,
- there is no possibility for quick comparison of experimental and theoretical results,
- chemical shifts are really good only for the routine analysis of chemical compounds.

Recently we have demonstrated a new method of  $^1\text{H}$  and  $^{13}\text{C}$  shielding measurements available for isotropic species on any standard nuclear MR spectrometer [7]. It is based on the magnetic shielding in an isolated helium-3 atom ( $^3\text{He} = 59.96743$  ppm) [6], on our investigation of resonance frequency for the same atomic object [12] and the determination of unknown shielding according to Eq. (6):

$$\sigma_X = 1 - \frac{\nu_X}{\nu_{\text{He}}} \cdot \frac{|\mu_{\text{He}}|}{|\mu_X|} \cdot \frac{I_X}{I_{\text{He}}} (1 - \sigma_{\text{He}}) \quad (6)$$

where  $\nu$ ,  $\mu$  and  $I$  are the resonance frequencies in a constant external magnetic field, the nuclear magnetic moments [3, 13] and the spin numbers of helium-3 and another observed nucleus (X), respectively. Let us add that the resonance frequencies are strictly proportional to nuclear magnetic shielding in a constant magnetic field. Eq. (6) is applied to the shielding measurement of any nucleus if the magnetic moment of X is accurately known. As shown, the chemical shifts ( $\delta_i$ ) can be replaced by the shielding constants ( $\sigma_i$ ) if the MR measurements of resonance frequencies are simultaneously performed for X and  $^3\text{He}$  nuclei. The isolated helium-3 atom is used as the primary reference standard of shielding, and it is essential that this standard be applied for all the other magnetic nuclei. For the sake of convenience, the absolute shielding scale can be transferred from the helium-3 isolated atom to another reference standard, such as

**Table 1.  $C_X$  Parameters for the Direct Measurements of Shielding for Different Nuclei [14]**

Nucleus	$C_X$ Parameter
$^1\text{H}$	0.153506104
$^{11}\text{B}$	0.478413866
$^{13}\text{C}$	0.610389782
$^{15}\text{N}$	1.514602904
$^{17}\text{O}$	1.132052741
$^{19}\text{F}$	0.163114336
$^{29}\text{Si}$	0.772395075
$^{31}\text{P}$	0.379087277

for example deuterated lock solvent and this procedure can be easily applied in MR practice. It means the new standardization of MR spectra is available for everyone and it is consistent with theoretically calculated shielding values and with scientific approach to the analysis of compounds in chemistry, pharmacy and medicine as according to simple Eq. (7):

$$\sigma_X = 1 - C_X(\nu_X/\nu_D)(1 - \sigma_D^*) \quad (7)$$

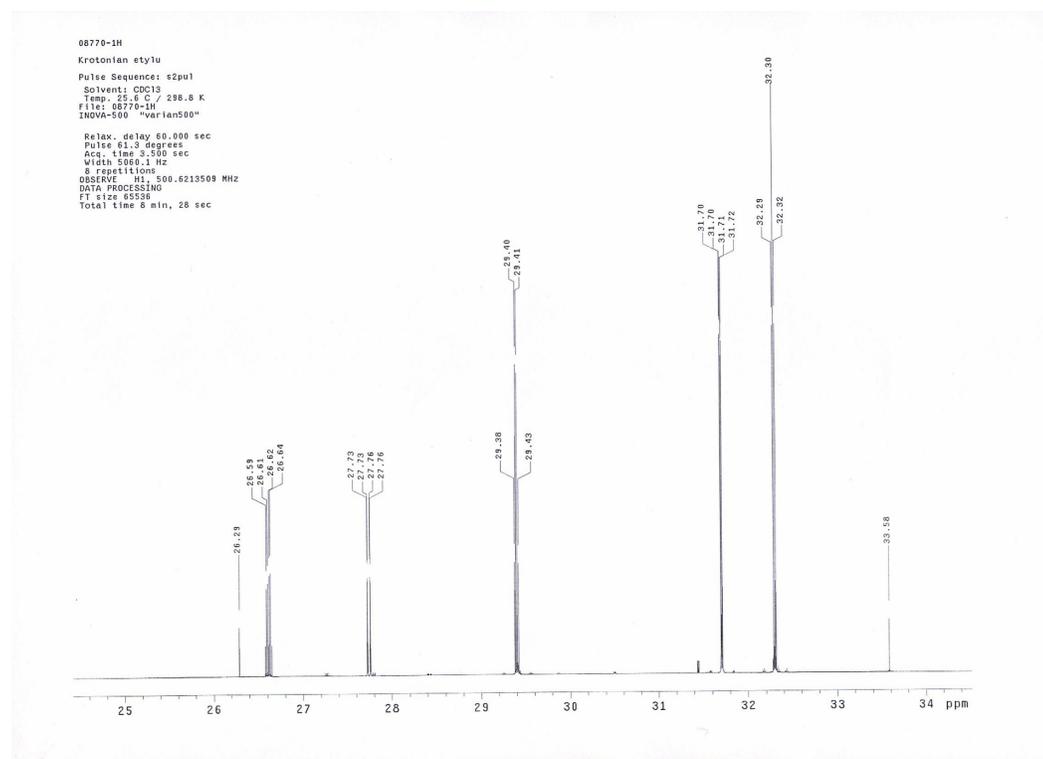
where  $\sigma_D^*$  represents the shielding of deuterons in selected liquid solvent [7] and  $C_X$  parameters are already known for many light magnetic nuclei:  $^1\text{H}$ ,  $^{11}\text{B}$ ,  $^{13}\text{C}$ ,  $^{15}\text{N}$ ,  $^{17}\text{O}$ ,  $^{19}\text{F}$ ,  $^{29}\text{Si}$  and  $^{31}\text{P}$  [14]. The values of  $C_X$  parameters necessary for the measurements of magnetic shielding for different nuclei are given below in Table 1.

At this point everything is ready for the recording of multinuclear MR spectra with the scale of magnetic shielding instead of chemical shifts. Applying the  $C_X$  parameters of Table 1, the  $\sigma_D^*$  values available from ref. [7] and Eq. (7) one can get such a spectrum using a standard MR spectrometer. It is illustrated in Fig. (2) where the  $^{13}\text{C}$  spectrum of liquid ethyl crotonate is shown as an example. As shown, the MR studies in the gas phase are very useful for the development of new experimental techniques and they have influence on the whole area of magnetic resonance spectroscopy, also the application of MR methods in pharmacy and medicine.

## CONCLUSIONS

As shown, the chemical shifts can be completely replaced by the measurement of shielding constants and this alternative method of standardization of nuclear MR data has numerous distinct advantages.

- (1) It unifies multinuclear methods into one nuclear MR spectroscopy because the values of magnetic shielding have the same meaning independently of observed nuclei and the same reference standard of shielding – an isolated helium-3 atom.
- (2) The experimental shielding values are suitable for the verification of calculated shielding constants for the same molecules.



**Fig. (2).**  $^{13}\text{C}$  MR spectrum of liquid ethyl crotonate obtained on a 500 MHz Varian INOVA spectrometer with the scale of magnetic shielding. The weak signal at  $\sigma = 33.58$  ppm comes from a small amount of tetramethylsilane (TMS) present in this sample.

- (3) Experimental shielding is determined with the same precision as the appropriate chemical shift because it is based on the same reading of MR frequencies.
- (4) The new method allows the measurement of first order isotope effects in shielding as it was recently shown for hydrogen isotopomers [15].
- (5) There is no need to use any additional reference standard if nuclear MR experiment is carried out with deuterated lock solvent.
- (6) Shielding measurements performed relatively to any external or internal deuterated solvent give practically the same results.
- (7) The measurement of shielding can be easily extended on MAS nuclear MR experiments as it was already shown for  $^{13}\text{C}$  spectra [16].
- (8) Experimental shielding parameters can be always converted into chemical shifts according to Eq. (5) if the shielding of reference compound is known.

All the above conclusions are true and vital for the method of shielding measurements. Some of them were already carefully verified, the others have been drawn from our preliminary MR studies in gases and liquids.

#### CONFLICT OF INTEREST

The author confirms that as I am the single author.

#### ACKNOWLEDGEMENTS

The author thanks Dr. Marcin Wilczek for the recording of  $^{13}\text{C}$  MR spectrum of ethyl crotonate shown in this work.

Support from the National Science Centre (Poland) grant DEC-2011/01/B/ST4/06588 is gratefully acknowledged.

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Received: May 07, 2013

Revised: August 09, 2013

Accepted: August 29, 2013

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